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ISSUE HIGHLIGHTS

- Recounting COVID-19 associated complement-mediated coagulopathies. Triggers and controls
- Association of circulatory chemerin levels with the severity of pre-eclampsia: A systematic review and bootstrapped meta-analysis
- Bacterial etiology among diarrheal cases
- NAMS task force report on gunshot and blast injuries
- NAMS task force report on cervical cancer

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Editorial

Corneal blindness and eye banking: Current status and challenges ahead

Maj Gen JKS Parihar¹

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Corneal blindness is the second most common cause of preventable blindness in India. It is estimated that more than 1.3 million people are affected with bilateral corneal blindness. Around 10.6 million were reported to suffer due to unilateral corneal blindness in 2020, having vision less than 6/60. The global statistics revealed bilateral corneal blindness in 5.5 million cases, while unilateral blindness and visual impairment may be more than 20 million.¹

China and India share a big burden of almost 49% of the world's total quantum of blindness and vision impairment, proportionally much higher than their share of 37% of the world population.²

The prevalence of corneal blindness ranges between 4 and 6% among all causes of blindness in India with much higher engagement in third-world countries and the African continent. The common causes of corneal blindness are injuries including occupational and environmental hazards, domestics, sports, infections including trachoma, infectious keratitis of viral, bacterial, or fungal, xerophthalmia congenital dystrophies, and degeneration as well as iatrogenic as a sequelae of surgical procedures or complications. The most common fungi involved in corneal blindness are *Candida*, *Aspergillus*, and *Fusarium*, with *Aspergillus* being the most common in India.^{3,4} Corneal transplantation is the only known cure for corneal blindness, however, the number of eye donations in India is low due to a lack of awareness and myths and fears about eye donation. Around 10 million deaths occur every year in India. However, the number of corneal collections was 55,260 in 2019, and its utilization was only 26,416. The COVID-19 period witnessed a major setback in tissue collection. The corneal collection dropped to

21,493, and corneal transplants were 13,323 in 2020. Despite an increase in the corneal collections in subsequent years, we have to attain the level of the pre-COVID-19 period. As per the available cumulative data with EBAI and Govt of India, 47,676 corneas were retrieved and 29,057 were utilized in the year 2023, which is much less than the need of around 100,000 corneal transplantations per year to clear the backlog.

Keeping the prevailing utilization rate of corneal tissue around 60%, India needs to set a target to collect at least 200,000 corneas per year. Hence, meticulous planning and resources have to be galvanized to clear this backlog.^{5,6}

Dr. Eduard Konrad Zirm, an Austrian Ophthalmologist, performed the first full-thickness human corneal transplant on December 07, 1905. Dr. R. Townley Paton and Dr. Ramon Castroviejo have the distinction of pioneering corneal transplant surgery in New York, in 1937. Dr. R. Townley Paton founded the first eye bank in New York City, USA in 1944. Dr. R.E.S Muthayya performed the first corneal transplant in India in 1948. He also established the nation's first eye bank in 1945 in the Regional Institute of Ophthalmology and Government Ophthalmic Hospital in Chennai.⁷

Eye Bank is a community nonprofit, charitable organization dedicated to restoring sight to those who are blind or visually impaired through promoting and advancing Eye donations. The Eye Bank Association of America (EBAA), founded in 1961, remained the first and leading eye bank across the globe. The concept of the Eye Bank Association was conceived in the USA in the early sixties to provide a common platform and to act as a facilitating agency to promote eye banking, set standard protocols, and develop a bridge among all the

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stakeholders, including government agencies for the singular cause of handling the burden of corneal blindness.⁸

The Eye Bank Association of India (EBAI) was formed in 1989. The Eye Bank associations across the globe are instrumental in propagating awareness, and catalysts to develop a platform of technology transfer, skill development, accreditation, and tissue distribution systems in the country. The eye banks also play a crucial role as an interface among all stakeholders including global coordination of eye banking activities.^{4,9}

The EBAI is one of the largest professional bodies of eye bankers, tissue collection centers, corneal surgeons, non-governmental organizations (NGOs), and other nonprofit organizations worldwide engaged with the cause of the promotion of corneal tissue collection and transplant of tissues.

EBAI has a membership of more than 2500 members, including 941 Eye Banks and ERCs registered and 915 corneal surgeons. EBAI has very strong affiliations with the GAEBA (Global Alliance of Eye Bank Associations) and AEBA (Association of Eye Banks of Asia) to coordinate the process of standardization of the Eye Banking guidelines.

EBAI also participates in activities to upgrade the training of the technicians, eye bankers, the central corneal tissue distribution system (CDS), supply of preservative media as well as an interface with the government of India, respective state authorities, and eye bankers in the process of policymaking, accreditation, and issues linked with the THOTA (The Transplantation of Human Organs and Tissues Act,) and other governmental regulations and acts.⁹

The eye bank is a link between the donor family and a cornea recipient to procure quality tissue through voluntary donations or HCRP (Hospital Cornea Retrieval Program). Eye Banks also screen and evaluate eyes or tissue as per eye bank standards and ensure the suitability of the tissue by initiating testing to rule out HIV, Hepatitis, and other contraindications as per the norms and guidelines.^{9,10}

The eye banking activities in India have shown quantum improvement in the process of accreditation, upgradation, and training in a decade or so. The avenues for training corneal surgeons and eye bank technicians have shown a remarkable positive trend.

Eye banking accreditation has been introduced in collaboration with the National Accreditation Board for Hospitals (NABH) to develop uniform standards of quality control of operative procedures and technical aspects that are at par with the international quality control standards.

India has shown a significant shift toward focused HCRP programs from the voluntary base nonhospital collection

of the cornea. There is a quantum jump of 20% increase in tissue utilization after starting HCRP in 2004 in India. The amendment in the THOA Act in 2011 has categorized cornea as a tissue rather than an organ, thereby facilitating the collection by allowing trained technicians the enucleation of the cadaveric eye. As such, corneal retrieval can only be performed from cadavers hence regulations applicable to live organ donors were unwarranted. The amendment has also redefined the requirement of infrastructure, equipment, and human resources for retrieval, storage, and transplantation, thus making mandatory registration under the act simple.¹⁰

Despite positive trends in the field of eye banking and corneal transplantation, there are significant hurdles still prevailing and need to be addressed on a very positive and decisive note by the government to ensure certain changes in the policies to facilitate the process of cornea donation. Mandatory notification of any death in the hospital to the nearest eye bank for eye donation counseling and access to trauma centers/mortuaries and mandatory HCRP at large or medium mortality hospitals will also boost tissue collection. The amendment of the request law to extend “accepted medical standards” in articulating policies for the identification of “potential” organ donors will enhance the scope of tissue collections. The government may also consider providing legal status to the first-person consent and telephonic consent for the same purpose.¹¹

Cost coverage of cornea donation is a major concern for any eye bank to be self-sustained being a nonprofit institution. The donations received, and the grant from the government is highly inadequate and insufficient to run the eye bank. Hence, there is a need to legalize the cost coverage, including the cornea processing fee.

The country needs to have an equitable distribution system equipped with a freely accessible and transparent interactive online portal governed by a unique identification number for every patient in a well-established national corneal transplantation registry system linked with better data tracking and patient discovery programs.

India has the biggest challenge of achieving 100,000 corneal transplants annually to clear the burden of corneal blindness, including a backlog considering less than 30,000 corneal transplants and 47,000 tissue collections. A herculean task is ahead to collect at least 200,000 corneas annually as well as increasing the tissue utilization rate by improving the quality of harvesting time by early retrieval of the tissue.¹²

The use of intermediate-period cornea preservative media such as optisol and cornisol over short-term preservative media such as McCarey-Kaufman (MK) medium will also improve the quality of tissue and surgical outcome. However, the increased cost burden has to be subsidized.

Hence, all-out efforts are the call of the hour to combat corneal blindness.

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Review Article

Recounting COVID-19 associated complement-mediated coagulopathies: Triggers and controls

Prem Lata¹, Mridul Madhuri¹, Asgar Ali¹, Bandana Kumari¹, Meenakshi Tiwari², Abhinash Kumar¹, Krishnan Hajela³, Divendu Bhushan⁴, Sadhana Sharma¹

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to a global health crisis, prompting extensive research into its pathogenesis and potential therapeutic interventions. One area of increasing interest is the interaction between SARS-CoV-2 and the complement system, a crucial component of innate immunity. This review explores the intricate relationship between COVID-19 and the complement system, shedding light on how the virus exploits and manipulates the complement components to induce inflammatory responses leading to coagulopathies. The activation of the complement pathway simultaneously activates the coagulation cascade due to the presence of common substrates of mannan-binding serine proteases of the lectin complement system in the coagulation pathway. This cross-talk between the components of the complement and coagulation system further aggravates the dysregulation of immune responses, contributing to the cytokine storm observed in severe COVID-19 cases. A comprehensive understanding of this crosstalk is crucial for developing targeted therapeutic strategies to mitigate the hyperinflammatory state associated with severe disease. Understandings into the molecular mechanisms governing this interaction may pave the way for the development of novel antiviral diagnostics and therapies based on immunomodulatory interventions, offering better management for such cases.

Keywords: COVID-19, SARS-CoV-2, Complement system, Innate immunity, Coagulopathy, Cytokine storm, Therapeutic strategies

INTRODUCTION

In December 2019, Coronavirus disease 19 (COVID-19) originated in Wuhan city in China. The causative agent was severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It caused 6,945,714 deaths globally, as reported by the World Health Organization (WHO) on June 21, 2023.

COVID-19 was primarily a respiratory illness that affected the lungs and appeared with predominant clinical symptoms of mild fever, cough, and shortness of breath.¹ In some patients, it even progressed to life-threatening pneumonia, acute respiratory distress, and multiple organ failure.²

In COVID-19 infection, dysregulated coagulation is a quite common feature which leads to thrombosis in the respiratory, cardiovascular, and venous systems.³ The altered coagulation pattern in COVID-19 patients was termed as COVID-19-induced coagulopathy (CIC), which caused acute

cardiovascular complications, potentially leading to death in some patients.⁴

Different presentations of the coagulopathies in COVID infection

The different forms of thrombotic abnormalities reported in COVID-19 are listed in Table 1. Among these, disseminated intravascular coagulation (DIC)⁵ and venous thromboembolism (VTE) were the most common,⁶ which could potentially give rise to strokes and other heart complications.⁷

DIC is marked by dysregulated systemic activation of the coagulation pathway. The excessive thrombotic and hemorrhagic complications due to intravascular fibrin formation and microangiopathic thrombosis lead to exhaustion of coagulation factors and platelets, resulting in life-threatening hemorrhage.⁸ VTE is a condition where

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Table 1: COVID-19-associated coagulation abnormalities and their clinical manifestations

COVID-Associated Thrombotic Complications	Clinical Manifestation
Disseminated Intravascular Coagulation (DIC)	Upregulated pro-inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1), decreased fibrinolysis
Venous Thromboembolism (VTE)	Immunological activation of thrombin and hemostasis impairment
Thrombotic Microangiopathy (TMA)	CD4 aggregation around thrombotic blood vessels, hemorrhage intense endothelial inflammation
Sepsis-Induced Coagulopathy (SIC)	Hypercoagulability, endothelial dysfunction, microthrombosis, and stroke

clot formation occurs inside the veins. In pulmonary embolism, clots in veins break and reach the lungs through bloodstreams. Thrombotic microangiopathy (TMA) is a syndrome comprising a triad of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two pro-types of thrombotic thrombocytopenia purpura (TMA). TTP is a life-threatening condition associated with the formation of blood clots in small blood vessels, thus limiting the flow of blood to vital organs such as heart, brain, and kidney. When clot formation occurs in the damaged and inflamed small vessels of the kidney and blocks the filtering system of the kidney, the condition is referred to as HUS; sepsis-induced coagulopathy (SIC) spans from precise activation of coagulation (shown by sensitive markers of the coagulation factor activation) to much sturdy activation of coagulation accompanied by a decrease in platelet count and an increase in clotting time to DIC.⁹

Pathophysiology of thrombotic events in COVID-19 patients

Angiotensin-converting enzyme 2 (ACE-2) receptors present in different organs (such as lung, kidney, and heart) facilitate entry of SARS-CoV-2 into host cells.¹⁰ This phenomenon led to viremia, causing internal injury of the blood vessels and in some cases, ultimately gave rise to severe fatal outcomes such as vascular blockage, thrombosis, and multiple organ failure.¹¹ Entry of the pathogen also induced an inflammatory immune response (cytokine storm) as a preventive measure, which expedited the clotting cascade and negatively resulted in the obstruction of blood vessels.^{11,12} Upregulation of

plasmin inhibitors (alpha-2 antiplasmin and plasminogen activator inhibitor-1) eventually decreased plasmin-mediated fibrinolysis, which resulted in persistent clot accumulation. Further, downregulation of thrombomodulin also induced hypercoagulopathy in COVID-19 patients.¹³ SARS-CoV-2 viruses use extracellular vesicles for their active migration to nearby or distant sites in a maintained physiological state,¹⁴ which are potent inducers of the coagulation system.^{15,16} von Meijenfeldt *et al.* (2021) showed a link between COVID-19 and the coagulation pathway, where patients harbor elevated thrombin generation potential and diminished fibrinolytic ability.¹⁷ A probable explanation for the hypercoagulable and hypofibrinolytic states was the prolonged activation of the endothelium, which resulted in increased plasma levels of factor VIII and PAI-1.¹⁷ Markers of thrombotic events in COVID-associated coagulopathy (CAC) are summarized in Figure 1

Aggravated thrombosis in COVID-19 infection, as demonstrated by a couple of studies, suggested the role of autoantibodies in COVID-19. The literature suggests that the antiphospholipid autoantibodies (APL) are also an important factor for the stimulation of endothelial cells and platelets,^{3,18} although the exact role of these autoantibodies remains unclear.

Upon infection, the viral nucleocapsid and spike proteins trigger the mannose binding lectin (MBL)/Ficolins pathway, which eventually activate lectin pathway proteases such as mannose binding lectin (MBL)-associated serine proteases (MASP)-2, a key factor in inducing prothrombin-mediated clotting.¹⁹ COVID-19 patients showed four dysregulated coagulation factors, namely prothrombin (F2), FXI, FXII, and FXIIIa.²⁰ During infection, there is an increase in the level of FXIIIa and von Willebrand factor (VWF) glycoprotein in the renal cortex, which is associated with blood clotting in the renal cortex.²¹ Serpin Family D Member 1 (SERPIND1) and Serpin peptidase inhibitor (SERPINE1) were downregulated and upregulated, respectively, in the renal cortex, which caused microthrombi formation in COVID-19 patients.²⁰

Significantly higher levels of D-dimer²² and fibrinogen, along with mild thrombocytopenia, are biomarkers of COVID-19-associated hypercoagulopathy²³ due to varying underlying reasons.

Crosstalk between complement and coagulation system in COVID-19-associated coagulopathies?

The possible mechanisms involved in coagulopathies with known facts about SARS-CoV-2, the causative agent of contagious COVID-19, are shown in Figure 2. Its spike (S) protein cleavage by furin protease and further priming of the activated S protein by transmembrane protease serine

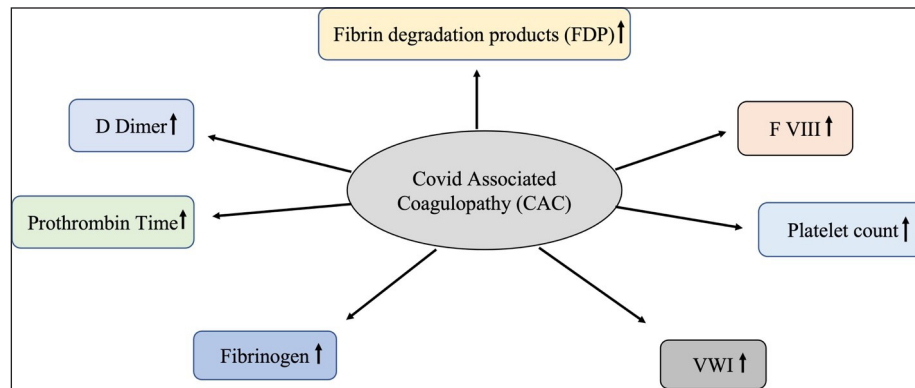


Figure 1: Markers of coagulopathy during COVID-19 infection: An increase is observed in the levels of fibrin degradation products (FDP), factor VIII (F VIII), platelet count, von Willebrand factor (VWF), fibrinogen, prothrombin time, and D-dimer during SARS-CoV-2 infection.

2 (TMPRSS2) facilitated viral attachment with the host's ACE-2, which acts as a receptor to mediate its entry into the host cells.²⁴ Therefore, the receptor protein ACE-2 was instrumental in viral transmission and pathogenesis. SARS-

CoV-2 interaction with ACE-2 also hinders its physiological role discussed in Figure 2.

The complement system plays a critical role in augmenting the coagulation process during COVID infection. Activation of

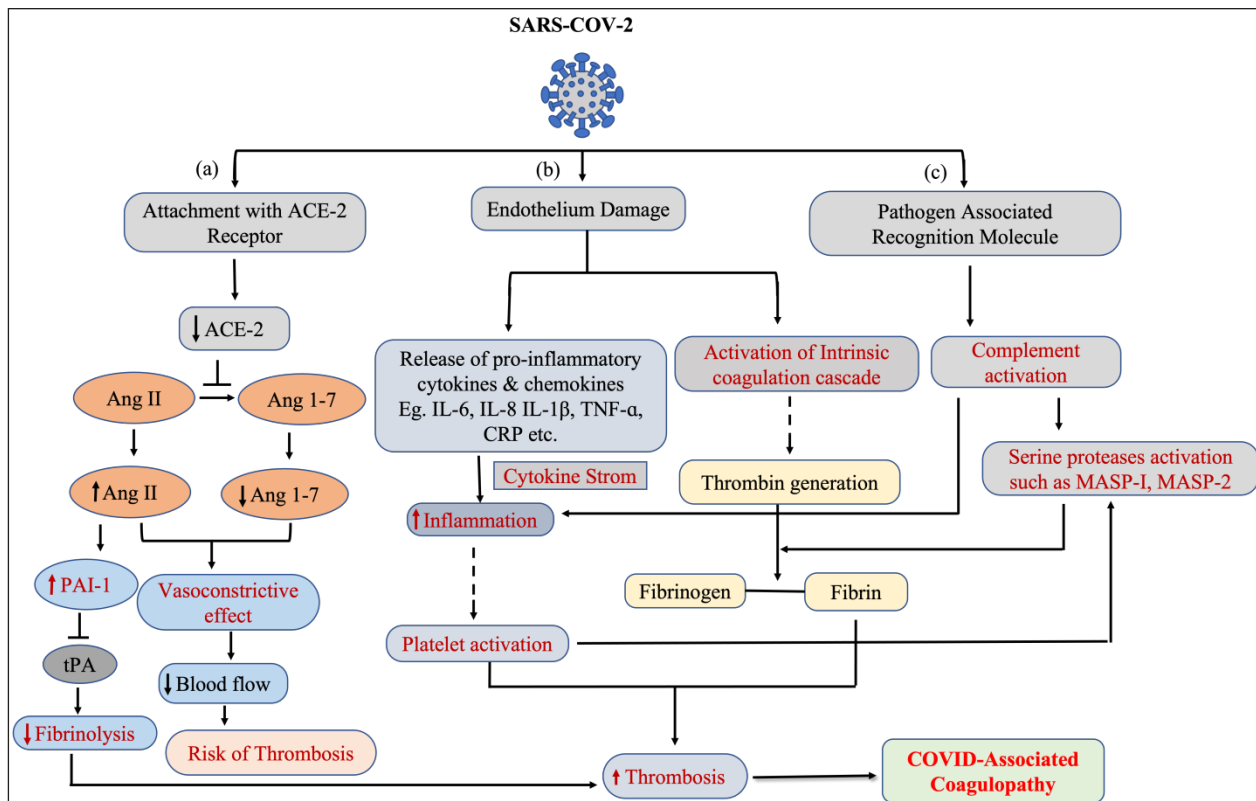


Figure 2: Schematic representation showing the pathophysiology of COVID-associated coagulopathy. SARS-CoV-2 activates three different pathways. (a) The antithrombotic physiological role of ACE-2 is impaired due to interaction with SARS-CoV-2, resulting in hypofibrinolysis and vasoconstriction. (b) Virus-induced endothelium damage led to simultaneous activation of the classical coagulation cascade and immunothrombosis. (c) Complement activation in response to the recognition of pathogen-associated molecular patterns (PAMPs) contributes to inflammatory thrombosis and nonclassical (MASP protease mediated) fibrin clot generation. ACE: angiotensin-converting enzyme 2, Ang: Angiotensin, MASP: MBL-associated serine proteases, tPA: tissue plasminogen activator, TNF: tumor necrosis factor, CRP: C-reactive protein, IL: interleukin, PAI-1: Plasminogen activator inhibitor-1.

proteins of the complement system and coagulation pathway, namely thrombin, trypsin, and plasmin, significantly contributes to COVID-associated thrombotic events.^{25,26} Previously, an *in vivo* study with C3 null mice indicated the involvement of the complement pathway in COVID-19 infection.²⁷ Bhagwat *et al.* (2022) demonstrated that mannan-binding lectin-associated serine proteases (MASP-1 and MASP-2) of the *lectin complement pathway* also have substrates in the coagulation pathway.^{28,29} Importantly MASP-1, which has thrombin-like activity, may have played a key role in COVID-19-associated coagulopathies.³⁰ Furthermore, the lectin pathway was also found to be activated in SARS-CoV-2 infection, particularly through the recognition of the nucleocapsid and spike proteins (S protein) of the virus.³¹ It induced lectin pathway via downstream activation of MASP-1 and 2 leading to thrombotic events.³¹ Gao *et al.* (2020) also suggested that in response to SARS-CoV-2, autoactivation of MASP-2 occurred, which eventually activated the lectin pathway via a series of enzymatic cascades.³² In addition, hypercoagulation in COVID-19, marked by VWF,³³ was observed consistently, and the literature suggested that it could be the outcome of crosstalk between the complement and coagulation systems.^{34,35}

Furthermore, S protein of SARS-CoV-2 played a key role by binding with heparan sulfate and factor H, which dysregulated the *alternative pathway* of the complement system.^{36,37} Moreover, antibodies such as immunoglobulin G (IgG) and immunoglobulin M (IgM) produced against specific domains of viral spike proteins were capable of activating the *classical complement pathway*.³⁸ Therefore, SARS-CoV-2 potentially dysregulated or hyperactivated the different components of the complement system, which, in turn, led to endothelialopathy and thromboinflammation, the classical pathophysiology associated with COVID-19.³⁷

Although the exact reasons why other people were predisposed to severe illness while some remained asymptomatic remain undeciphered; the hypercoagulable state and COVID-19 are interconnected [Figure 2].

Complications of complement-mediated coagulopathies in COVID-19: Different forms of thrombotic complications have been reported in clinical patients, which originally initiated in the lungs³⁹ and eventually led to multiple organ failure.⁴⁰ Pulmonary arterial and venous thrombosis, microangiopathy, and pulmonary embolism were the major clotting-associated complications in COVID-19 patients due to the altered complement system.^{41,42} Furthermore, diffuse microvascular thrombosis in the capillaries of different vital organs, such as the lung, kidney, and myocardium, along with deposition of complement activation products, were also reported in patients with COVID-19 infection.^{40,43,44} Niederreiter *et al.* (2022) showed the deposits of complement

proteins, namely C1q, MASP-2, complement factor D, C3c, C3d, and C5b-9, in lungs and kidney samples of COVID-19 patients using immunohistochemical studies, which clearly explains the involvement of the *lectin pathway* in COVID-19.⁴⁵ Another study by Carvelli *et al.* (2020) reported that MASP-2, C4, MAC, and macrophages with overexpressed C5aR1 are associated with endothelium damage and microthrombi formation.⁴⁶ Clinical studies with critically ill COVID-19 patients demonstrated significantly elevated levels of circulating markers of complement activation. In addition, upregulated alternative pathways along with markers of endothelial injury (i.e., angiotensin-2) and hypercoagulability (i.e., thrombomodulin and VWF) were reported as the most common features of COVID-19 patients.³³

Systemic activation of the complement and coagulation cascade in response to the viral pathogen also promotes localized complement protein production by lung cells.³⁷ Therefore, complement-targeting therapies have been developed as an attractive therapeutic strategy for COVID-19. Although the pernicious effects of hyperactivated complement pathways in COVID-19 are quite evident, an in-depth understanding of the driving molecular mechanisms is not there. Several studies have demonstrated that the complement system, especially the *lectin pathway*, is indeed instrumental in viral illness and plays a crucial role in COVID-19 pathogenesis.

CONCLUSION

The COVID-19 pandemic has emerged as a challenging threat to global health in this century. A comprehensive understanding of disease pathophysiology, risk factors, and therapeutic regimens is essential for disease management in future episodes. This knowledge will have beneficial effects in future research for disease control and prevention.

However, the molecular mechanisms underlying the pathogenesis still require attention. Extensive multiomics approach may help us in obtaining an in-depth understanding and may provide new insights for the development of novel prophylactic and therapeutic strategies to combat this viral illness.

Authors' contributions

PL, MM and AA: conceptualization, writing the original draft, BK and MT: writing-review, and editing, AK: coordinated revisions, KH and DB: conceptualization, writing-review, and editing, SS: conceptualization, writing the original draft, writing-review, and final editing. All authors approved the submitted version.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Review Article

DPI: A paradigm shift from nebulizers to dry powder inhalers

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ABSTRACT

Drug delivery to pulmonary routes was once considered a challenging task. The emergence of inhalation therapy paved the way for drug delivery to the lungs. With various advances in inhalation therapy, modern-age drug delivery systems include nebulizers, pressurized metered-dose inhalers, and dry powder inhalers (DPIs). The following review discusses the development stages of DPIs and also gives an insight into the current formulation aspects of DPI, animal models used for evaluation of drug release parameters, and the Anderson cascade impactor and its possible correlation with human respiratory tract with regards to drug deposition and particle size. Today, DPIs have brought about a revolution in drug delivery to lungs, and also offer more advantages with regards to consistency of dose delivered, stability, and ease of administration. Dry powders have been extensively used in the treatment of asthma and various other respiratory disorders. With the introduction of nanoformulations, a wide sector of researchers is working toward developing DPIs that may be used to target diseases like lung cancer.

Keywords: Aerodynamic diameter, dry powder inhalers, preclinical testing, lactose, nanoformulations

INTRODUCTION

The use of inhalation therapy for administering drugs finds its origin around 4000 years ago. Datura roots smoke as a bronchodilator was used in India in 2000 BC.¹ Vapors of black henbane, which contained anticholinergic compound hyoscyamine were used by physicians in Egypt for treating breathing issues in 1554 BC.² Since then, many methods were employed as inhalation therapies for administering drugs to treat diseases associated with respiration. However, the development of drug delivery systems to deliver the drugs to the lungs can be traced back to the 1950s when Riker laboratories commercialized a pressurized metered-dose inhaler (pMDI) in 1956.³ This paved the way for researchers to introduce drugs for treating asthma and other diseases associated with respiration. With the increasing use of pMDI, the concern related to the depletion of the ozone layer owing to the use of chlorofluorocarbons was postulated in 1974.⁴ The chlorofluorocarbons were substituted by hydrofluoroalkanes in 1995, which were considered more eco-friendly, and they were assumed not to deplete the ozone layer.⁵⁻⁷ Various drawbacks of pMDIs were responsible for the introduction of dry powder inhaler (DPI) as a drug delivery device.

The drawbacks of pMDIs are:⁸⁻¹¹

- Low solubility
- Chemical instability
- Crystal growth phenomenon
- Instability of suspensions
- Inaccuracies in metering doses
- Limitations in drug loading capacities
- Limited drug targeting capacities
- Reduced patient compliance owing to the freon effect

The following review discusses in brief the journey of DPIs and their formulation aspect. It also highlights the use of Anderson Cascade impactor.

The first DPI, Spinhaler was introduced in the market by Fison (Ipswich, UK) in 1967.^{2,12} They are devices that work on the concept of breath actuation, that is, they are activated by the patient's inspiratory flow rate. These devices offer various advantages over other inhalational drug delivery systems and are known for their effectiveness in the treatment of pulmonary diseases.¹³ As DPI has several advantages over pMDIs, there has been tremendous growth in the formulation of DPI in the

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past few decades with several clinical trial phases, and many DPIs are available in the market.¹⁴

Pulmonary route of drug administration

The respiratory tract: The respiratory tract is divided into the upper and lower respiratory tract. Nose, nasal cavity, thorax, pharynx, and larynx form the upper respiratory tract, whereas trachea, bronchi, bronchioles, and alveolar region form the lower respiratory tract. The alveolar region is responsible for gaseous exchange. It consists of bronchioles, alveolar ducts, and alveoli.¹⁵ Figure 1 describes the human respiratory tract.¹⁶

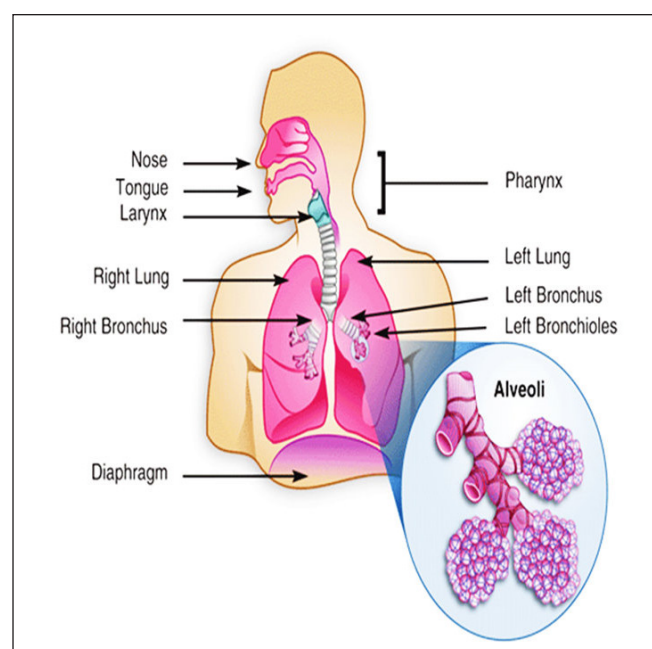


Figure 1: Human respiratory tract.

The morphometric model of human lungs was proposed by Edward Weibel in 1963 to promote the idea of a quantitative description of pulmonary anatomy and its correlation with physiology. According to this model, the lung is divided into 24 compartments with each compartment analogous to a generation of the model. It speculates that each generation of airways branches symmetrically into two equivalent generations. According to this model generation, 0–16 consist of the trachea-bronchial region and 17–23 comprise the alveolar region.¹⁷ Together, these provide a large surface area of approximately 140 m².¹⁸

Delivery of drug to lungs: Over the years, drug delivery to the respiratory tract has gained a lot of attention by researchers and has so far been considered as one of the best alternatives to other routes of drug administration.¹⁹ The

conventional routes for treating respiratory diseases have various limitations, which have paved the way for researchers to focus on targeting drugs to a specific site. Pulmonary drug delivery offers this advantage of being site-specific, both for systemic and local drug delivery. Many drugs have displayed an appreciable increase in bioavailability post-pulmonary administration. It can be associated with the factors like (1) greater surface area of alveoli, (2) comparatively low metabolic activity, and (3) increased blood flow responsible for the rapid distribution of drugs in the body.²⁰

Delivery of drugs to the lungs offer advantages of both local and systemic drug delivery. Local effects can be observed in treating diseases like asthma and chronic obstructive pulmonary disorder, whereas the natural permeability of the lungs can be beneficial for transferring drugs via systemic routes.^{21–25}

Advantages of a pulmonary drug delivery system:^{26,27}

- Avoids hepatic first-pass metabolism
- Noninvasive route of drug administration
- Rapid onset of action
- Targeted drug delivery can be achieved
- Negligible side effects
- Dose reduction can be accomplished
- Provides a large surface area for absorption of drugs

While developing formulation for efficient deposition of drugs in the lungs, it is necessary to consider factors like physical, chemical, and physiological properties of inhaled particles, barriers to deposition of drug and absorption of drugs, other barriers such as the thickness of mucus lining, phagocytosis by macrophages, proteolytic degradation, and so on.^{28,29}

Factors governing deposition of particles in the lungs: For a drug to be delivered in the lungs, it must be administered in aerosol form. Drug deposition in the deeper sections of the lungs is governed by various biophysical parameters:

- Aerodynamic diameter
- Inspiration pattern of patients
- Anatomy of the respiratory tract of the patient

Particle size plays a very important role in determining the site of deposition of the drug within the respiratory tract.

Aerodynamic diameter of particle: It is defined as the diameter of a sphere of unit density that has the same terminal settling velocity as the particle under consideration. Similarly, aerosol particles with varying densities and shapes can be categorized according to their aerodynamic properties.

Aerodynamic diameter usually depends on the airflow (particle Reynolds number, Re) and particulate properties, including geometry, size, shape, and density of the particle.

With Stokes flow regime of $Re < 0.1$, the aerodynamic diameter of particle (dA) can be calculated as:

$$dA = dv \sqrt{\rho/x\rho_o}$$

dv: Volume equivalent diameter

ρ : Particle density

ρ_o : Unit density (1g/cm^3)

x: Dynamic shape factor

Dynamic shape factor is the ratio of drag force on the particle to the drag force on the particle volume equivalent sphere at the same velocity for the spherical particle; the dynamic shape is 1.³⁰

Deposition of particles in the respiratory tract

Particle deposition occurs when particles come in contact with the respiratory surface and do not ricochet or are not suspended back in the airstream. Particles that remain suspended in the airstream are exhaled out and do not deposit in the respiratory tract. The different mechanisms by which particle deposition occurs and the particle size range of deposition is given in Table 1.

Table 1 gives an overview of various mechanisms of particle deposition and site of deposition of a drug at a specific site, depending on the particle size.

Inertial impaction: It is a velocity-dependent mechanism. Larger particles ($>5\ \mu\text{m}$) follow this principle of drug deposition. It is one of the most common mechanisms of particle deposition. It occurs at bifurcations of the respiratory tract where the change in the direction of airflow is observed, but the particles in the airstream follow the predefined route rather than adjusting to the change in the direction of airflow. This leads to the deposition of particles in the upper respiratory tract (nose, larynx) and conducting airways (trachea, bronchi).^{29,31}

Gravitational Sedimentation: Deposition of particles by sedimentation occurs due to gravitational forces. This process

being time-dependent, an increase in the deposition of particles is observed with an increase in the residence time of that particle in airways and alveoli. The particles which tend to get deposited by this mechanism are usually in the size range of $0.5\text{--}3\ \mu\text{m}$. It is important to consider the fact that particles with diameters $< 1\ \mu\text{m}$ have negligible sedimentation velocity, and hence, increasing particle size will eventually increase the settling velocity.^{23,29}

Brownian Diffusion: It is a result of the random motion of particles that are suspended in the aerosol stream and collide with gas molecules. These result in the haphazard motion of particles from aerosol clouds and results in deposition on the walls of the airways. In this mechanism, deposition of particles is inversely proportional to the particle diameter. Hence, it is a very important mechanism for the deposition of particles with a diameter $< 0.5\ \mu\text{m}$ deep within the lungs.^{23,24,29}

Dry powder inhaler: These are the devices that store the drug as fine aggregates and deliver the dry powder of medicament in the lungs for its local or systemic effect. The drug is usually stored in a reservoir at the bottom of the inhaler device.³² For delivery of a drug, the patient's inspiration force plays an important role in initiating the actuation of the inhalation device. However, some DPI devices appear to be relatively independent of the patient's inspiratory rate.³³

DPIs are commonly used for local as well as systemic administration of drugs. Drugs effective in cystic fibrosis, asthma, a chronic obstructive pulmonary disorder, and lung cancer can be administered locally with a noticeable reduction in systemic side effects and localized concentration of drug at the target site.^{34–39}

Delivery devices for dry powders for inhalation: Tables 2, 3, and 4 describe the different types of DPIs.

Table 2 gives an idea of different types of first-generation dry powder inhaler devices along with the mechanism of delivering the drug.

Table 3 gives an overview of different types of second-generation dry powder inhaler devices.

Table 4 gives an idea of different types of third-generation inhaler devices along with the mechanism of drug delivery.^{40–48}

Advantages and disadvantages of dry powder inhalers

Advantages

- Most DPIs are breath-actuated devices. Hence, the patient's coordination is not needed.
- The dosage form is in powdered form which enhances the physicochemical stability of the formulation.

Sr. No	Mechanism of particle deposition	Particle size (μm)	Location of particle deposition
1	Inertial impaction ³²	>5	Upper respiratory tract and large conducting airways
2	Gravitational sedimentation ²⁴	$0.5\text{--}3$	Airways and alveoli
3	Brownian diffusion ^{24,25}	<0.5	Deep lungs

Table 2: First-generation dry powder inhaler devices.

Sr. No	Device	Type	Company	Reservoir system	Mechanism
1	Spinhaler	Single unit dose	Aventis	Capsule	Passive (breath actuated), the drug delivered due to puncturing of the capsule by two pins present in the system.
2	HandiHaler	Single unit dose	Boehringer Ingelheim/Pfizer	Capsule	Passive (breath actuated), the drug delivered due to puncturing of the capsule by pins in the system.
3	Aerosolizer	Single unit dose	Novartis	Capsule	Passive (breath actuated), the drug delivered due to puncturing of the capsule by four pins in the system.
4	Cyclohaler	Single unit dose	Teva	Capsule	Passive (breath actuated), the drug delivered due to puncturing of the capsule by pins in the system.
5	Rotahaler	Single unit dose	Glaxo	Capsule	Passive (breath actuated), the drug delivered due to puncturing of the capsule by pins in the system.

Table 3: Second-generation dry powder inhaler devices.

Sr. No.	Device	Type	Company	Reservoir system	Mechanism
1	Turbuhaler	Multiple dose	Astra Zeneca	Powder Reservoir	Passive (breath actuated)
2	Clickhaler	Multiple dose	Innovata Biomed	Powder Reservoir	Passive (breath actuated)
3	Easyhaler	Multiple dose	Orion Pharma	Powder Reservoir	Passive (breath actuated)
4	Novolizer	Multiple dose	Astra Medica (Viatris GmbH)	Cartridge	Passive (breath actuated)
5	Pulvinal	Multiple dose	Chiesi	Powder Reservoir	Passive (breath actuated)
6	Diskhaler	Multiunit dose	GlaxoSmithKline	Single dose in Blister/Disks	Passive (breath actuated)
7	Accuhaler/Diskus	Multiunit dose	GlaxoSmithKline	Single dose in Blister/Disks	Passive (breath actuated)
8	Elliptia	Multiunit dose	GlaxoSmithKline	Single dose in Blister/Disks	Passive (breath actuated)

Table 4: Third-generation dry powder inhaler devices.

Sr. No.	Device	Type	Company	Reservoir System	Mechanism
1	Exubera	Multiple dose	Nektar Therapeutics (Pfizer)	-	Active (Compressed Gas)
2	Afrezza	Technosphere	Mankind Corp Inhaler (Dreamboat inhaler)	Cartridge	Active

- The system is environmentally friendly as it does not use propellants for delivering the drug to the lungs.
- Compact nature makes them easy to carry.
- Easy to use.
- Deliver high drug payloads to the lungs.
- Spacers are not required.^{23,49-51}

Disadvantages

- Manufacturing of DPIs is complex and any errors during preparation might be critical.
- The emission of dose and deposition efficacy is dependent on the patient's inspiratory flow.
- If the inspiration speed is too slow, very little or no dose is emitted from the device.
- It is easily affected by environmental factors like humidity. Hence, they must be stored in a cool and dry place.

- Some inhaler devices need to be shaken before use.
- Expensive as compared to pMDIs.

Ideal properties of dry powder inhaler devices

- They must be easy to use.
- They must be economic and compact.
- Minimum loss of drug must occur during respiration.
- They must be able to protect against an accidental overdose of the drug.
- They must provide maximum aerosolization with minimal efforts for asthmatics or small children and geriatrics.
- They must deliver the drug accurately.

General requirements of dry powder inhaler

- The particle size of the drug: 1–10 μm .
- Drug content uniformity.

- Stability of powder toward different environmental conditions such as humidity, temperature, and so on.⁵²

Formulation strategies for dry powder inhaler

- *Drug carrier:* DPIs hold the drug for delivery in either a blister or capsule or a reservoir, where the quantity of the drug is as low as 1 µg and is difficult to deliver. Moreover, the ideal aerodynamic diameter of particles that is desired for the delivery of drugs must range from 1 µm to 5 µm. The problem while using the power of such a small particle size is that it significantly increases cohesiveness and adhesiveness owing to their high surface free energy. This results in poor flow and aerosolization behavior of particles as they are confined to the device when used alone. To improve the flow properties, there is a need to use a carrier whose size range varies from 50µm to 100µm along with the drug. The blending process results in the drug particles adhering to the carrier particles. These carriers act as diluents and eventually improve the flow properties. The problem with this approach is that the increased volume of powder that is inhaled drastically reduces the quantity of drug reaching the lungs.^{53,54}

Process of the detachment of particles from the carrier surface

When a mixture of the drug along with the carrier is inhaled, the process of detachment of drug particles from the carrier surface occurs in three steps:

- Fluidization of mixture in the airstream
- A detachment of drug particles or agglomerates from the carrier surface
- Breakdown of detached agglomerates into primary particles

Once the particles are detached from the carrier surface, they will be deposited in the lungs, whereas the larger particles, that is, carriers, will be swallowed following impact in the

mouth and back region of the throat. Figure 2 shows the process of detachment of particles from the carrier surface.⁵⁵

Carriers used in the formulation of dry powder inhalers:

- *Lactose:* It is the most widely used carrier of dry powder for inhalation and is available in various inhalation grades. It has been approved as a carrier in DPIs by the US Food and Drug Administration (FDA). Lactose has been extensively used as a carrier, but its limitations regards to certain drugs and peptides restrict its use as a carrier in such formulations, thus emphasizing the need for alternative carriers for DPIs.^{56,57}
- *Mannitol:* This is the best alternative for lactose as a carrier for DPI. It has overcome the problems of using lactose in scenarios where the sugar moiety interacts with the drug (e.g., protein and peptides).⁵⁸ Another problem observed with lactose is related to patients where, in some cases, lactose intolerance is observed.⁵⁹ Unlike lactose, mannitol lacks reducing sugar moiety and its less hygroscopicity adds to the advantage when compared to lactose.⁶⁰ Improved patient compliance owing to its sweet aftertaste is observed.⁶¹ Currently, D-mannitol is available as pulmonary diagnostic dry powder inhalation aerosol and therapeutic dry powder inhalation aerosol for the treatment of cystic fibrosis and chronic bronchitis (Bronchitol™) in some countries and has been recently approved by US FDA and Europe, the Middle East, and Africa (EMA).⁶²
- *Sorbitol:* Lactose reacts with lysine residues present in the proteins and generate lactosylated protein molecule.⁶³ Sorbitol is useful in such cases as it serves as a stability enhancer during formulation and does not react with protein, thus forming a stable respirable protein powder. Sorbitol also plays a crucial role in producing respirable powder of Interferon β as stability during jet milling can be achieved due to the presence of Sorbitol.^{64,65}

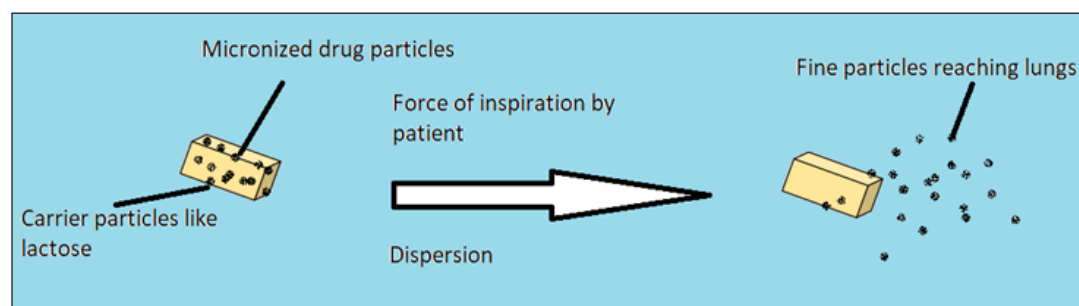


Figure 2: Detachment of drug particles from the carrier surface.

- *Erythritol*: Various fruits and fermented foods have shown the presence of this naturally occurring sugar alcohol. The industrial process of making erythritol includes glucose fermentation.⁶⁶ Low hygroscopicity, thermal stability, sweet taste, and low toxicity contribute to its efficacy as a carrier for DPIs.⁶⁷ Its compatibility with a wide range of drugs makes it an interesting candidate for use.⁶⁸
- *Trehalose*: Trehalose dihydrate is a nonreducing sugar. Its use as a carrier in DPIs was reported with drugs like albuterol sulfate, ipratropium bromide, monohydrate disodium cromoglylate, and fluticasone.⁶²

Integration of Formulation into a device

On blending the drug with the carrier, it is filled into a reservoir system which is then placed in the inhaler device. Various systems are:

- *Capsules*: These are used by the first-generation DPIs, where the powder is filled in a capsule and the capsule is loaded into the device before use. Drug delivery is achieved either by the opening of the capsule within the device or by piercing the walls of the capsule with the help of pins present in the device.⁴⁷ The material used for making capsules is hydroxypropyl methylcellulose and hard gelatine. The use of hydroxypropyl methylcellulose has gained attention recently as it contains less water as compared to gelatin and is useful in the case of hygroscopic drugs.⁶⁹ Also, the fragmentation due to the piercing of pins is less, even at low humidity.⁷⁰ Although the capsule-based system is comparatively inconvenient for single-dose containers, certain modifications like using capsule size larger than three and using mechanisms such as the opening of capsule rather than piercing may prove to be beneficial and also serve as an area for further innovations.⁷¹
- *Blister system*: This reservoir system is used by DPI devices like Diskhaler. In such a system, on actuation, the upper and lower surfaces of blisters where the drug is placed are pierced by a needle and the drug is dispersed into the airstream as the patient inhales. The disk then rotates to introduce the next blister for piercing on repriming.⁴⁷
- *Carrier-free particles*: Formulation of carrier-free particles overcomes the major disadvantages of carrier-based systems, such as blend uniformity issues, and it is also beneficial in cases where delivery of high payload of the drug is essential, especially in the case of antibiotics. In this strategy, the drug is available either as a single compound or multi-compound composite of encapsulated particles. The particle size plays a very important role in formulating carrier-free systems. The particle size must be below 5 μm . With the view on improving the efficacy, different

techniques have been used to formulate respirable drug particles. These include milling, crystallization, spray drying, spray freeze drying, supercritical fluid technology, and antisolvent technology. Crystallization and milling are not suitable for processing drugs for pulmonary use as they cannot produce particles with optimum shape, size, and particles with low surface energy.^{26,52,72}

Animal models used to access the pulmonary delivery of aerosol during preclinical phase

Different animals have been used to determine the effect of inhaled material. The different parameters that are considered while selecting animals are cost, disease pathology, and comparison of the immunological response to humans.^{18,73}

Although the data obtained from preclinical studies are valuable, its direct correlation to effects in humans is difficult since animals have different nasal, tracheobronchial, and deep lung regions than humans, and these vary in different species too. It is, therefore expected that the anatomy of the respiratory tract of animal models should draw a significant correlation to the human respiratory tract. The breathing pattern of humans is different from rodents. Rodents cannot breathe through mouth, whereas adult humans can breathe through mouth as well as nose. As rodents are obligate nose breathers, the data obtained for lung deposition has limited relevance with data for humans. The data for animals are obtained by nose-only exposure system and whole-body exposure system. The absence of respiratory bronchioles in some animals shows limitations while comparing data of drug deposition in different areas of lungs when compared with humans.⁷⁴ The cell lining varies in animal models too, for example, human alveolar macrophages are estimated to be more in number and are also larger as compared to rodents.⁷⁵

Preclinical inhalation methodologies

The lack of preclinical pulmonary devices is one of the major hindrances in evaluating the efficacy of DPI devices. The devices used for human beings work differently than those used in preclinical models. There are two different categories of devices that are used for preclinical studies viz. passive inhalation devices and direct inhalation devices. In passive inhalation devices, the animal's respiratory force is considered for delivering content, whereas for direct inhalation devices the aerosol is forced through the upper respiratory tract, which is usually under anesthetic condition.

Passive inhalation devices utilize whole-body inhalation chamber and head and nose only chambers. For animals such as rabbits and rodents, the drug passes through nasal cavities before reaching the lungs.⁷⁶ They being obligate nose breathers with different nasal anatomy, the amount of drug

deposition in the lungs will vary and will also be different from humans. In the whole-body chamber, the animal is exposed to aerosol. The benefit of such a system is that they can house many animals at once and access to food and water can be given. Examples of such devices include Glascol®, inhalation exposure system, and other units from TSE systems and Shibaba Biotechnology.^{77,78} Despite various advantages offered by the whole-body exposure system, it has certain flaws like extra pulmonary exposure via other routes like skin and oral/GI tract. It also requires a large dose and shows the difficulty in quantification and characterization of the amount of drug delivered in the lungs. Such chambers can be used for studying environmental exposure that needs long-term dosing. Figure 3⁷⁹ gives an idea of the whole-body exposure system.

In head and nose-only exposure chambers, the animals are held in such a way that they are immobilized and only animals' nose or head is exposed to the drug present in the airstream. Figure 4 gives an idea of the head and nose-only exposure system.⁷⁹

The benefit of such a system is that it reduces extra pulmonary exposure of the drug to other routes, thus minimizing the amount of API and excipients required for the experiment. The problems with this system are the deposition of almost 80%–90% of the drug in the nasopharynx region and upper respiratory tract.^{80,81} Quantification of the dose is difficult as less quantity of drug reaches the lungs; moreover, this system induces stress on animals owing to mobility issues and deprivation of food and water access.

Direct inhalation devices include intratracheal methods for the delivery of drugs. In such systems, the animals are

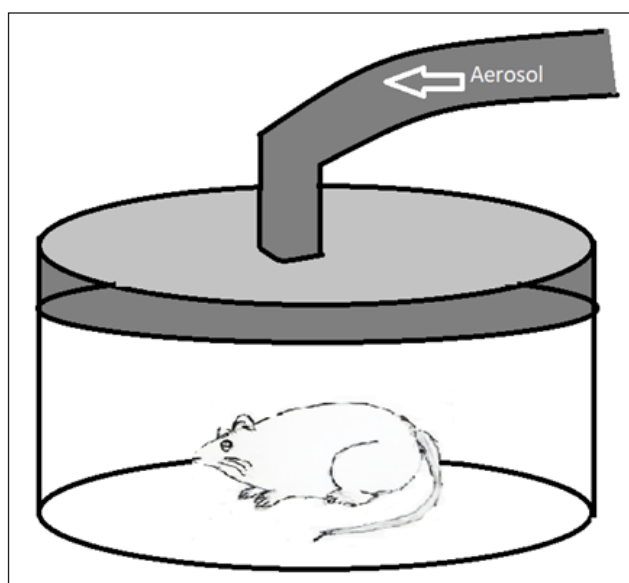


Figure 3: Whole body exposure chamber.

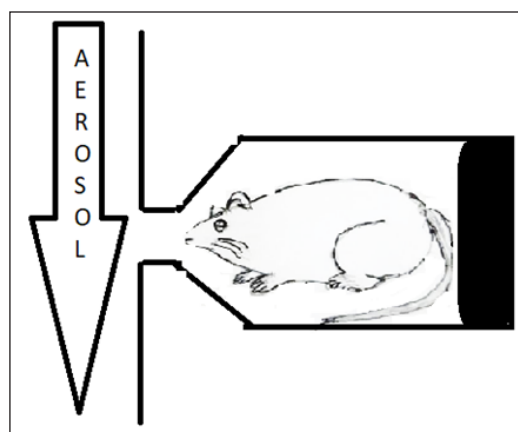


Figure 4: Head and nose-only exposure chamber.

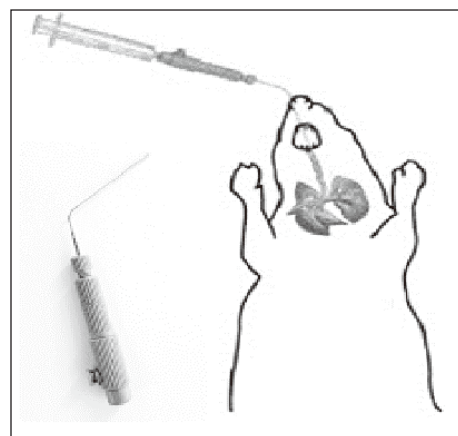


Figure 5: Intubated rodent and Penn Century Insufflator device.

anesthetized and aerosol is forced into the trachea. In these systems, quantification of drug delivered in the lungs is easier.⁷⁶ Tools for delivering dry powders include the Penn Century Insufflators™ and Biolite intubation system (Braintree Scientific Inc).^{82,83} Figure 5 shows an intubated rodent and Penn Century Insufflator device.⁷⁹

The anesthetized rodent is intubated with the insufflator tube or catheter up to the first bifurcation of the lungs. Dry powder is then aerosolized into the lungs with the help of a syringe or pipette bulb. With this system, repeated dosing and long-term studies can be carried out.⁸³

Andersen cascade impactor

The use of Andersen Cascade Impactor to assess the size distribution of particles has been reported extensively. To determine the particle size, usually the formulation in the form of the aerosol is aspirated through a series of impaction stages in order of their decreasing pore size.

Development of Andersen Impactor:

Andersen Impactor is a widely used cascade impactor for determining the particle size distribution. The original design was framed by Andersen. The design consisted of various stages arranged in series with increasing efficacy. Each series consisted of several identical circular accelerating jets (usually 400) arranged in circular patterns facing toward an 82 mm diameter collection plate. When the aerosol impinges the plate, it moves radially outward to the edge of the plate and moves to the next plate taking a turn of 180°. There are different versions of this instrument. The different developmental stages of this sampler are:^{84–86}

- A six-stage cascade impactor was developed by Andersen in 1958 to collect airborne bacteria. In this system, the bacteria impacted on the surface of the agar in a petri dish which was calibrated by counting and sizing of collected wax spheres by optical microscopy. The same design was applied in 1966 to collect nonviable particles on stainless steel or glass impaction plate.
- The sampler was redesigned in 1970 to further categorize incoming dust into eight different fractions (Stages 0–7) with the inclusion of an integrated backup filter. This version was named MK I.
- Later in 1977, the MK II version of the sampler was introduced with contributions from McFarland *et al.*⁸⁶ (1977) in 1977 who emphasized the need to redesign the top two stages and apply a pre-impactor.

Various studies on impactors have concluded that impactors can be designed according to the size specificity criterion.

Operational principle of cascade impactor

The functioning of the cascade impactor is based on the principle of inertial impaction. Each stage of the impactor consists of a single or series of nozzles or jet, through which the sample is introduced in the form of aerosol and directed toward the collection plate of that stage. The chances of particles impacting the stage depend on its aerodynamic particle size. Smaller particles will pass to the next stage owing to less inertia. The process is repeated for the next stages, too. The different stages are arranged in decreasing order of particle size. With the reduction of the orifice of the jet, the increase in velocity of air is observed which enables the collection of finer particles. If any particle remains, it is collected after the filter. Figure 6 gives a brief view of the different stages of Anderson cascade impactor and possible sites of drug deposition.⁸⁷

Table 5 gives an idea of the relation between Andersen Cascade impactor and possible particle size deposition within the respiratory tract.

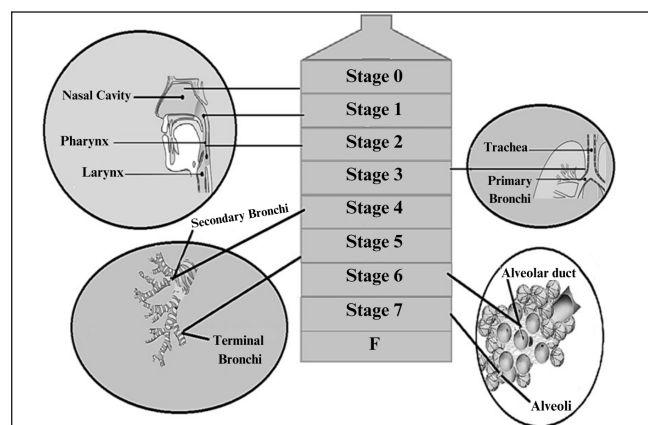


Figure 6: Relation between Andersen Cascade Impactor and respiratory tract.

Table 5: Relation between Andersen Cascade impactor and possible particle size deposition within the respiratory tract.

Sr No	Stages of anderson cascade impactor	Particle size per stage in μm	Probable site of drug deposition	Aerosol size in μm
1	Stage 0	9.0–14.0	Upper respiratory tract	9.0–10.0
2	Stage 1	5.8–9.0	Upper respiratory tract	5.8–8.9
3	Stage 2	4.7–5.8	Pharynx and larynx	4.7–5.7
4	Stage 3	3.3–4.7	Trachea and primary bronchi	3.3–4.6
5	Stage 4	2.1–3.3	Secondary bronchi	2.1–3.2
6	Stage 5	1.1–2.1	Terminal bronchi	1.1–2.0
7	Stage 6	0.65–1.1	Alveoli	0.7–1
8	Stage 7	0.43–0.65	Alveoli	0.4–0.6
	Filter	Below 0.4		

CONCLUSION

DPIs have been an interesting area of research with newer trends like nanoparticulate systems, self-aggregating systems, microparticulate systems, liposomal drug delivery, and delivery of proteins and peptides gaining attention in recent years. The future of DPIs looks promising with researchers experimenting extensively on the use of different formulation strategies as well as the use of different excipients for safe and efficacious delivery of drugs directly to the lung in the form of dry powders for inhalation.

Authors' contributions

HSM has contributed to concept of the review article and has revised it critically for important intellectual content; PSP has collected the data and drafted the article.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Review Article

Association of circulatory chemerin levels with the severity of pre-eclampsia: A systematic review and bootstrapped meta-analysis

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ABSTRACT

Introduction: This study presents a systematic review and meta-analysis to investigate the association between circulating chemerin levels and the severity of preeclampsia (PE).

Material and Methods: A thorough search was conducted across multiple databases, including PubMed/MEDLINE, SCOPUS, and the Cochrane Library, up to March 31, 2024, focusing on observational studies that compared chemerin levels in patients with severe versus mild PE. Two independent reviewers extracted mean and standard deviation (SD) values of chemerin levels from these studies. The quality and risk of bias of the included studies were assessed using the Newcastle–Ottawa Scale. Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated to evaluate the difference in chemerin levels between severe and mild PE groups. Sensitivity analyses were performed to address heterogeneity and ensure the reliability of the findings. Additionally, a bootstrapped meta-analysis with 1,000 and 10,000 simulations was conducted to further validate the results.

Results: Six observational studies were included in the analysis. The findings revealed that patients with severe PE had significantly higher chemerin levels compared to those with mild PE (SMD 1.55, 95% CI 0.67–2.43, $p < 0.0001$). The bootstrapped meta-analysis supported the accuracy of these findings (SMD = 1.54, CI = 0.74–2.38). No publication bias was identified using Begg's and Egger's tests, and the sensitivity analysis confirmed the robustness of the results.

Conclusion: This meta-analysis provides compelling evidence that chemerin levels are significantly elevated in patients with severe PE compared to those with mild PE. Further research is warranted to investigate the potential of circulating chemerin as a diagnostic marker for PE severity.

Keywords: Adipokine; Chemerin; Pre-eclampsia; Systematic review; Meta-analysis

INTRODUCTION

Complications related to pregnancy significantly increase mortality risk, especially in developing countries. Preeclampsia (PE), characterized by hypertension and proteinuria after 20 weeks of gestation, can manifest as either mild or severe. While mild PE includes symptoms like chest pain, vomiting, and high blood pressure, severe PE involves more serious conditions like abdominal pain, kidney failure, and blurred vision. PE is associated with liver and kidney dysfunction, pulmonary edema, thrombocytopenia, and a higher risk for diabetes and cardiovascular diseases. According to the World Health Organization, the global incidence of PE ranges from 2 to 10% of pregnancies, with a related mortality rate of 12%.^{1,2}

The exact pathophysiology of PE is not fully understood, but it is believed to involve placental hypoxia, oxidative stress, and immune modulation, leading to the production of proinflammatory cytokines. Adipokines, such as chemerin, are gaining attention as potential early biomarkers for PE. Chemerin is involved in processes like adipogenesis, energy metabolism, and inflammation. Recent studies have suggested a link between chemerin levels and PE, but there is limited direct evidence on whether these levels correlate with PE severity.^{3–5}

This systematic review and meta-analysis aim to provide precise information on the association between circulating chemerin levels and PE severity by comparing severe and mild PE groups. Sensitivity and bootstrapped meta-

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analyses were also conducted to ensure robust and precise outcomes.

MATERIAL AND METHODS

This review followed the PRISMA (Preferred Reporting Items For Systematic Reviews And Meta-Analysis) guidelines and was registered with PROSPERO (CRD42024526676).

Search strategy

We conducted a comprehensive literature search up to March 31, 2024, using PubMed, Cochrane Library, Scopus, and other databases. The search terms included “Chemerin” and “preeclampsia” without any time or language restrictions. Additional articles were identified through manual searches of bibliographies and contacting authors for unpublished data. Three researchers independently performed the literature searches. Any differences in their findings were resolved through discussions with other authors. Additionally, efforts were made to acquire any unpublished data. When necessary, the corresponding authors of the respective articles were contacted for further information.

Study selection criteria

To be included, studies had to be observational, focused on circulating chemerin levels in preeclampsia (PE), and compared levels between severe and mild PE groups. Participants needed to be human, with PE diagnosis criteria defined according to guidelines⁶ from the ‘American College of Obstetricians and Gynecologists (ACOG) or the International Society for the Study of Hypertension in Pregnancy (ISSHP). The studies also had to be written in English. Exclusion criteria included studies that did not specify whether PE was severe or mild, studies that only compared chemerin levels between PE and control groups, studies focusing on diseases other than PE, duplicate reports, reviews, experimental animal studies, letters to the editor, and commentaries.

Data extraction and quality assessment

After applying the inclusion criteria, the following details were extracted from each included study: first author names, country and year of publication, number of participants in severe and mild PE groups, PE diagnosis criteria, means, and standard deviations (SD) for age, anthropometric data, and circulating chemerin levels, as well as the chemerin measurement method and units. If data were reported in quartiles or as medians and ranges, conversions were performed to make them suitable for meta-analysis.^{7,8} Study quality was assessed using the Newcastle–Ottawa Scale

(NOS) for observational studies, which scores studies from 0 to 9 based on selection, comparability, and exposure criteria.⁹

Statistical analysis

The meta-analysis aimed to compare chemerin levels between severe and mild preeclampsia (PE) groups using standardized mean difference (SMD) with a 95% confidence interval (CI) as the outcome measure. A random-effects model was applied to the data. Heterogeneity was assessed using the DerSimonian-Laird estimator, Q-test, and I^2 statistic. If heterogeneity ($\tau^2 > 0$) was detected, a prediction interval for true outcomes was calculated. Potential outliers and influential studies were identified through studentized residuals and Cook's distances, with outliers defined using Bonferroni correction and influential studies identified if Cook's distance exceeded the median plus six times the interquartile range.

Funnel plot asymmetry was examined using the rank correlation and regression tests, with the ‘trim-and-fill method’ applied to adjust for significant publication bias. The robustness of the meta-analysis was evaluated through a one-study leave-out sensitivity analysis. All analyses were two-tailed, with a significance threshold of $p < 0.05$. The primary analyses were performed using Review Manager (version 5.4), Jamovi (version 2.3), and OpenMeta(Analyst), while the bootstrapped meta-analysis was conducted using OpenMEE software.

RESULTS

Search results and study characteristics

The literature search identified 27 articles on chemerin levels in PCOS. After removing duplicates, reviews, and commentaries, 11 studies were selected for full-text review. Of these, five did not report chemerin levels between severe and mild PE patient groups, leaving six studies for the final analysis.^{10–15} The PRISMA flow diagram is shown in Figure 1.

Study characteristics and Newcastle–Ottawa Scale quality scores are detailed in Supplementary Material [Table 1], with scores ranging from 6 to 8, indicating medium to high quality. All six studies measured serum chemerin using the ELISA method. PE diagnosis followed ACOG guidelines, with criteria including gestational blood pressure >140 mmHg systolic or >90 mmHg diastolic and proteinuria in previously normotensive patients before 20 weeks of gestation. Maternal age averaged between 25 and 34 years. Gestational age was reported in three studies as being in the third trimester,^{10,12,14} and in two studies as either second or third trimester,^{11,13} while one study sampled in the first trimester before PE diagnosis.¹⁵ The studies had either cross-sectional^{10–14} or prospective cohort designs.¹⁵

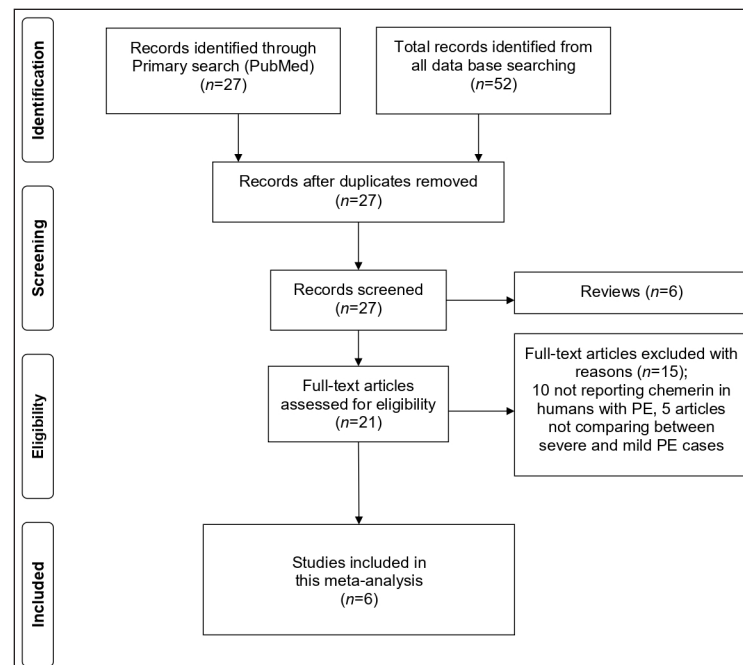


Figure 1: The study flowchart.

Table 1: Characteristics of included studies comparing the circulating chemerin between severe and mild PE patients.

Study, Year, Country	Severe PE						Mild PE						Sample, Method, Units	Confounder adjustment	NOS score
	n	Mean age	Mean GA	Mean BMI	Chemerin (Mean)	Chemerin (SD)	n	Mean age	Mean GA	Mean BMI	Chemerin (Mean)	Chemerin (SD)			
Al-Refai AA. ¹⁰ (2012), Saudi Arabia	10	34.37	32.68	30.46	479	158.56	19	34.37	32.68	30.46	281.95	144.54	Serum, ELISA, ng/mL	Age, BMI, GA	8
Cetin O et al. ¹¹ , (2017), Turkey	43	27.65	NA	26.10	394.72	100.01	45	28.11	NA	26.86	322.11	37.6	Serum, ELISA, ng/mL	Age, GA	7
Duan DM et al. ¹² , (2012), China	23	29.19	35.83	23.34	289.6	74.43	49	29.19	35.83	23.24	228.1	87.99	Serum, ELISA, ng/mL	Age, GA	7
Murad AM et al. ¹³ , (2020), Iraq	33	24.45	NA	28.43	435.06	55.4	33	25.00	NA	26.61	227.49	57.4	Serum, ELISA, ng/mL	Age, BMI, GA	8
Wang L et al. ¹⁴ , (2015), China	30	28.5	37.4	28.65	493.83	105.23	30	27.9	38.5	27.49	330.23	56.22	Serum, ELISA, ng/mL	Age, GA	7
Xu QL et al. ¹⁵ , (2014), China	18	27.2	10.67	25.4	365.5	116.5	23	27.2	10.67	25.4	270.3	91.8	Serum, ELISA, ng/mL	Age, GA	7

BMI: Body mass index, GA: Gestational age, PE: Preeclampsia, NA: Not applicable, NOS: Newcastle-ottawa Scale, ELISA: Enzyme-linked immunoassay, SD: Standard deviation.

Circulating chemerin between severe and mild PE patients

Six studies comparing chemerin levels between 157 severe PE and 199 mild PE patients were included.¹⁰⁻¹⁵ The meta-analysis using a random-effects model estimated an average standardized mean difference of 1.55 (95% CI: 0.67–2.43),

showing significantly higher chemerin levels in severe PE [$z = 3.46$, $p = 0.0005$, Figure 2]. The Q-test indicated heterogeneity among true outcomes ($Q(5) = 46.38$, $p < 0.0001$, $\tau^2 = 1.0891$, $I^2 = 91\%$). A 95% prediction interval for true outcomes ranged from -0.67 to 3.77 , suggesting that while the average outcome is positive, some studies might report negative outcomes. One

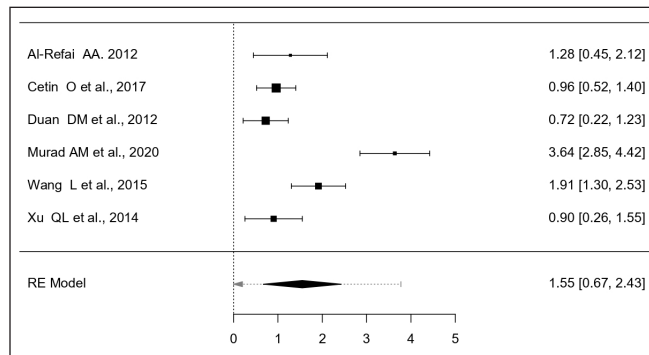


Figure 2: The forest plot comparing serum chemerin between severe and mild PE patients. PE: Preeclampsia.

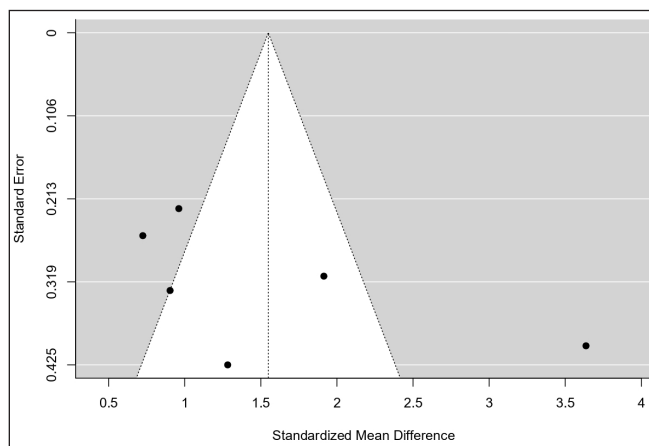


Figure 3: The funnel plot for publication bias.

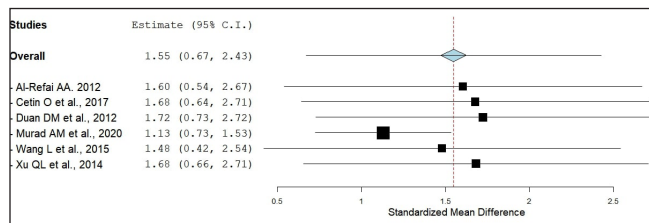


Figure 4: The results of sensitivity analysis.

study¹³ was identified as a potential outlier with a studentized residual larger than ± 2.63 and was also considered overly influential according to Cook's distances.

Publication bias and sensitivity analysis

As shown in Figure 3, there was no evidence of funnel plot asymmetry. Both the rank correlation and regression tests indicated no asymmetry ($p = 0.27$ and $p = 0.18$, respectively). A one-study leave-out sensitivity analysis confirmed the stability of the results, indicating consistently higher chemerin levels in severe PE regardless of which study was omitted [Figure 4].

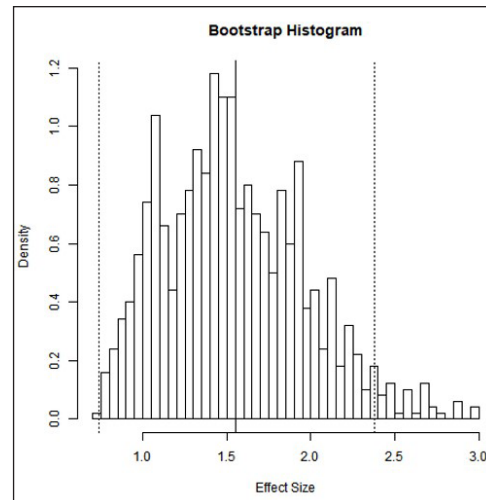


Figure 5: The histogram of bootstrap analysis using 1000 replicates.

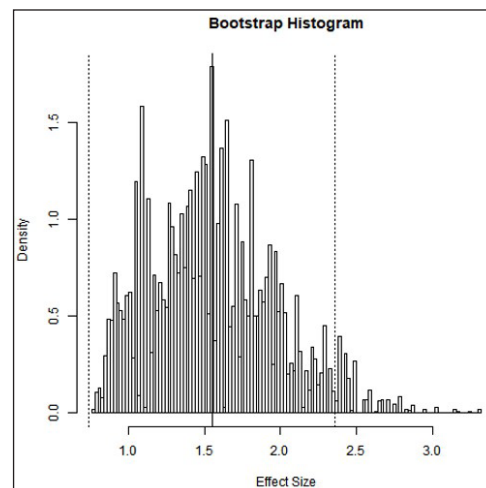


Figure 6: The histogram of bootstrap analysis using 10,000 replicates.

Bootstrapped meta-analysis

A bootstrapped meta-analysis with 1000 and 10,000 replicates [Figures 5 and 6] supported the accuracy of the original meta-analysis. The mean SMD over 1000 replicates was 1.54 (95% CI, 0.74–2.38), and over 10,000 replicates was 1.55 (95% CI, 0.74–2.36), as shown in Table 2. Bootstrapping is particularly valuable when dealing with a small sample size, an unknown population distribution, or a complex or non-standard statistics. It also helps assess the stability of results by repeatedly resampling from the original data to calculate confidence levels and other accuracy measures.

DISCUSSION

This meta-analysis reveals that chemerin levels are significantly higher in severe preeclampsia (PE) patients compared to

Table 2: The results of a bootstrapped meta-analysis.

Description	Observed effect size (SMD)	95% CI	Figure
Meta-analysis (9 studies)	1.55	0.67:2.42	Fig. 2
Bootstrapped meta-analysis	Mean over the replicates	95% CI	
Bootstrap replicates: 1000	1.54	0.74:2.38	Fig. 5A
Bootstrap replicates: 10000	1.55	0.74:2.36	Fig. 5B

CI: Confidence interval, SMD: Standardized mean differences.

those with mild PE ($p < 0.0001$). This finding underscores the association between elevated circulating chemerin levels and PE severity. However, substantial heterogeneity (91%) was observed [Figure 2]. Sensitivity analysis identified the study by Murad *et al.* (2020) as a potential source of this heterogeneity.¹³ Excluding this study reduced heterogeneity to 59%, while the significant association between higher chemerin levels and severe PE persisted (SMD = 1.13, 95% CI: 0.72 to 1.54, $p < 0.0001$). This indicates that although the study by Murad *et al.*¹³ (2020) contributes to heterogeneity, it does not alter the overall conclusion of increased chemerin levels in severe PE.

The heterogeneity could stem from the younger maternal age and gestational stage (second or third trimester) in the Murad *et al.*¹³ (2020) study. Elevated circulating chemerin in severe PE is likely due to increased proinflammatory adipokine synthesis from the placenta during pregnancy.^{16,17} While the precise mechanisms linking chemerin to PE are not fully understood, recent studies suggest that elevated placental chemerin disrupts normal placental development, contributing to PE onset.¹⁸ Chemerin inhibits trophoblast migration, invasion, and tube formation, affecting trophoblast lipid metabolism and promoting pyroptosis and inflammation, thereby playing a role in PE development.¹⁹⁻²¹

PE is associated with altered body mass index (BMI), insulin resistance, and glucose and lipid metabolic abnormalities, which may contribute to heterogeneity. However, the limited number of studies precluded a meta-regression analysis of these covariates. Nonetheless, recent evidence indicates that chemerin's association with PE is independent of BMI and obesity status.^{4,5} The included studies in this meta-analysis reported comparable maternal age, gestational age, and BMI for PE patients. Sensitivity analysis [Figure 4] confirmed the robustness of the finding of elevated chemerin in severe PE, with no single study overly influencing the outcome. Additionally, no significant publication bias was detected [Figure 3]. Despite the limited number of studies, further

research on chemerin's role as a marker for PE detection and severity progression is needed. The accuracy of our meta-analysis was validated through bootstrapped meta-analyses with 1000 and 10,000 replicates, confirming the association of higher chemerin levels with severe PE [Table 2].

Strengths and limitations of this meta-analysis should be noted. Limitations are inherent to the observational study designs included, and heterogeneity may arise from methodological and clinical variations across studies in design, setting, participant selection, and demographic, hormonal, and metabolic parameters. We addressed this through random effects meta-analysis and sensitivity analyses. The quality assessment of individual studies indicated medium to high quality. Due to the limited number of studies available for comparison (only six), it was not feasible to conduct a separate subgroup analysis. Nevertheless, the overall meta-analysis results were robust and stable, as confirmed by sensitivity and bootstrapped analyses. Consequently, this meta-analysis supports the association of higher circulating chemerin levels with PE severity. Further well-controlled studies with larger sample sizes are warranted to evaluate chemerin's utility for PE diagnosis and disease progression monitoring.

CONCLUSION

This is the first bootstrapping meta-analysis to assess the association of circulating chemerin with PE severity. The results indicate significantly higher serum chemerin levels in severe PE patients compared to mild PE patients, supporting chemerin measurement as a potential method for identifying severe PE. The findings' validity, robustness, and accuracy are confirmed through sensitivity and bootstrapped meta-analyses. However, further research is needed to explore the diagnostic accuracy of serum chemerin for PE diagnosis and monitoring severity progression.

Authors' contributions

SRV, MM, SS: Conceptualization; SRV, AA, KG, JJ, AR, AK, BK: Data curation, analysis, methodology and software; MT, SS: Supervision, validation; SRV, MM, AA, KG, JJ: Writing-original draft; BK, MT, SS: Writing-review and editing. All authors approved the final manuscript.

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Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Modulation of sleep quality, cardiac autonomic activity, and cognition by yoga in medical students

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ABSTRACT

Objectives: The disturbed sleep quality among medical students due to their hectic schedule may negatively impact the cognition, consequently affecting their academic performance. With the hypothesis that short duration of simple yogic exercises may improve sleep quality and heart rate variability (HRV), and thus may improve cognitive abilities, the study aims to evaluate the outcome of short duration yoga training on HRV, cognition, and sleep in medical students.

Material and Methods: The participants of the study were young and apparently healthy medical students. The study commenced after the Institutional Scientific Research and Ethics Committee approval. The informed consent was taken from all the participants in writing. All parameters (height, weight, age, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR]) along with HRV, sleep quality (using Pittsburgh Sleep Quality Index [PSQI]), and cognitive ability (using Trail Making Tests Parts A & B [TMTs-A&B]) were assessed in the participants at baseline. Thereafter, the students practiced yoga (asanas, pranayama, and meditation) under supervision of a yoga instructor and a faculty for the duration of one hour every day for six weeks. Measurements were repeated after six weeks. Depending on the normality of data and data distribution, the comparison was done using Wilcoxon Signed Rank Test or dependent samples t-test. The level of significance was kept as $p < 0.05$.

Results: Following six weeks of yoga sessions, a significant improvement in the high frequency power normalized unit (HFnu) and total power in comparison to baseline values was observed: 53.25 ± 10.14 versus 59.57 ± 9.61 and 3238 ± 1133 versus 3473 ± 1130 , respectively. Significant difference at six weeks between baseline and post yoga values was observed in TMT-A (30.16 ± 5.04 vs 19.84 ± 2.76) and TMT-B (69.96 ± 12.99 vs 49.24 ± 10.99). Sleep quality also improved significantly after yoga sessions (baseline PSQI score of 10.68 ± 1.79 and post-PSQI score of 4.12 ± 1.67).

Conclusion: It was concluded that one hour of supervised yoga session every day for six weeks can improve HRV, sleep quality, and cognitive ability among medical students. Medical students should practice yoga regularly to improve cognitive function and sleep and to reduce cardiovascular morbidity.

Keywords: Cognition, Heart rate variability, Meditation, Sleep quality, Yoga

INTRODUCTION

Good quality sleep is an important indicator of a healthy life. Inadequate sleep has deleterious effects on mental as well as physical health. Inadequate sleep is a predisposing factor for cardiovascular morbidity,¹ and sleep deprivation may lead to drastic deficits in cognitive processing and academic performance.² Yoga intervention has proved to be beneficial in managing sleep-related problems in diseased as well as healthy individuals.³ Various aspects of yoga like asanas, meditation, and mindfulness have been implemented at universities and higher education institutions for improving mental health.⁴ Research has shown that Long Sudarshan Kriya, a form of yoga and meditation technique,

may be helpful in improving heart rate variability (HRV) as it increases parasympathetic and decreases sympathetic activity.⁵ Research has proved that simple yogic exercises for a duration of six weeks decreases heart rate (HR) and blood pressure in young women.⁶ HRV, a noncomplex, noninvasive index of cardiac autonomic activity, is widely used to identify risk of cardiovascular morbidity.⁷ HRV has also been used as a biomarker of cognitive impairment in apparently healthy population, as presented in the Systematic review by Forte *et al.*, (2019).⁸

Medical students have poor sleep pattern due to their hectic schedule.⁹ In the pandemic time, a sequence of national lockdowns forced the students to stay inside their houses,

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which has further deteriorated or altered the sleep cycles of the medical students, and the pattern is continuing till date.¹⁰ The disturbed sleep quality may negatively impact the cognition, consequently affecting their academic performance.¹¹ This could also have a negative impact on the students' mental and physical health. We hypothesize that a short duration of simple yogic exercises may improve sleep quality and HRV, thus leading to improved cognitive abilities. The studies on yoga training in medical students are sparse; hence we planned this study to evaluate how short-term yoga influences sleep quality, HRV, and cognitive function in medical students.

MATERIAL AND METHODS

This study commenced in the Department of Physiology after approval from the Institutional Ethics Committee was granted. All participants provided written informed consent. A sample of 50 participants was selected based on the willingness of the students to participate in the research. Young, apparently healthy adults of both gender 18–25 years of age who consented to participate were included in the study. Individuals actively involved in physical activity, yoga, or meditation; individuals with physical disability to perform pranayama/yoga postures, color vision deficiencies, significant physical or mental health conditions, and individuals on regular medications; individuals who drink alcohol, smoke, or used recreational drugs regularly were excluded from the study. The participants with body mass index (BMI) < 18 kg/m² or > 25 kg/m² were also excluded.

After recording all baseline parameters, the selected participants were trained in yoga for six weeks, 60 minute/day in the evening at 6 PM by a trained yoga expert under the supervision of a department faculty to ensure compliance. The sequence of yoga asanas and pranayam was adapted from the Common Yoga Protocol given by the Ministry of AYUSH.¹² The asanas practiced were SukṣmaVyāyāma (Loosening Practices), Uttanasana (Standing Forward Bend), Badhakonasana (Butterfly pose), Parivrtta Sukhasana (Easy Seated Twist Pose), Setu Bandha Sarvangasana (Bridge Pose), Halasana (Plough Pose), Viparita Karani (Legs Up the Wall Pose), variation of Sukhasana (Easy Forward Bend), Balasana (Child Pose), Janu Sirsasana (Head to Knee Pose), and Savasna (Corpse Pose). Among the Pranayamas, Anuloma Viloma, Bhramari, and Kapalbhāti were practiced.

The following parameters were recorded at baseline and after six weeks of yoga training:

- Age, height, weight, arterial blood pressure, and HR. BMI was calculated from height and weight using Quetelet's Index.
- Sleep quality was assessed using the freely available Pittsburgh Sleep Quality Index (PSQI).¹³ PSQI is a self-reported test using pencil and paper. It usually takes between 5 and 10 min for completion. Each of the 19 self-reported items in the questionnaire falls into one of seven subdivisions: subjective sleep quality, sleep duration, sleep latency, sleep disturbances, habitual sleep efficiency, use of sleep medication, and daytime dysfunction.
- HRV was measured after the participants were comfortable and relaxed for at least ten minutes. Following the standard procedure recommended by the Task Force on HRV,¹⁴ electrocardiogram (ECG) recordings were performed for 10 minutes to analyze short-term HRV. HRV was then evaluated using both the time domain and frequency domain analyses. The ECG was captured using a computer-based digital data acquisition system with PowerLab[®] electrocardiographs (ADInstruments, Australia). Recordings were processed and stored with LabChart[®] v. 8.0 software (ADInstruments) at a sampling rate of 500 Hz and a time resolution of 1 ms. Artifacts were visually inspected on the computer display, and only segments with more than 90% pure sinus beats were included in the final analysis. The HRV data were analyzed using the Kubios HRV[®] software (version 2.2, Finland), with a signal sampling rate set at 1 kHz to ensure the precise detection of parameter changes.
- The paper and pencil Trail Making Cognitive tests (TMT-A&B) were used to assess cognitive function.¹⁵ The participants were asked to perform practice sessions before the start of the test. In Trail Making Tests Parts A (TMT-A), the participants were asked to draw a straight line to connect 25 consecutive numbered circles. In Trail Making Tests Parts B (TMT-B), participants were directed to draw lines connecting numbers and letters in a specific sequence, alternating between numbers and letters. For both tests, the score was based on the total time (in seconds) required to complete the tasks. The time for the tests was measured with a stopwatch. The result was interpreted as given in Table 1.

Statistical Analysis: Data was analyzed using GraphPad Prism (GraphPad Software version 8 for windows, San Diego,

Table 1: Trail making test interpretation

Trail making test	Average time (seconds)	Time suggestive of defective cognition (s)
TMT-A	29	> 78
TMT- B	75	> 273
TMT-A: Trail making tests parts A, TMT-B: Trail making tests parts B		

California, USA). For each parameter, the data was tested for normal distribution and expressed as mean \pm standard deviation. For baseline and post yoga comparison, depending on the normality of the data, paired t-test or Wilcoxon Signed Rank Test was used. The significance level was kept at $p < 0.05$ in the study.

RESULTS

During the training, a trained yoga instructor led the yoga sessions while an investigator was present. There was no loss to follow-up. All 50 students reported for the yoga session daily and for baseline and post yoga assessment of the required parameters. The average age, height, and weight of the participants were 21.86 ± 2.6 years, 162.90 ± 9.9 cm, and 61.09 ± 10.8 kg, respectively. The calculated mean BMI was 22.47 ± 3.9 kg/m².

The cardiovascular parameters are shown in Table 2. A significant difference was witnessed in the systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR after six weeks of yoga training in comparison to the baseline values. Mean blood pressure did not show any significant changes.

The baseline and post-intervention values of HRV parameters are shown in Table 3. There was a significant difference in the high frequency power normalized unit (HFnu) and total power (TP) between the two recordings (baseline and post yoga).

The participants demonstrated a significantly enhanced performance on the TMT-A&B tests after six weeks of yoga practice. Additionally, the PSQI revealed a notable improvement in sleep quality following yoga practice compared to baseline values. These results are detailed in Table 4.

Table 2: Cardiovascular parameters in the participants at baseline and after six weeks of yoga training

S.No	Parameters	At baseline	After six weeks of yoga	p-value
1.	SBP (mmHg)	116.6 ± 2.04	111.8 ± 8.10	0.049*
2.	DBP (mmHg)	80.88 ± 2.17	78.72 ± 2.3	0.0026*
3.	MBP (mmHg)	92.77 ± 3.34	92.00 ± 1.77	0.23
4.	HR (BPM)	83.44 ± 3.81	80.88 ± 4.23	0.010*

The values are in Mean \pm SD. In the table, Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean blood pressure (MBP), and Heart rate (HR) refers to systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate, respectively. A p-value of less than 0.05 was taken as statistically significant. The data were compared using dependent samples t-test. The significant values are marked as '*'. SD: Standard deviation.

Table 3: HRV parameters in the participants (n = 50)

S.No.	Parameters	Values		p-value
		Baseline	Post Yoga	
1.	Standard deviation of normal to normal interval, SDNN (ms)	61.10 ± 8.71	59.36 ± 8.87	0.19
2.	Square root of the mean of squares of the differences between adjacent NN intervals, RMSSD (ms)	56.55 ± 8.76	56.08 ± 7.7	0.81
3.	Proportion derived by dividing NN50 by the total number of NN intervals, PNN50 (ms)	45.84 ± 9.5	44.74 ± 9.66	0.35
4.	Low-frequency power normalized unit, LFnu	49.48 ± 9.12	48.12 ± 7.87	0.31
5.	High-frequency power normalized unit HFnu	53.25 ± 10.14	59.57 ± 9.61	0.03*
6.	LF/HF	0.96 ± 0.33	0.87 ± 0.26	0.12
7.	Total power	3238 ± 1133	3473 ± 1130	0.015*

The values are in Mean \pm SD. A p-value of less than 0.05 was taken as statistically significant. The pre-and post-intervention data was compared using the Wilcoxon Signed Rank Test. SD: Standard deviation, HRV: Heart rate variability, The significant values are marked as '*'.

The correlation between HRV parameters (HFnu and TP) with PQSI and TMT-A&B score is given in Table 5. No significant correlation was found among these parameters except in TMT-B score, which was found to have a significant negative correlation with TP.

DISCUSSION

As a lifestyle intervention, yoga has shown to ease stress and reinstate disturbed autonomic nervous system balance. This study examined the impact of six weeks of yoga training on autonomic activity (HRV), sleep quality, and cognition in medical students. We hypothesized that a short duration of simple yogic exercises may improve sleep quality and HRV, thus leading to improved cognitive abilities. This study

Table 4: Values of trail test and the PSQI in the participants (n = 50)

S.No.	Parameters	Values		p-value
		Baseline	Post yoga	
1	Trail A (s)	30.16 ± 5.04	19.84 ± 2.76	≤0.0001*
2	Trail B (s)	69.96 ± 12.99	49.24 ± 10.99	0.0008*
3	PSQI	10.68 ± 1.78	4.12 ± 1.67	≤0.0001*

The values are in Mean ± SD. PQSI: Pittsburgh Sleep Quality Index. A p-value of less than 0.05 was taken as statistically significant. The pre- and post-intervention data was compared using Wilcoxon Signed Rank Test. The significant values are marked as '*'. SD: Standard deviation.

Table 5: Correlation of significant HRV parameters with PSQI and trail test scores

Scores	HRV parameters	Baseline		Post yoga	
		R	P	r	P
PSQI		-0.17	0.43	-0.25	0.21
Trail A	HFnu	0.07	0.74	-0.07	0.75
Trail B		0.07	0.73	-0.29	0.15
PSQI	Total power	0.18	0.27	-0.32	0.12
Trail A		0.39	0.19	-0.27	0.18
Trail B		0.03	0.89	-0.41	0.04*

A p-value of less than 0.05 was taken as statistically significant. PQSI: Pittsburgh Sleep Quality Index; HFnu: High frequency power in normalized unit, HRV: Heart rate variability, TP: Total power. Correlation was calculated using Spearman's Rank Correlation test. The "*" denotes significant value.

found a significant reduction in cardiovascular parameters, including SBP, DBP, and HR, after six weeks of yoga practice. Of all the recorded HRV parameters assessed, only HFnu and TP showed a significant increase.

Similar to our study, fall in blood pressure and HR following yoga training was observed by other researchers also.^{16,17} Om chanting and yoga nidra have shown to lower blood pressure and improve lipid profile in hypertensive patients.¹⁶ Simple yogic exercises for the duration of six weeks have shown to lower blood pressure and HR in young women.⁶ Papp *et al.* (2013) have observed that eight weeks of hatha yoga increased HRV but has no effect on blood pressure.¹⁸ Some of yogic asanas have proved beneficial in elderly patients with essential hypertension where the possible mechanism could decrease stress-induced sympathetic hyperactivity and plasma renin activity after yoga training.¹⁹ Hagins *et al.* (2013), in a systematic review, suggested yoga to be an effectual intervention for reducing blood pressure.²⁰

The improved HFnu and TP in this study are suggestive of increased parasympathetic activity after practicing yoga for six weeks. However, no changes were observed in other parameters

which could be due to less duration of the training. Most of the researchers have shown improvement in HRV of healthy and diseased adults after yoga sessions (asana, breathing exercise & meditation) ranging from four weeks to six months.^{21–23} Similar to this study, Papp *et al.* (2013) observed significant increase only on pNN50 after hatha yoga of eight weeks duration, suggesting an improved parasympathetic tone.¹⁸ The study by Bhasker *et al.* (2017) found that pranayama and meditation in Long Sudarshan Kriya significantly increased parasympathetic activity and decreased sympathetic activity in the heart.⁵ This suggests that these practices may be effective in improving HRV. Additionally, a six-month study of yoga breathing practice in healthy adolescents showed a continued shift toward parasympathetic dominance in their cardiac autonomic tone. While the exact mechanism by which yoga influences autonomic activity is still being researched, some yoga practices appear to directly stimulate the vagus nerve, leading to increased parasympathetic output and improved HRV. These effects have been observed after just a few weeks of yoga practice.

The sleep quality improved significantly after six weeks of yoga practice, as suggested by the decreased scores of the subjective PSQI. The benefit of yoga on sleep has been studied by many researchers. Consistent with our study, yoga training resulted in improvements in the sleep-wake cycle and PSQI scores in the yoga-trained group compared to the nontrained control group.⁹ A systematic review and meta-analysis found that yoga interventions are more effective than nonactive control groups in addressing sleep-related issues in women.⁴ Another trial with the eight-week Kundalini yoga intervention has proved that yoga may benefit patients with insomnia as an adjunctive therapy to cognitive behavioral therapy.²⁴ Sleep deprivation is akin to stress-like situation that may activate the sympathetic nervous system and increase cortisol secretion, leading to a rise in blood pressure.²⁵ By activating the sympathetic nervous system, sleep leads to decreased HRV.²⁶ One possible explanation for improved sleep quality in terms of improved sleep latency and more deep sleep without disturbances after yoga could enhance physical and mental relaxation due to stretching and relaxing of muscles and brief meditation. Another possible mechanism by which yoga improves sleep could be a decrease in the sympathetic nervous system activation.

Cognitive ability as tested by the TMTs-A&B was found to significantly improve after practicing yoga for six weeks. Various studies have also shown a direct relation between mindfulness training, yoga, meditation, and improved cognition.^{27,28} In a meta-analysis by Gothe and McAuley (2015), it was concluded that both the short and long duration of yoga practice leads to better cognitive functions. However, the sample size, characteristics of the sample population,

type of yoga asanas and breathing exercises, and cognition tests in these studies were different, which limits the positive association.²⁹ Yoga training improves HRV by enhancing vagal activity.¹⁰ The improvement in cognitive abilities by enhancing the vagal tone can be explained on the basis of the neurovisceral integration model.³⁰ Yoga, meditation, and cardio training for over five weeks have enhanced cognitive functions, including attentiveness and decision-making capacity, in young adults.³¹ HRV has many implications in psychophysiological research. Thayer *et al.* (2010) recognized the existing functional association between the prefrontal lobe and heart via the central autonomic connections involved in stress regulation, emotional reactions, limbic system, cognition, and reward and punishment responses.⁷ Resonance breathing, a type of pranayama, when practiced for a short duration of 20 minutes daily for a month has shown to enhance parasympathetic tone and depress sympathetic activity. Resonance breathing has also shown to enhance cognitive abilities and reduced apparent stress in adults.³²

Yoga, meditation, and cardio training for over five weeks have enhanced cognitive functions, including attentiveness and decision-making capacity, in young adults.³¹ HRV plays a significant role in psychophysiological research. Thayer *et al.* (2010) demonstrated a practical link between the prefrontal cortex and the heart through the central autonomic network, which is involved in stress regulation, emotional responses, limbic system functions, cognition, and reward and punishment mechanisms.⁷ Additionally, practicing resonance breathing, a form of pranayama, for 20 minutes daily for over four weeks has been found to increase parasympathetic activity, decrease sympathetic activity, improve cognition, and reduce perceived stress levels in young adults.³²

In this study, significant correlation was observed in TP and cognitive ability by TMT-B test. This shows that with the increase in HRV, there is improvement in cognitive abilities. It has been postulated that HRV is an important biological marker of health, disposition, and adjustment,¹⁴ and hence improvements in HRV due to yogic practice may lead to improved health, cognition, and sleep quality. This study corroborates this postulation.

This study is limited by its study design. Further, we did not test autonomic reactivity through the Conventional Autonomic Function Tests. This study can further be extended as a randomized control trial with greater sample and detailed autonomic assessment and electrophysiological assessment for cognition.

CONCLUSION

This study demonstrated that daily one-hour yoga sessions including asana, pranayama, and meditation over six weeks enhanced heart rate variability (HRV) among medical

students, as indicated by increases in HFnu and TP values. Regular yoga sessions also improved sleep quality and cognitive function in these students. These findings suggest that regular yoga is an effective approach for managing stress, improving sleep quality, enhancing cognition and cardiovascular health in young adults. Hence, regular yoga practice is recommended for young medical students for better physical and mental health.

Authors' contributions

All authors have made substantial contributions to the conception and design of the work; in the acquisition, analysis, or interpretation of data; and in drafting and revising the manuscript and all authors have approved the submission.

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Ethical approval

The research/study approved by the Institutional Review Board at the Government Institute of Medical sciences, Greater Noida, number GIMS/IEC/HR/2022/25, dated 22nd July 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate participants consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Original Article

Bacterial etiology among diarrheal cases

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ABSTRACT

Objectives: The main objective of this article was to check the bacterial etiology to find out the routes of infection, which might help with control strategies. As Nalbari is one of the most common flood-affected districts in Assam, India, we chose Nalbari district as our study area. The socioeconomic factor enhances the transmission of bacteria easily, as every year during floods, pictures of water from neighboring hilly states or countries (e.g., Bhutan)—rain, waterlogging, and more—are seen.

Material and Methods: Stool samples or rectal swabs were collected from the patients who had reported to the District Public Health Laboratory (DPHL) with acute diarrheal disease in Nalbari. Patients or their attendant's consent was collected prior to collecting samples. Samples were processed for culture, gram stain microscopy, and biochemical tests to isolate the organism.

Results: Test results showed *Escherichia coli* (*E. coli*) 40.95%, *Salmonella* 2.86%, *Shigella* 1.42%, and *Campylobacter* 0.48%. No other bacteria were isolated during the study period. Maximum cases were reported during the rainy season.

Conclusion: *E. coli* can transmit through fecal-oral means; *Salmonella* through contaminated food, water, contact with infected people/animals, and so on; *Shigella* through fecal-oral, contaminated food, water, oral-anal sexual routes, and more; and *Campylobacter* through contaminated or raw food, milk, water, and so on. This study concludes that water can easily transmit bacteria to other people. Health hygiene, economic condition, living behavior, awareness, and administration's activities all might play an important role in minimizing this burden. Making plans prior to flood by administration and more research studies can help in controlling this disease burden.

Key words: Water, Flood, Culture, Bacteria, Hygiene, Awareness

INTRODUCTION

Diarrhea is a common high-risk disease in developing countries. Every year, worldwide, nearly 1.6 million death occurs only due to diarrheal diseases in developing countries.¹ Both the adult and child populations are equally at risk for diarrhea. Most of the diarrheal cases and diarrheal deaths (89.37%) are reported from South Asia and sub-Saharan Africa.² In India, 120,000 children die due to diarrheal diseases, which is a huge contribution to global—half million—diarrheal child deaths.³ From 2011 to 2020, diarrhea outbreaks were reported from Tamil Nadu, Maharashtra, West Bengal, Punjab, Karnataka, and Madhya Pradesh in India.⁴ In 2000 and 2001, a rural remote village in the Sivsagar district of Assam reported 1077 and 1719 diarrheal cases, respectively⁵ (this is the data of only one village in a district of Assam, India). The data itself reveal how many cases report from a block that includes many villages, from a

district that includes many blocks, from a zone that includes many districts, or finally from the state of Assam. From the Tinsukia district of Assam, India, a big diarrhea outbreak was reported where 11 people died within ten days in May 2024.⁶ From time to time, these diarrhea outbreak cases are reported from various districts of Assam, India. Assam is a flood-affected state where people are demanding to declare this center as a national issue because it's affecting people's lifestyle, living behavior, and so on. During flood season, bacteria may transmit easily to the community, leading to diarrheal cases in the locality. There could also be some other factors that may need to be studied. Limited study in etiology, affecting factors, treatment patterns, and more, may hinder control of the disease.

The main aim of this study was to check the bacterial etiology and correlate it with the rainfall or flood.

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Study area

This study was conducted in the Nalbari district of Assam, India, after ethical approval. Nalbari is one of the common flood-affected districts, with Baralia River, Pagladiya River, and Brahmaputra River the three main rivers of this District. Water from Bhutan plays a major role during floods, which is only 67.6 km from Guwahati, the capital city of Assam.

MATERIAL AND METHODS

All acute diarrheal cases reported to the District Public Health Laboratory (DPHL), Nalbari, were included in the study. All age groups and both sexes were included in the study who reported to the DPHL with acute diarrheal disease or loose, watery stool. Stool samples or rectal swabs were collected as per the patient's clinical condition. Sample collection was preferred prior to antibiotics, but patients' samples who reported to the DPHL with antibiotics were also collected.

Stool sample collection: Instructions were given to the patient or attendees to prevent contamination of the sample with water, urine, or soil. To prevent contamination, sterile bags were used; and the patients, attendees, or collectors were instructed to wash their hands before collection. Sterile, clean disposable bags were placed in the toilet before passing the stool [Image 1a]. Clean, sterile stool collection containers [Image 1b] were given for sample collection. After passing the stool, it was collected in a container with proper gloves and mask to prevent contamination. Samples were inoculated in different culture media within one hour of collection.

Rectal swab collection: Rectal swabs were collected in Cary Blair (CB) transport media [Image 2] with the help of a sterile swab stick. Samples were processed within one to two hours after collection. Before collection, hands were washed carefully with soap. Instructions were given to the patients to sleep sideways and comfortably in bed. Sterile swab sticks were moistened with the CB transport media, and then they were inserted into the rectum of the patients, about 1–2 inches



Image 1: (a) Sample collection bag on bowl. (b) Sample collection container.



Image 2: Cary Blair transport media without rectal swab and with rectal swab.

(3–5 cm), and gently rotated clockwise for five to ten seconds. Swabs were withdrawn without touching the skin and placed in CB transport media. The outer wooden parts of swab sticks were broken and recapped into the CB media after collection [Image 2]. The collected rectal swab samples were placed at 2–8°C till inoculation.

Culture media were prepared in the DPHL and stored in the refrigerator. Before inoculation of samples in the culture plates, plates were allowed to dry in an incubator at 37°C. XLD (Xylose-Lysine-Deoxycholate) Agar, BA (Blood Agar), MAC (Macconkey) Agar, TCBS (Thiosulphate-Citrate-Bile-Salt Sucrose) Agar, SS (Salmonella-Shigella) Agar, and MH (Mueller-Hinton) Agar were used for inoculation and isolation of bacteria. Isolated bacteria were confirmed with Gram Stain and microscopy with different biochemical tests. The common biochemical tests used for confirmation are the Indole test, Oxidase test, Methyl Red test, Voges-proskauer test, Citrate Utilization test, Urease test, Triple Sugar Ion (TSI) test, H₂S test, Coagulase test, Catalase test, Oxidase test, Methyl Red test, Voges-proskauer test, Citrate Utilization test, Urease test, Triple Sugar Ion (TSI) test, H₂S test, Coagulase test, Catalase test, and more.

After clarification of bacteria, whether gram positive or gram negative, morphology (Cocci, Bacilli, or other) cluster or single and more by gram stain and microscopy, further biochemical tests were chosen. The comparison of biochemical tests results, growth characteristics, and gram stain microscopy altogether helps to identify bacteria. Indole test shows positive by *E. coli*, *Proteus*, *Flavobacterium sp.*, *Hemophilus influenza*, and more. Oxidase test shows positive by *Vibrio cholerae*, *Campylobacter jejuni*, *Helicobacter pylori*, *Pseudomonas aeruginosa* etc. Methyl Red test shows positive by *E. coli*, *Proteus vulgaris*, *Salmonella*, *Shigella*, and so on. Voges-proskauer test shows positive by *Enterobacter*, *Klebsiella*, *Serratia*, *Vibrio cholerae*, and so forth. Citrate

Utilization test shows positive by *Proteus mirabilis*, *Klebsiella*, *Salmonella*, *Citrobacter*, and more. Urease test shows positive by *Proteus*, *Klebsiella*, *Helicobacter pylori*, *Staphylococcus*, and so on. Triple Sugar Ion test shows positive by *E. coli*, *Salmonella*, *Shigella*, and so on, but with different color pigmentation. H_2S test shows positive by *Campylobacter*, *Citrobacter*, *E. coli*, *Salmonella*, and so on. Coagulase test shows positive by *Staphylococcus*. Catalase test shows positive by *Staphylococcus* and *Micrococcus*.

RESULTS

A total of 210 patients were enrolled in the study, from January 2022 to July 2024. It was observed after analysis of the data that maximum diarrhea positive culture cases were isolated with *E. Coli* 40.95% (86/210), followed by *Salmonella* 2.86% (6/210), *Shigella* 1.42% (3/210), and *Campylobacter* 0.48% (1/210). No other bacteria like *Vibrio cholera*, *Yersinia species*, *Aeromonas species*, *Klebsiella* or *Enterobacter species*, *Pseudomonas*, *Proteus*, *Citrobacter* and so on were isolated during the study period. The highest numbers of bacteria were isolated in 2024 which is 40.62% (39/96), followed by 2023 which is 35.42% (34/96), and 2022 which is 23.96% (23/96). Year wise graphical analyses are shown in Figure 1. If we analyzed the data month wise, the highest positive cases

were reported in July, followed by June [Figure 2]. Nalbari district's highest rainfall season is the monsoon season, which is June to October.⁷ If we compare the data with rainfall, the maximum cases reported were from May to September. If we analyze the data sex and year wise, it was observed that both sex groups were equally affected in those three years [Figure 3]. Blockwise analysis showed that maximum cases were reporting from Ghograpar Block, followed by Chamata Block [Figure 4]. Ghograpar Block is the neighboring block of Baksa district of Assam and Bhutan.

DISCUSSION

In a study by Alzahr *et al.*, (2022), the maximum stool-isolated organism was *salmonella* followed by *Shigella*, but according to the study, the maximum isolated organism was *E. Coli* followed by *salmonella*, *Shigella*, and so on.⁸ They had isolated some other organisms too not found by us during our study, like *Vibrio cholera*, *proteus* and more. Okada *et al.* (2020) reported that in Thailand, *E. Coli* was the most common isolated bacteria from stool samples of diarrhea patients, which was similar to our studies.⁹ Another study by Ballal M *et al.* (2014) also found *E. Coli* as the most common isolated bacteria from stool samples in India.¹⁰ They have isolated 46.3% *E. coli* from positive stool culture, followed

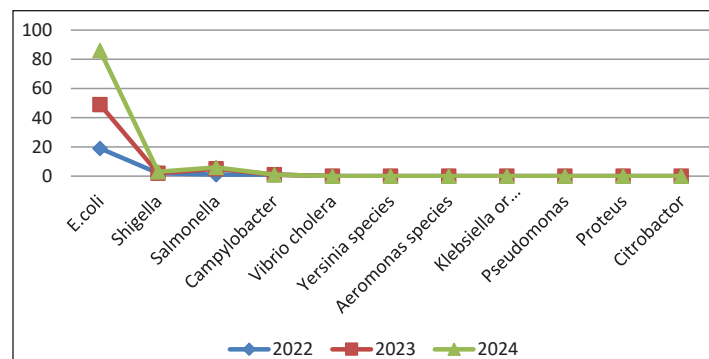


Figure 1: Year wise bacterial etiology.

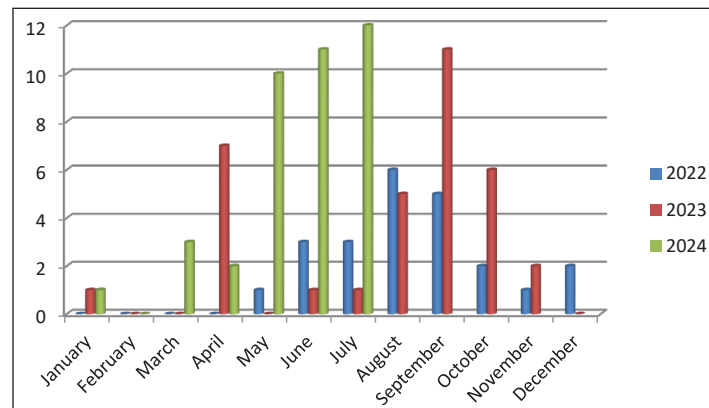


Figure 2: Month wise analysis of the positive cases.

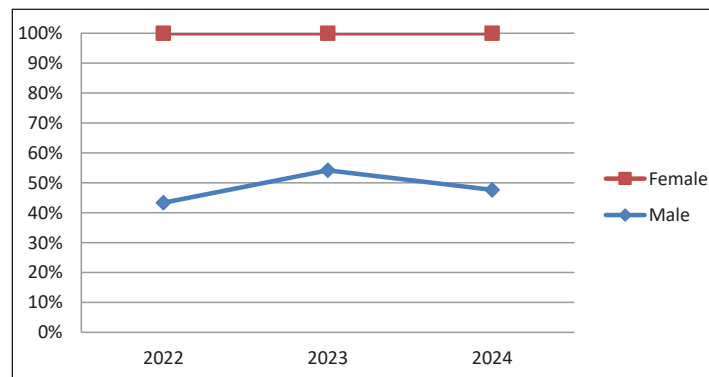


Figure 3: Acute Diarrheal Disease cases sex and year wise.

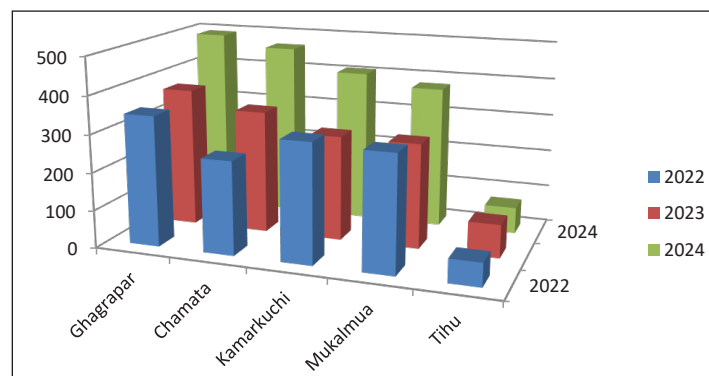


Figure 4: Block wise affected cases.

by *salmonella* and *Shigella*. In our study, it was 40.95% for *E. Coli*, followed by *Salmonella* and *Shigella*. Rathur *et al.* (2014) studied childhood diarrhea and found that *E. Coli* was 44.2%, *Shigella* 28.2%, *Salmonella* 13.6%, *Klebsiella* 7.8%, and *Campylobacter* 6.1%.¹¹ In our study, *Klebsiella* was not isolated, and the isolate highest after *E. Coli* was *salmonella*.

Moharana *et al.* (2019) studied childhood diarrhea and found maximum cases in the month of September; in our study, it was July. The study by Moharana *et al.* was held in Eastern Odisha, India.¹² The rainfall rate of Odisha in the month of September is 242 mm, as per different studies.¹³ Pokharel *et al.* (2009) isolated the highest bacteria from stool specimens of diarrhea cases in the month of July, followed by June.¹⁴ The study was done in Kathmandu, Nepal, which is similar to our studies. But this study included child groups below 12 years only, whereas we have included all age groups in our study. In a study from 2003 to 2013 by Sharma *et al.*, Assam also found maximum diarrhea cases during the rainy season as per their month wise table.¹⁵ The study was about *Vibrio cholerae* serotype isolation. This included Dhubri, Barpeta, Nalbari, Kamrup-Metro, Kamrup-Rural, Sonitpur, Nagaon, Golaghat, DimaHasao, Chachar, and Karbialong districts of Assam. Though the cases increased in the rainy season in our study too, no *Vibrio cholerae* were isolated in our study.

Different studies have already proved that water is one of the main causes of diarrhea or other similar diseases, though other factors are also equally responsible, like hygiene, awareness, living behavior, immunity, nutrition, age factors, and so on.^{16,17} Our study analyzed the diarrhea causing bacterial etiology and relation with flood, rain, or water. But diarrhea due to parasites, viruses, and more is also equally important.^{18,19}

CONCLUSION

Diarrhoea is a common burden for every district of Assam. Bacteria, viruses, parasites all may be the causing agents for this disease. Much more research is required to know all details, including control and treatment strategy. Health departments must get help from other departments to control the burden, like meteorology, irrigation, agriculture, Flood Control Board, media houses, district administration, food and supply, public health, and engineering. Public awareness might play a very important role to minimize the disease risk and transmission.

Authors' contributions

Each author has equal contribution.

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Ethical approval

The research/study is approved by the Institutional Ethics Committee at District Health Society, IDSP; Nalbari, number: IDSP/NLB/DPHL/SW/2022/13, dated 22nd December 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Case Report

Osteocartilaginous choristoma of palatine tonsil: A rare entity

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ABSTRACT

Choristoma is the presence of normal tissue in an abnormal anatomical location. The presence of mature cartilage in the tonsil represents a choristoma as it is not a normal constituent of the tonsil and is a very rare entity. More than 70% of lingual choristomas occur in females; the tongue is the most common site, accounting for 80% of the cases. Osseous choristoma of the tongue is a rather rare entity, with less than 100 cases reported in the literature. We hereby report an osteocartilaginous choristoma of the palatine tonsil in a 42-year-old male patient who presented with a sore throat and difficulty in swallowing, for which he underwent tonsillectomy. Choristoma was an incidental discovery. Histopathology features were consistent with chronic tonsillitis along with incidental occurrence of hyaline cartilage and bone. As choristoma is a benign tumor that usually does not require any further treatment after simple excision, therefore no further treatment was given. The patient is currently under a 2- year follow-up and does not show any signs of recurrence. This case creates awareness about this rare entity among pathologists and clinicians so that overzealous and unnecessary treatment is avoided.

Keywords: Choristoma, ectopic tissue, heterotopic tissue, Palatine tonsil, oral cavity

INTRODUCTION

The neck region is known for various embryological anomalies on account of its complex development.¹ Choristoma is a developmental anomaly of the second pharyngeal arch,² which refers to the presence of histologically normal tissue or cells at an abnormal location. Cartilaginous choristomas occur in young females and are presented as firm to hard, painless nodules reported in the head and neck region.¹

Osteocartilaginous choristoma, consisting both osseous and cartilaginous tissues, is extremely rare in the oral cavity with only 10 cases documented in the English literature. In the oral cavity, the dorsum of the tongue is the usual site among women in their fifth decade of life. Etiology remains uncertain.³ Osteo-cartilaginous choristoma is very rare in tonsils.⁴⁻⁶

Osteocartilaginous choristoma is a well-defined swelling containing both osseous and cartilaginous tissues⁴. In the oral cavity, it is extremely rare with only nine cases reported in the English-language literature. At this site, these lesions especially involve the dorsum of the tongue in women from the 5th decade of life⁴. Etiology remains uncertain⁵ and

histopathology is characterized by a mass of osseous and cartilaginous tissues⁴. Management is based on complete surgical resection.⁶ Osteocartilaginous choristoma is a well-defined swelling containing both osseous and cartilaginous tissues⁴. In the oral cavity, it is extremely rare with only nine cases reported in the English-language literature. At this site, these lesions especially involve the dorsum of the tongue in women from the 5th decade of life⁴. Etiology remains uncertain⁵ and histopathology is characterized by a mass of osseous and cartilaginous tissues⁴. Management is based on complete surgical resection⁶ Osteocartilaginous choristoma is a well-defined swelling containing both osseous and cartilaginous tissues⁴. In the oral cavity, it is extremely rare with only nine cases reported in the English-language

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literature. At this site, these lesions especially involve the dorsum of the tongue in women from the 5th decade of life⁴. Etiology remains uncertain⁵ and histopathology is characterized by a mass of osseous and cartilaginous tissues⁴. Management is based on complete surgical resection⁶

CASE REPORT

A 42-year-old male presented to the clinic with recurrent episodes of sore throat for the past 2 years, along with difficulty in swallowing and snoring for the past 1 month. There was no history of ill-fitting dentures or any other dental problem. On examination, bilateral tonsils were enlarged with firm to hard areas on palpation. A provisional diagnosis of chronic tonsillitis with tonsilloliths was made. The dental examination was within normal limits. The rest of the head and neck regions did not reveal any abnormality. Bilateral tonsillectomy was performed, and the specimen was sent for histopathological examination. Written consent was obtained from the patient.

We received specimens of bilateral tonsils measuring $2 \times 1 \times 0.5$ cm and $2 \times 1.5 \times 0.5$ cm. Both cut surfaces were gray-white with few chalky white areas [Figure 1]. Histopathological examination revealed lymphoid hyperplasia, fibrosis areas, and mature hyaline cartilage islands [Figures 2a], occasional focus of mature bone formation [Figure 2b] and high power



Figure 1: Gross photograph of cut surface of bilateral tonsils revealing gray white with few chalky white areas.

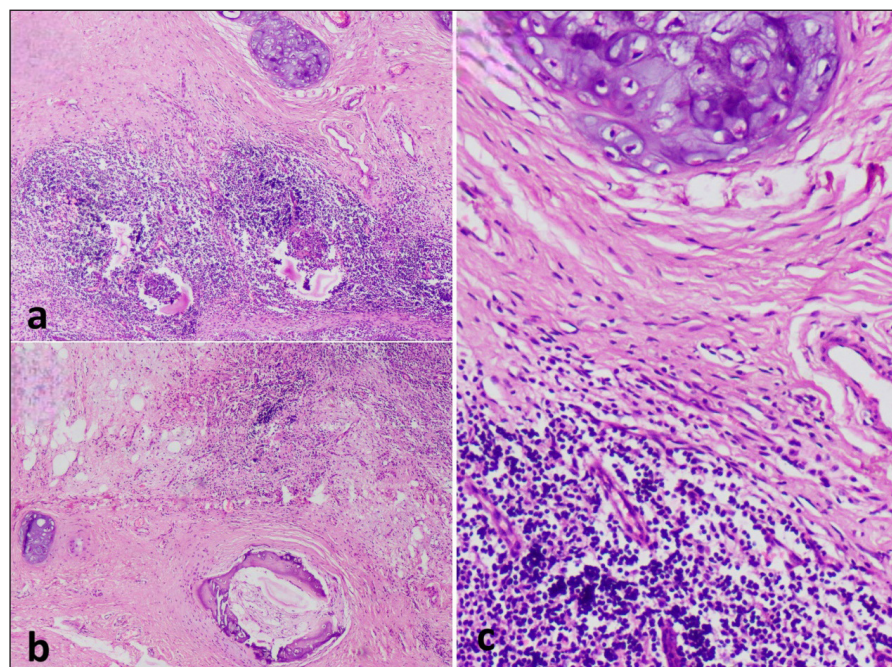


Figure 2: Microphotograph revealing (a) lymphoid hyperplasia, areas of fibrosis, and islands of mature hyaline cartilage (H&E; 40x); (b) occasional focus of mature bone formation (H&E; 40x) and (c) high power view of cartilage (H&E; 100x). H&E: Hematoxylin and eosin stain.

view of the cartilage [Figure 2c]. A diagnosis of osteocartilaginous choristoma of the tonsil was rendered. As choristoma is a benign tumor that usually does not require any further intervention or treatment after simple excision, and so no further treatment was given. The patient is currently under a 2-year follow-up, without any signs of recurrence.

DISCUSSION

Choristomas are benign lesions characterized by the presence of histologically normal tissue in abnormal locations due to developmental defects.¹ The age of diagnosis ranges from 10 to 80 years.⁷ Cartilaginous choristomas of the oral cavity are rare, and most of the choristomas are osseous with a predilection for the tongue followed by buccal mucosa and soft palate.^{4,8} Chondroid choristomas of the tongue mostly occur in females, while no sex predilection has been observed in palatine tonsil.⁷ Osseous choristoma of the tongue is a rather rare entity, with less than 100 cases reported in the literature. So far, very few cases of cartilaginous choristomas of the tonsils have been reported.

Usually, they are observed as incidental findings during histopathological examination of tonsillectomies performed

due to chronic tonsillitis. Erkilic *et al.* (2002) reported an incidence of 3% on tonsillectomy specimens.⁹ Sulhyan *et al.* (2016) in their study on tonsillar lesions found the incidence to be 2.84%.¹⁰ The present case is similar to the case by Pandey *et al.*² (2012), where patient presented with recurrent episodes of chronic tonsillitis and was diagnosed as choristoma later.

Several hypotheses have been proposed to explain the pathogenesis of choristoma. Haemel *et al.* (2008) concluded that it arises from mesenchymal progenitor cells having multilineage potential, which were able to differentiate into various mesenchymal cell types.¹¹ Lindholm *et al.* (1973) proposed that chemical or physical changes induced by chronic inflammatory processes could be responsible for the liberation of osteogenic substances, which stimulate heterotopic proliferation of cartilage.¹² The lateral part of the second pharyngeal arch leads to the development of tonsils. Partihiban *et al.* (2011) postulated that choristomas of the tonsil arise from embryological anomaly of the second pharyngeal arch, which leads to the occurrence of abnormal mesenchymal tissue in the tonsil.¹³

Table 1 depicts the spectrum of choristoma cases of the oral cavity over the last decade.

Table 1: Spectrum of choristoma cases of oral cavity over the last decade.					
Authors	No. of cases	Age	Gender	Site	Type
Goncalo <i>et al.</i> ¹⁴ (2024)	1	72	F	Tongue	Cartilaginous
Ali <i>et al.</i> ¹⁵ (2024)	1	30	M	Nasopharynx	Cartilaginous
Shamloo <i>et al.</i> ¹⁶ (2023)	1	51	F	Palate	Osseous
Pol <i>et al.</i> ¹⁷ (2022)	2	30	F	Soft palate	Osseous
		52	M	Gingiva	Osseous
Amaral <i>et al.</i> ¹⁸ (2022)	1	38		Tongue	Osteocartilaginous
Arimoto <i>et al.</i> ¹⁹ (2021)	1	11	F	Tongue	Osseous
Gautam <i>et al.</i> ²⁰ (2021)	1	38	F	Tonsil	Cartilaginous
Bairwa <i>et al.</i> ⁶ (2018)	1	11	M	Tonsil	Osteocartilaginous
Camara <i>et al.</i> ³ (2017)	1	59	F	Tongue	Osteocartilaginous
Yoshimura <i>et al.</i> ²¹ (2018)	1	7	M	tongue	Osseous
Qin <i>et al.</i> ²² (2014)	1	8	M	Tongue	Osteocartilaginous
Meram <i>et al.</i> ²³ (2017)	1	3 months	F	Skull	Osteocartilaginous

Cartilage choristoma needs to be differentiated from metaplasia. Metaplasia is characterized histologically by diffuse calcific deposits and scattered chondrocytes in various stages of maturation single or as foci, whereas only mature tissue is present in choristoma.⁴

Excision remains the mainstay of treatment. In view of high recurrence rates in certain extraoral cases, excision should involve the removal of perichondrium as it has the potential to develop new cartilage, if left behind.⁷

CONCLUSION

Choristomas although rare entity, are usually discovered incidentally and are of academic interest only. They may be confused with true neoplasms if large in size or tonsilloliths in case of osseous or chondro-osseous choristoma. Moreover, the pathologist must be aware of this entity to avoid misdiagnosis of a benign incidental finding as some neoplasm.

Authors' contributions

M.P, A.K: Idea and design; A.B, K.S: Data acquisition; S.D, A.K: Analysis; S.D, K.S: Interpretation of findings; A.B: Preparation of manuscript; M.P: Critical revision.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Case Report

Celiacomesenteric trunk – A not so common variation

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ABSTRACT

The Coeliac trunk is the first ventral branch of the abdominal aorta and is the artery of the foregut, which supplies the derivatives of the foregut i.e., oesophagus, stomach, liver, gallbladder, pancreas, and the second part of the duodenum, up to the level of the opening of the major duodenal papilla. The superior mesenteric artery is the next branch of the abdominal aorta, which arises most commonly at the level of the first lumbar vertebra and supplies embryonic derivatives of the midgut i.e., from the second part of the duodenum (below the level of major duodenal papilla) to the proximal two-thirds of the transverse colon. Sometimes coeliac trunk and superior mesenteric artery arise as a common celiacomesenteric trunk. The embryological basis of celiacomesenteric trunk is discussed in the current case report. Also, the clinical significance of celiacomesenteric trunk in various conditions is described. During complex interventional procedures, this type of variation must be looked at carefully in radiological images to reduce the chances of postoperative complications.

Keywords: Celiac trunk, Celiacomesenteric trunk, Foregut, Midgut, Superior mesenteric artery

INTRODUCTION

Coeliac trunk (CT) is the first branch of the descending aorta after its passage via diaphragm at the level of 12th thoracic vertebra and supply the derivatives of the foregut. Following its origin at the junction between T12 and L1 vertebrae, CT runs a quick course and gives three branches, i.e., the left gastric artery (LGA), common hepatic artery (CHA), and splenic artery (SA). CT supplies Gastro Intestinal Tract (GIT) from the oesophagus to second part of duodenum (up to the level of major duodenal papilla), apart from liver, gallbladder, and pancreas.¹

Superior mesenteric artery (SMA) is the next branch of abdominal aorta, given at the level of first the lumbar vertebra. SMA passes forwards and inferiorly after its origin, posterior to the body of pancreas, and anterior to uncinate procedure to enter the root of mesentery of small intestine and supplies embryonic derivatives of midgut i.e., from the second one part of the duodenum (below the level of major duodenal papilla) to proximal two-thirds of the transverse colon.¹

GIT is supplied by the arteries derived from the primitive dorsal aorta as four splanchnic roots which are connected through a longitudinal ventral anastomosis. During the development, following obliteration within the anastomosis

results in CT, SMA, and inferior mesenteric artery (IMA).² Incomplete obliteration of the anastomosis leads to variation in origin of CT, SMA, and IMA or their next branches.³ Information about variations in origin and course of these branches is very important to evade any injury or bleeding during any intra-abdominal surgery.

In the current case report, a common celiacomesenteric trunk (CMT) has been reported which was found in a female cadaver, where CT and SMA had common origin but normal course and branching pattern, thereafter.

CASE REPORT

During cadaveric dissection of the abdomen region of a female body for first years medical undergraduate (UG) students, a CMT was found, which originated from abdominal aorta at first lumbar vertebra level and then bifurcated into CT and SMA [Figure 1]. Further, these two arteries followed a typical course anatomically, had standard branching pattern and the lumen of both arteries was of almost same size [Figure 2].

DISCUSSION

Initially, the growing embryo is supplied by a longitudinally located pair of dorsal aortae. As the growth progresses,

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Figure 1: Showing orientation of arteries as observed in the cadaver 1 – Abdominal aorta, 2 – Superior mesenteric artery, 3 – Coeliac trunk, 4 – Common hepatic artery, 5 – Gastroduodenal artery, 6 – Proper hepatic artery, 7 – Splenic artery.

ventral splanchnic arteries (paired segmental branches to the digestive tube), dorsal somatic arteries (intersegmental branches to the body wall), lateral splanchnic arteries (paired segmental branches to the urogenital system) are given via each primitive dorsal aorta and progress caudally to the body stalk as umbilical arteries.

Distribution to the capillary plexus of the yolk sac is furnished by paired ventral splanchnic arteries. On fusion of the dorsal aortae, the pair of ventral arteries merge to shape unpaired trunks which supply the primitive digestive tube – linked

dorsally and ventrally by longitudinal anastomotic channels (dorsal and ventral splanchnic anastomosis). This anastomosis reduces the ventral splanchnic trunk to three major arteries: CT, SMA, and IMA. These arteries migrate from their initial place of origin as the viscera descend downwards in the following manner:

- a. CT from C7 to T12
- b. SMA from T12 to L1
- c. IMA from T12 to L3

Tandler described origin of visceral arteries from the primitive dorsal abdominal aorta as four splanchnic roots (LGA, CHA, SA, and SMA) which are connected through a longitudinal ventral anastomosis.² The anastomosis is commonly obliterated above SMA, during the development, resulting in continuation of visceral arteries as CT, its three visceral branches – SA, LGA, CHA, and SMA. Further, SMA provides – the inferior pancreaticoduodenal artery, right colic artery, middle colic artery, ileocolic artery, and jejunal and ileal branches [Figure 3].

The current case report describes presence of a CMT on the anterior surface of the aorta due to incomplete obliteration of the longitudinal ventral anastomosis and giving CT and SMA. The prevalence of variation was found to be 1%–2.7%.³ Similar types of variation had been mentioned in the past.^{4,5} Rusu *et al.* (2021) have described the frequencies of occurrences of the different vertebral level origins of the CT and SMA.⁶ Vidya CS *et al.* (2021) have discussed the anatomical variations in the course of CT and its branching pattern with subsequent surgical implications in an urban population.⁷ Panagouli E *et al.* (2013) have reported the distinctive kinds of anatomical

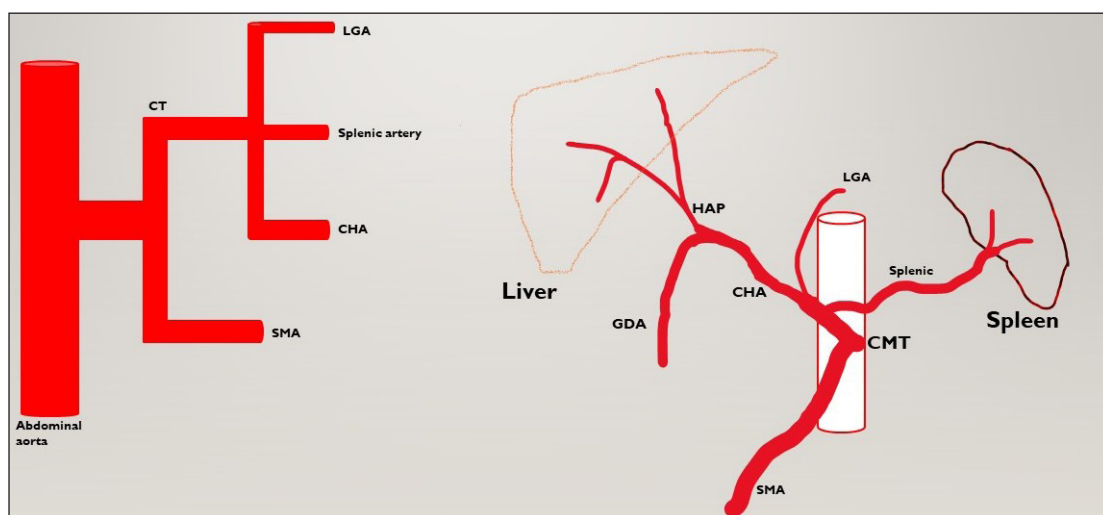


Figure 2: Depicting the common origin of coeliacomesenteric trunk. CT: Coeliac trunk, LGA: Left gastric artery, CHA: Common hepatic artery, SMA: Superior mesenteric artery, GDA: Gastroduodenal artery, HAP: Hepatic artery proper, CMT: celiacomesenteric trunk

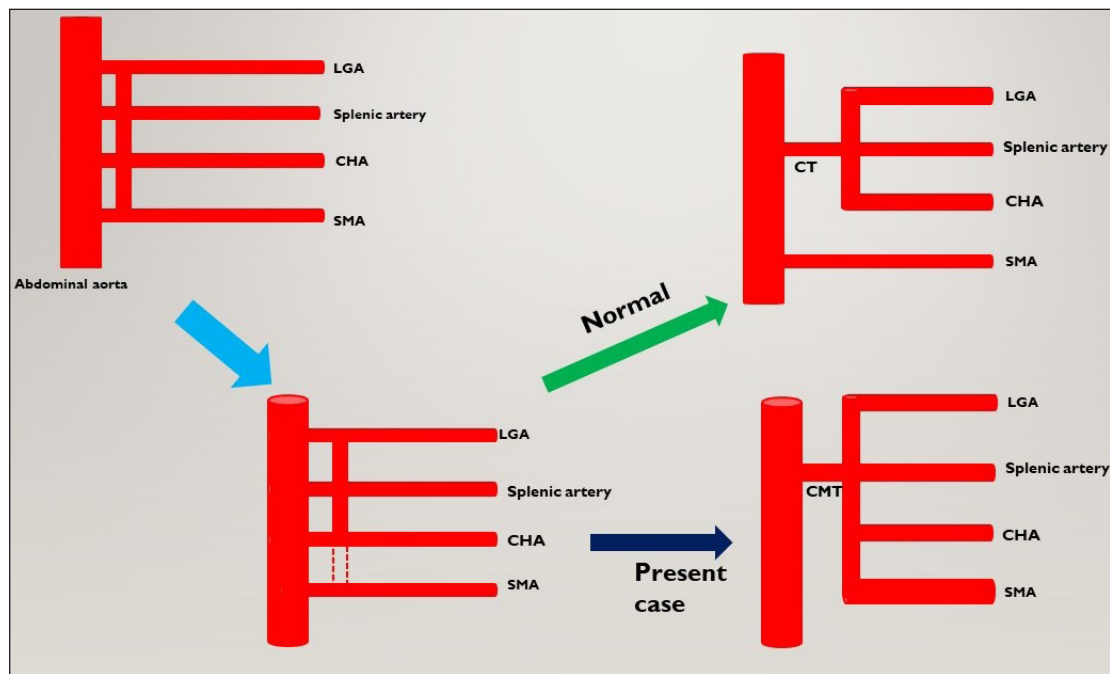


Figure 3: Depicting short-type coeliacomesenteric trunk. CT: Coeliac trunk, LGA: Left gastric artery, CHA: Common hepatic artery, SMA: Superior mesenteric artery, GDA: Gastroduodenal artery, HAP: Hepatic artery proper, CMT: celiacomesenteric trunk

variations of CT along with the probable effect of genetic factors and the incidence which was found to be 0.76%. Also, as per Panagouli's Classification, CMT belonged to type IV of Celiac Trunk.⁸ Wang, Y. *et al.* (2010) described a case of saccular aneurysm at the bifurcation of a CMT using celiac digital subtraction angiography (DSA), which was surgically removed to avoid the risk of a rupture of the aneurysm.⁹ These various types of variations were accidentally found during aneurysms rupture, sometimes, presented with lower limb ischemia and were treated by aortic bypass surgeries or reimplantation, and transplantations.¹⁰

Nutcracker syndrome is a rare clinical scenario due to entrapment of the left renal vein between the aorta and SMA, mostly due to presence of CMT or an unusual origin of SMA from the aorta resulting in renal venous hypertension. The signs and symptoms of Nutcracker syndrome range from asymptomatic haematuria to excessive pelvic congestion. Al-Zoubi *et al.* (2017) have reported the association between CMT and Nutcracker syndrome.¹¹ Peterson J *et al.*, (2017) described presence of CMT, associated with left renal vein compression manifesting as dilatation and engorgement, thus indicating association between CMT and Nutcracker syndrome.¹² A rare variety of CMT along with retro-aortic left renal vein was reported in a young male cadaver in 2018, which had features suggestive of posterior nutcracker syndrome.¹³ Nutcracker syndrome has comparable pathophysiology with SMA syndrome which is due to reduced angle between the

origin of SMA and the abdominal aorta leading to reduction in lumen of the third part of duodenum and culminating in bowel obstruction. Thus, coexistent SMA and Nutcracker syndrome have been reported in past, but, isolated Nutcracker syndrome causing narrowing or compression of the third part of duodenum have not been reported.¹⁴⁻¹⁷

A new classification for the CMT was proposed by Tang W *et al.* (2019) using multi-detector computed tomography (MDCT) angiography to identify types and prevalence in a large study population.¹⁸ A newborn was found to have CMT along with a massive omphalocele but the association among the two could not be established. No case of CMT has been reported in association with malrotation of intestine.¹⁹

CONCLUSION

Identification of the possible variations of the arteries supplying the foregut and midgut along with radiological studies helps to reduce the risk of surgical iatrogenic injuries. Careful observation of these variations in radiological images should be of utmost importance prior to complex surgical interventional procedures to reduce the risks of postoperative complications. Arterial variation should be correctly identified along with the dimensions before surgeries such as transplantation, tumor resection or chemoembolization of gastrointestinal malignancy, and abdominal laparoscopic surgeries. Hence, the variation found in this case report is of surgical and therapeutic significance.

Authors' contributions

RP: Conceptualization; AN, TA: First draft; RP, MA, AK: Critical review.

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Institutional Review Board approval is not required.

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Patient's consent not required as there are no patients in this study.

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There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

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Perspective

Kota suicides for National Eligibility cum Entrance Test—A problem demanding urgent attention

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Student suicide has become an issue so big that even the Prime Minister had to intervene and take matter into his own hands and conduct *Pariksha pe charcha*. What is going on here? Why are the children so tense? Where is that happy childhood gone? Where is that adventurous and fun-filled adolescence? Does anyone know that in 2019, as many as 7% of all deaths by suicide were in students? According to the National Crime Records Bureau (NCRB), over 13,089 students died by suicide in 2021 and the number of students who committed suicide in India rose by 70% between 2011 and 2021!¹ Is this not a matter of concern?

The big change that has come about in our education system since we were in school is the undermining of the regular schooling system and the extraordinary importance that is being given to the coaching classes today. Schooling is a very important part of our lives, not so much because of the new knowledge it imparts but because of everything else that it offers to shape our personality and turn us from children into confident young adults. Education is what remains in us after we have forgotten everything that we had learnt inside classrooms. Now, if one takes a child out of school and puts him/her in a coaching class in Kota, far away from home, the intentions might be noble, and the child might happily agree with the decision, but we have not let his/her brain attain that level of maturity which the new life with a grueling schedule in an alien city without parental support demands. That is the nidus from where the problem starts.

These coaching classes are not cheap. Middle-class families often take bank loans—mortgaging their house or their agricultural land—and the child knows it. The coaching is intense and fiercely competitive. After some time, if the child finds the going tough and falls behind the batch toppers, his/

her anxiety level starts rising. This is an unfamiliar situation for these children. Throughout, they have been toppers in their school and even their district. They are used to success, but that success came when they were in the care of their loving parents. Here, the children are fighting a lone battle for scholastic excellence to qualify for a competitive examination and not a simple qualifying examination. A competitive examination in which only 2% get selected! Or, in other words, 98% will not be selected, will not be able to pursue their dreams, and will not be able to live up to their parents' expectations! Imagine the state of mind of these children; they are not able to keep up with the toppers and they cannot go back home! Is it in any way justifiable to put these children under so much stress that they start thinking of ending their lives?

Every child is precious. The lost child may not have qualified the Joint Entrance Exam (JEE) and become a Visheshwarraiya, may not have passed the National Eligibility cum Entrance Test (NEET) and become Christian Bernard, but he could have been the next Raja Ravi Verma or Jamini Roy, he could have become the next Uttam Kumar or Amitabh Bachchan, he could have matured into the next Shakespeare or Munshi Premchand, he could have become the next Sachin Tendulkar or Kapil Dev! How can the nation afford to lose even a single precious gem from its glorious future necklace?

Suicide is a disease

Suicide is a disease, and one doesn't commit suicide on the spur of the moment. The tension gradually builds up, the child shows definite signs:

- He/she tries to reach out to the parents, gives them hints that things are getting more and more difficult.

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- He/she becomes less attentive in class and then starts skipping classes.
- He/she starts giving away books and notes to friends with whom he/she is in competition.
- He/she starts withdrawing from friends and starts studying in solitude.

These are early signs, and parents should be able to pick up these signs; they should go to Kota to spend some quality time with these children, reassuring them, and encouraging them to do their best without an iota of worry because failing in the upcoming competitive exam will not make them useless. If there are 3000 seats for which 1,500,000 students are competing, then how can the guy in 3000th position be smart and the one in 3001 position be useless? Not being able to compete should not be interpreted as a failure. All it means is that this is not the child's chosen destiny; this is not his/her true field of interest. He/she is going to excel in some other field.

Suicide Cluster

The situation in the coaching institutes of Kota needs our urgent attention. Eighteen students committed suicide in 2022, and in 2023 till the end of August, 24 students committed suicides. The US Center for Disease Control and Prevention defines a group of suicides or, suicide attempts or self-harm events that occur close together in time and space than normally expected in a given community as "Suicide Cluster." Kota coaching classes should surely qualify to be labeled as a suicide cluster. One person's suicide due to circumstances and the publicity around it triggers the risk of suicide ideation, suicide attempt, and death by suicide of others; this is surely a contagion. This contagion affects the most immature, the most vulnerable, and the most hyper-ambitious, leading to suicide clusters. Failure in examination was listed as the cause of suicide in 1,673 cases in 2021. Failure in examination was the reported reason for suicide in 1.2% of students, and suicide clusters have been reported in Kota, Thrissur, and Chennai as these cities are famous for their coaching institutes targeting competitive professional examinations.²

So what can be done about this?

This is a serious problem and addressing it requires a multipronged approach. There are specific things which parents, coaching teachers, coaching institutes, policy-makers, job recruiters, and society should be doing to put a stop to this menace.

Parents

The parents should educate themselves. The world changed a long while back, and medicine and engineering

are not the only two professions for earning a decent livelihood. The fact is that doctors in India do not earn much, and some can't even afford to retire. There are far fewer fabulously rich doctors with ranches and private planes than the number of superstars in Bollywood. Engineers are so many that they have either branched out into sales and management or are unemployed. But there are opportunities galore for your children, as many more industries are prospering and flourishing in India like sports, business and finance, real estate, advertisement, entertainment, research, education, biotechnology, and travel and tourism. There is enormous scope for attaining dizzying heights of success in all these spheres, and most certainly earn a decent living and lead a respectable life. So please stop imposing our dreams on the children. They surely deserve better parenting. The authoritative parenting style, which fosters a supportive and communicative environment, may help students handle the stresses of competitive exams more effectively. In contrast, authoritarian or neglectful parenting styles may contribute to higher levels of stress and anxiety, potentially leading to suicidal ideation in highly pressured environments like Kota's coaching centers.³

Once a child is admitted in a coaching center in Kota, the responsible parents should remain in close touch and do a video call at least once a day. It's advised that the parents talk to them less and listen to them more. It's important to pick up the first and the faintest hint of concern or anguish in their voice and leave everything and reach out to them. If the child wants to quit, it is important to respect their decision and not to make them feel guilty about it. They have tried their best, and now they want to go home and try something else; so encourage them at every step.

Coaching Teachers

The teachers at the coaching center should remember that their role doesn't end in the coaching class. They are actually a foster parent for the child, and so they identify the signs of concern in a vulnerable child and have a heart-to-heart conversation with them. They should also decide whether the parents should be informed and do so well in time. They will soon come to know the child and perhaps be the first person to realize whether the child has the aptitude for the chosen field. They should give unbiased feedback to the parents and suggest other alternative career options. They should do the psychological autopsy where the student's state of mind and stream of thoughts are picked up ahead of the tragedy. The "Gatekeeper Training Program" should be initiated where teachers are trained to identify the students at risk by teaching them the signs of the suicidal tendency.

Coaching Centers

Kota is now home to a INR 60 billion coaching industry. The fact that this coaching is a business enterprise is perfectly understandable, but business should be conducted fairly and not “at any cost.” They are competing with other coaching centers in attracting children from all over the country with glossy advertisements, attractive social media pop-ups, and enticing phone calls all that is acceptable. But along with weaving the dreams of a golden future, which even they know is there for only 2% of their students, have they thought what will happen to the remaining 98%? Are they offering them other bail-out career options?

Within two months, they are in a position to identify a small subgroup of excellent performers, and these centers put them in a STAR batch and put all their energies in teaching this group how to crack the coming competitive examination. But what is happening with the mediocre and the tailenders? They should put in extra effort with the mediocre students so that they also could have an equal chance of going through and achieve a level playing field to score. And, even more importantly, these coaching centers should be telling the parents of the tailenders that they are wasting their time in this field and they should seek different pastures. Encouraging the meritorious with scholarships is good, but unnecessarily fleecing the parents of the tailenders, and wasting the parent's money and the child's time can surely not be honorable.⁴

Policy-makers

Our people in the Department of Education must think why is it that only a bunch of Indian Institutes of Technology (IITs), Indian Institutes of Management (IIMs), and medical colleges in the country are considered premier institutes, worthy of aspiration of so many students? Why are other educational institutions not equally good? What is being done to improve their standard and their reputation? Why are overseas educational institutes of excellence not opening campuses in India? Post liberalization in 1991, we opened our automobile sector and the inefficient perished, but the industry flourished, and Indian companies are today purchasing even overseas automobile companies. When will the education sector see a similar liberalization? Let the mediocre institutions perish and let the best prosper.⁵

Job recruiters

We always wonder why a company would need a B.Tech (Civil/Mechanical Engineering) and MBA to sell medicines, hire people for a call center, or plan holidays in a travel agency. How is her/his civil or mechanical engineering degree being used? If the corporates go for recruitment to only engineering

and management institutes even for jobs that do not require the skills taught there, then who will recruit the students passing out of degree colleges and universities? Surely they are not second-class citizens, but these job recruiters are making every effort to segregate society, and that too quite unnecessarily. This smart B.Tech, MBAs will skip from job to job for their career progress, which they should, but the institutions hiring them will suffer.

Students

The students should accept that life is a struggle. Qualifying and competitive examinations are two different animals: the former is docile, domestic, and a pet, the latter is ferocious, wild, and dangerous. One may not be a good lion trainer, but one can surely be an excellent wildlife conservationist. Not being among the 1–2% of the students who cracked NEET or JEE does not reduce the worth of students.

Failure, disappointment, and unfairness are all stepping stones of success. Not qualifying in NEET is certainly not time wasted or dreams shattered. It is just a nudge—telling the students to continue working to the best of their ability, but now in a different direction. This failure will make them battle hard in the future. The hard work they put in for the lost attempt in one career will prepare them better for an alternate career. In life, one must have a plan B and a plan C because the success of plan A is not guaranteed. The bottom line is that being an excellent car salesman is any day better than being a lousy surgeon! A recent study concluded that academic stress among medical students and residents and marital discord among physicians were the most noticeable reasons for suicide. The reported risk factors for suicide were mental health problems, negative or traumatic familiar issues, academic stress, social/lifestyle factors, violence, economic distress, and relationship factor.⁶ In a cross-sectional study, stress levels were found to be more prevalent in female students, 12th class students, those belonging to urban and middle-class backgrounds, and those whose stream was chosen by their parents.⁷

Last, it's important to remember that life is precious. Every student in a coaching center may have dreams, but they are also the dreams of many. If one has hit rock bottom today, then look at the brighter side, they can only go up now. So it's important to not abandon hope and not to end up doing anything stupid.

CONCLUSION

Suicide is not about a child losing hope and quitting life. It is not just loss of precious life, but the loss of hopes and dreams of a family and loss of the unknown and unexplored

talent that could have added infinite value to our society, to our nation, and to our world. It is time we wake up to this challenge and confront it head on.

Authors' contributions

KB and NB: Study conception and design; SB and NB: Data collection; KB, NB AND SB: Analysis and interpretation; KB, NB AND SB: Manuscript preparation.

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Perspective

Medical education in vernacular language in India: Potential advantages, challenges, and a way forward

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INTRODUCTION

The landscape of medical education is evolving, with a growing recognition of the need for inclusivity and accessibility. One significant aspect gaining attention is the prospect of delivering medical courses in vernacular languages.¹ This shift may hold the promise of addressing barriers to education and have the potential to produce a more culturally competent healthcare workforce.² Many developed countries like Germany, Japan, Korea, Norway, and Sweden are having their medical courses in the vernacular language.³ However, Indian medical education is in English. Although teachers may deliver the lectures and instruction in a combination of English with local languages, the written expression is always in English.⁴

India does not have a national language, but the official language are Hindi and English. There are a total of 22 scheduled languages, including Hindi.⁵ Hence, adding English to it makes the list 23. Indian states and union territories, along with the most spoken scheduled languages, are shown in Figure 1. Currently, many states are taking steps to implement medical education in vernacular language; the first step being taken is publishing books in the regional language. As this method is in a nascent phase, we, in this article, enlist potential advantages and challenges in its implementation.

ADVANTAGES

Implementing medical education in vernacular languages in India can offer several advantages. Potential advantages are enlisted in Table 1 and described briefly below.^{6,7}

Delivering medical education in vernacular languages enhances accessibility for a wider segment of students.

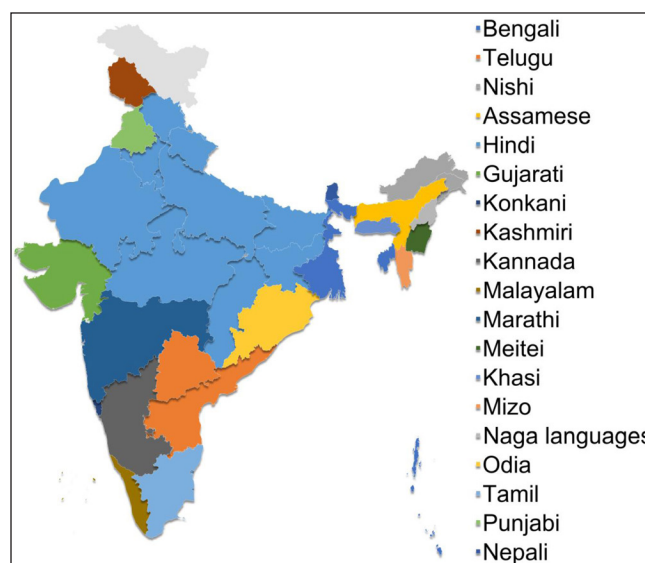


Figure 1: Indian states and union territories along with the most spoken scheduled languages. States are arranged alphabetically and the most spoken language is shown. Source: <https://censusindia.gov.in/nada/index.php/catalog/42561> (based on 2011 census)

Coming from a vernacular language background, many students face challenges when exposed to the English medical curriculum. For them, medical education in their vernacular language could break down linguistic barriers.⁸

Medical subjects can be highly complex, and language proficiency plays a vital role in comprehension. When the courses are offered in vernacular languages, students may grasp complex concepts more easily. This would lead to a stronger foundation in medical knowledge among students.⁹

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Table 1: Potential advantages and challenges in implementation of medical education in vernacular language in India

Advantages	Challenges
Increased accessibility	Standardization issues
Enhanced comprehension	Global recognition
Retention and academic performance	Limited educational resources
Improved communication skills	Faculty shortage
Community engagement	Technological challenges
National language preservation	Professional communication barriers
	Examination and licensing challenges
	Career mobility constraints

Students may experience improved retention and academic performance when studying in their mother tongue.¹⁰ This can lead to a higher success rate in medical examinations and better prepared healthcare professionals entering the workforce.

Medical graduates educated in their native language may exhibit stronger communication skills, both in interacting with patients and collaborating with fellow healthcare professionals.¹¹ This can result in more effective doctor-patient relationships and interdisciplinary teamwork. This will also help in engaging with the community and reduce the gap between the health professionals and the society.

Encouraging medical education in vernacular languages also plays a role in preserving and promoting linguistic diversity. It acknowledges the importance of regional languages in the broader context of the country's cultural heritage.

While these advantages are significant, it's essential to address the associated challenges to ensure that the implementation of vernacular language medical education is well rounded and meets the standards required for producing competent healthcare professionals.

DISADVANTAGES

Potential disadvantages at this moment are described briefly below.^{12,13}

Translating complex medical terminology into vernacular languages may lead to inconsistencies and challenges in maintaining standardized content.¹⁴ Ensuring that the curriculum aligns with national and international standards becomes more complex.

Medical professionals often need to communicate and collaborate on a global scale. Graduates of vernacular language

medical programs may face challenges in international contexts where English is the predominant language. This can potentially affect global recognition of their qualifications.¹⁵

Developing high-quality educational resources, including textbooks, research materials, and reference materials, in vernacular languages can be resource-intensive. This may result in a shortage of comprehensive and up-to-date materials, affecting the overall quality of education.¹⁶

Finding qualified faculty proficient in both medical knowledge and vernacular languages can be challenging as their training was in English and they have been in the profession for a long time. This shortage, along with the current shortage of medical teachers, may compromise the quality of education.¹⁷

Medical education often relies on advanced technology, digital platforms, and multimedia resources. The majority of the digital resources are not available in the Indian language. Adapting and translating these resources into vernacular languages may pose technological challenges and require additional investments in infrastructure.¹⁸

Medical graduates of vernacular language medical programs may face challenges in professional communication. At any international conferences, they may face challenges in presenting their work. Publications in journals in English may be another problem that may limit knowledge dissemination.¹⁹ Hence, this could impact the Indian presence in the global healthcare community.

Designing examinations and licensing procedures in vernacular languages that meet national and international standards can be complex. When India is preparing for a common exit test for graduation, it would be challenging to design those in regional languages.

Graduates from vernacular language medical programs may face limitations in career mobility, especially if they choose to practice in regions where a different language is predominant [Figure 2]. This could affect their ability to seamlessly integrate into healthcare systems outside their linguistic region.

Addressing these disadvantages requires a thoughtful and comprehensive approach to curriculum development, faculty training, resource allocation, and recognition of qualifications at a national and international level. Balancing linguistic inclusivity with global standards is crucial for the success of vernacular language medical education in India.

A WAY FORWARD

Mitigating the challenges associated with implementing medical education in vernacular languages in India requires a multifaceted and strategic approach. One key aspect is the standardization and development of curricula. National guidelines should be established to guide the translation



Figure 2: A girl's confusion about utility of vernacular medical education in India. Source: Part of the image was generated by artificial intelligence—Microsoft Image Creator from Designer on January 22, 2024, with authors' text input.

and standardization of medical terminology in vernacular languages. Collaborations between medical experts, linguists, and educators are essential for the creation of comprehensive and standardized vernacular language medical curricula. Additionally, regular updates to educational materials should be prioritized to ensure alignment with the latest advancements in medical knowledge.

Investing in educational resources is paramount for the success of vernacular language medical education. Adequate resources should be allocated for the development of high-quality textbooks,²⁰ reference materials, and multimedia resources in vernacular languages. Establishing partnerships with publishers, educational technology companies, and research institutions can provide valuable support for the creation of vernacular language medical resources.

Addressing the challenge of faculty proficiency involves the implementation of training programs. Faculty members should undergo training to enhance their proficiency in both medical knowledge and vernacular languages. Collaborative efforts between medical professionals and linguists can ensure the effective design of course content.

Addressing language-related challenges in examinations and licensing requires thoughtful adaptations. Examination and licensing procedures should assess competency in medical knowledge rather than relying solely on language proficiency. Collaboration with licensing bodies is necessary to ensure the recognition of vernacular language medical degrees at

both national and international levels, thereby facilitating smoother career transitions for graduates.

Promoting career development and mobility for healthcare professionals educated in vernacular languages involves offering language-specific continuing education opportunities. Policies should be developed to recognize the qualifications and skills of healthcare professionals across linguistic regions. They should have the opportunity to continue education in post graduation and higher level.

Finally, global collaboration and recognition are imperative for the success of vernacular language medical education on a broader scale. Advocacy efforts should be directed toward gaining international recognition of vernacular language medical degrees through collaborations with global accreditation bodies.

CONCLUSION

The implementation of medical education in vernacular languages in India presents a transformative opportunity with significant advantages and challenges. The journey toward vernacular language medical education requires a comprehensive and collaborative approach. Standardizing curricula, enhancing faculty proficiency, investing in educational resources, and integrating technology are vital components of success. Global recognition and adaptation in examination and licensing procedures are key considerations to ensure graduates' competitiveness on an international stage.

Authors' contributions

HM: Concept and design, literature search, drafting manuscript; SM: concept, literature search, editing manuscript.

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Brief Report

Single nucleotide polymorphism of IGF-1R (rs2229765) in acne and/or its severity

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ABSTRACT

Acne vulgaris is a common inflammatory disease of pilosebaceous glands diagnosed by dermatologists in teenagers. During puberty, a peak in the levels of hormones (growth factors and its terminal mediator insulin-like growth factor-1 (IGF-1)) is observed that plays a vital role in acne pathogenesis. IGF-1 and its polymorphism are known to positively correlate with acne and/or its severity. However, the role of polymorphism of IGF-1 receptor (IGF-1R) in acne and/or its severity has not yet been elucidated. Therefore, the study aimed to assess the association of IGF-1R polymorphism with the occurrence of acne and its severity. IGF-1R polymorphism was analyzed in acne patients (n = 100) and controls (n = 100) by the restriction fragment length polymorphism. IGF-1R polymorphism was found to be evenly distributed among the controls and patients. Although IGF-1 polymorphism positively correlates with acne and/or its severity, the polymorphism of its receptor IGF-1R was not significantly associated with acne. Furthermore, no significant association was observed between IGF-1R polymorphism and IGF-1R expression at messenger ribonucleic acid (mRNA) and protein level. A similar study with a larger study populations may be planned to validate or refute the observed findings.

Keywords: Acne, genotype, IGF-1 receptor (IGF-1R), Insulin like growth factor -1 (IGF-1), single nucleotide polymorphism

INTRODUCTION

Acne vulgaris is a common inflammatory skin disease among adolescents.¹ It is associated with elevated insulin-like growth factor-1 (IGF-1) level that exerts a wide range of biological effects¹ via activation of its tyrosine kinase receptor (IGF-1R).² IGF-1 level and its polymorphism positively correlate with acne and/or its severity.³ Studies in various carcinomas and autoimmune diseases have shown an important role of single nucleotide polymorphism (SNP) of IGF-1R (rs2229765).⁴ The role of IGF-1 in acne pathogenesis has been suggested by various studies, but the role of IGF-1R polymorphism in acne and/or its severity is still not established. In this study, we tried to assess whether an association exists between IGF-1R polymorphism and occurrence of acne or its severity.⁴

MATERIAL AND METHODS

The case-control study was conducted after approval from the Ethics Committee (Ref no. NK/2606/Study/116 dated

10.03.2016). Written informed consent was obtained from all the recruited patients and controls. Clinically confirmed patients with acne vulgaris (n = 100) were recruited after proper examination by an experienced dermatologist in daylight. An equal number of age and gender matched controls (n = 100), patients attending our outpatient department for another disease and not having acne, were recruited.

To study the polymorphism of IGF-1R, 2 ml venous blood sample was collected under aseptic precautions from all study participants in ethylenediaminetetraacetic acid (EDTA) vial for deoxyribonucleic acid (DNA) isolation using NucleoSpin® Blood DNA kits (Macherey-Nagel, Germany, REF 740951.250). The isolated DNA was amplified and digested overnight at 37°C by 1U MnII restriction enzyme (Thermo Scientific; Cat no-ER1071). Polyacrylamide gel electrophoresis (15%) was used to visualize the digested products on the Gel DOC System (Alpha Imager, USA) [Supplementary Figure 1].

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For expression studies, two biopsies (2 mm) from any two facial acne lesions of acne patients ($n = 100$) were taken under local anesthesia. One of the biopsy samples was used to study the expression of IGF-1R at gene level and the other one was used to study the expression of IGF-1R at protein level. From healthy controls ($n = 20$), one facial skin biopsy was taken under local anesthesia to study the gene expression of IGF-1R. For gene expression studies, ribonucleic acid (RNA) was isolated by TRIzol (Thermo Invitrogen, Cat no. 15596026) and converted to complementary DNA (cDNA) (Verso cDNA synthesis kit by Thermo Scientific; Cat no. #AB-1453/A) followed by Real Time-Polymerase chain reaction (RT-PCR) (Thermo Scientific; Cat no-F-416X) using SYBR green. Protein expression was analyzed by immunohistochemistry using a primary antibody against IGF-1R in formalin-fixed sample (Biorad, Cat no. MCA2344) [Supplementary Figure 2].

Statistical tests were carried out using SPSS version 16.

RESULTS

The mean age of controls and cases were 24.24 ± 4.8 and 23.09 ± 5.8 years, respectively. The genotypic distribution of IGF-1R polymorphism in controls and cases was nearly the same, that is, 16.7% of controls and 16.3 % of cases exhibited homozygous AA genotype; 52.2% of controls and 57% of cases had homozygous GG genotype; and 26.7% and 31.1% controls and cases had heterozygous GA genotype respectively [Supplementary Figure 3]. The association between the genotypes and acne or its severity was analyzed using the Chi-square test. It was observed that none of the genotypes were associated with acne (likelihood ratio 0.476, $p = 0.788$) and/or its severity ($p = 0.965$). The mRNA expression of IGF-1R was found to be significantly decreased ($p = 0.0418$) in cases (0.46 ± 0.82 , 95% CI 0.25–0.67) as compared to controls (1.52 ± 2.11 , 95% CI 0.53 – 2.57) [Figure 1]. At the protein level, 66.6% of the acne cases showed IGF-1R positivity of grade 2+ and 3+. However, the effect of polymorphism on the expression of IGF-1R at the mRNA level (spearman correlation, $r = 0.135$, $p = 0.25$) or protein level (spearman correlation, $r = 0.17$, $p = 0.11$) in acne patients was not found to be significantly correlated.

DISCUSSION

IGF-1 interaction with IGF-1R initiates a downstream cascade that leads to the regulation of genes/factors required in acne pathogenesis.^{1,2} All three genotypes (homozygous AA and GG and heterozygous AG) were equally distributed between controls and cases, suggesting that IGF-1R polymorphism is not associated with acne or its severity. However, discrepancy observed at mRNA and protein levels suggests that transcript

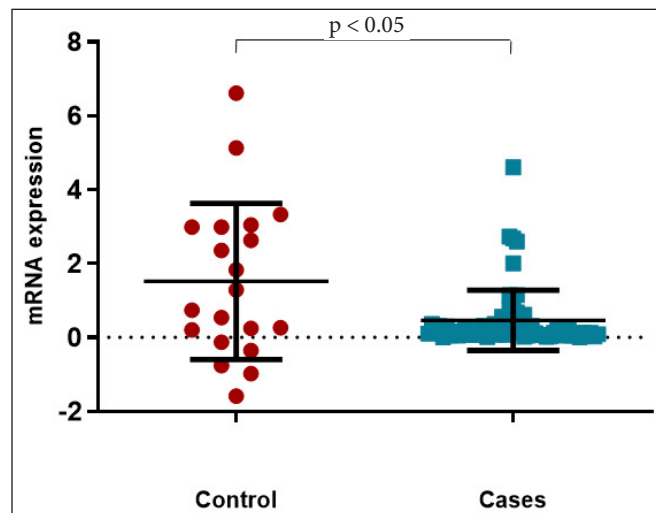


Figure 1: IGF-1R expression: Dot plot representing mRNA expression of IGF-1R in controls and cases. (Each red dot and blue box respectively represents individual healthy controls and acne patients recruited in the study.)

levels alone might not be sufficient to determine the protein expression.⁵ Furthermore, IGF-1R expression at mRNA and protein level was not associated with its polymorphism. Overall, it was inferred that IGF-1R polymorphism was not associated with acne and/or its severity, and IGF-1R genotype did not have an effect on the expression of IGF-1R at mRNA or tissue level. A formal sample size calculation was not done because of absence of data to do so. Sample size was limited by funds available. Results of this pilot study do not project a signal toward an association between IGF-1R polymorphism and acne or its severity. A similar study may be planned in a larger study population to validate or refute the observed findings.

CONCLUSION

IGF-1 and its polymorphism is known to play an important role in pathogenesis of acne and/or determines its severity. Binding of IGF-1 to its receptor (IGF-1R) initiates cascade of events that regulate genes/factors affecting acne pathogenesis. In our study, we observed that single nucleotide polymorphism (SNP) of IGF-1R was evenly distributed in controls and cases and was not associated with acne or its severity. Furthermore, no effect of IGF-1R polymorphism was observed at genetic and protein level. These findings suggest that IGF-1R polymorphism does not play any significant role in acne and/or its severity.

Authors' contributions

PK: Data collection, analysis and interpretation, manuscript drafting; AKA: Recruitment of patients and healthy controls;

NG: Sample collection; RK, SB and GD: Data collection; DD: Conceptualization, funding acquisition, patient recruitment, supervision, manuscript editing.

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Ethical approval

The research/study approved by the Review Board at Postgraduate Institute of Medical Education and Research, number NK/2606/Study/116, dated 10th March 2016.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Letter to Editor

Iatrogenic cushing's syndrome following potent topical steroid application in an infant

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Dear Editor,

Iatrogenic Cushing syndrome in children is an expected side effect of systemic corticosteroid use for autoimmune disorders. However, misuse and overuse of inhaled or topically applied steroid cream in young children may be rarely associated with systemic absorption, leading to hypothalamic-pituitary-adrenal (HPA) axis dysfunction and complications like Cushing syndrome.^{1,2}

A 9-month-old male child was brought with the generalized scaly lesions of 3 months duration. The infant was of 3rd order, born to non-consanguineous parents by normal vaginal delivery, adequately vaccinated and with normal milestones for age. Three months ago, the mother noticed a small ring-

shaped lesion on his lower abdomen for which she applied a topical fixed drug combination (FDC) containing Clobetasol Topical 0.05%w/w, Miconazole Topical 2%w/w and Neomycin 0.5%w/w twice daily. The initial partial response was followed by a sudden increase in the size and extent of lesions that became generalized within 6 weeks. Approximately 80 g of this formulation was used. The child gained excess weight with a puffy face, irritability, and lethargy. Mother had been self-medicating with similar FDC for extensive fungal infection for 6 months. Physical examination revealed an obese baby with overall poor hygiene, generalized scaling, and cushingoid features (facial puffing, buffalo hump, facial erythema, and telangiectasias, distorted ears [Figures 1 and 2]. His weight and height were 9.8 kg and 66 cm, respectively, with normal blood



Figure 1: A 9-month-old male infant with cushingoid features and erythroderma due to dermatophytosis.



Figure 2: Generalized dermatophytosis (erythroderma) involving entire body.

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pressure. Direct microscopic examination of skin scrapings in 10% KOH revealed branching septate hyphae and culture *T. mentagrophytes complex*. Similar results were obtained from the lesions in the mother. Morning serum cortisol levels of the infant revealed low levels of 0.67 µg/mL (normal 7–25 µg/mL). The rest of the investigations were within normal range except for low serum vitamin D level (13 ng/mL). A diagnosis of erythroderma secondary to extensive dermatophytosis with iatrogenic Cushing syndrome was made. Both mother and infant were prescribed 1% clotrimazole for topically with systemic antifungals.

India is witnessing an unprecedented increase in the cases of superficial dermatophytosis.³ There has been a dramatic clinico-epidemiological shift with the affection of children and young adults, atypical clinical manifestations, transition of an etiological agent from *Trichophyton rubrum* (*T. rubrum*) to *T. mentagrophytes complex* and emerging antifungal resistance.⁴ Use of the over-the-counter available potent topical steroid (Clobetasol Topical 0.05%) containing FDCs has been considered the major responsible factor for this change.⁵

Cushing syndrome is an endocrinological disorder characterized by increased free plasma glucocorticoid levels, either due to an excessive endogenous release of steroids or exogenous administration. In children, iatrogenic Cushing syndrome is relatively common secondary to oral/parenteral steroids prescribed for renal, hematological or autoimmune pathology. However, percutaneous absorption of potent topical steroids used for a long time rarely causes Cushing syndrome in young children. There have been few reports of iatrogenic Cushing syndrome secondary to the use of topical clobetasol propionate ointment for inappropriate indications such as diaper dermatitis.^{1,2}

Education of the pharmacist, parents, and physicians about the use of low-potency steroids for a limited duration may be a worthy exercise in preventing these complications.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

Dr. Archana Singal is on the Editorial Board of the Journal.

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Task Force Report

NAMS task force report on gunshot and blast injuries

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EXECUTIVE SUMMARY

War is the most expensive event in the life of a nation. Terrorism has the most devastating impact on the psyche of a nation. Crime and violence have the maximum impact on the social fabric of a nation. Collectively, these lead to the inability of a nation to rise to its true potential. The reason for the above is that no other event destroys the life and property of a nation as is done by war, terrorism, and crime. A rising aspirational nation like India must take note of this and develop capabilities to minimize its impact by dovetailing its policies on managing injuries due to firearms and explosives with the current capabilities in medicine, which is currently focused on treating diseases. Unlike diseases that can be effectively prevented, injuries due to firearms cannot be predicted and hence cannot be effectively prevented. However, the burden of its medical, physical, mental, and economic impact can be minimized by effective interventions.

The pattern of firearms has changed in the last few decades from single-shot weapons used 100 years ago to self-loading automatic carbines used for the past 50 years to current gas-operated magazine-fed assault rifles, which are fast replacing the carbines. Similarly, apart from the potential explosives being used in domestic life like liquid petroleum gas (LPG), the explosives used by the industries as well as terrorists are acquiring increasing lethality with the development of

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newer chemicals like hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) and azidoazide azide. Their use as remote-controlled explosives provides an ability to cause devastating injuries with unprecedented capability to mutilate and disrupt body parts. These issues need to be objectively addressed. Similarly, the real and large-scale threats to the military as well as civilian strategic targets being hit by drones and Quadru/Hexi/Octa/Multi/Hybrid copters should never be underestimated, reaffirming the need for a robust, workable competence-based region-wise chain of trauma care echelon.

Similarly, addressing the deficiencies in the abilities of the primary, secondary, and tertiary medical care setup limiting the provision of comprehensive trauma care, the inadequacies of ambulance services, gaps in training and record keeping, the need for creating a national registry for trauma, and creating a mobile app based interactive trauma teaching, training and response network using available disruptive and futuristic technologies freely available to all citizens of India will go a long way to reduce mortality due to firearm injuries. The need to ensure compliance with firearm regulations and enforcement of punitive measures for violation is a must to reduce violence in society.

The medical colleges and hospitals and level I, II, and III trauma centre should be able to provide the highest level of definitive and comprehensive care for patients with complex injuries. This will require a sustained effort toward developing competency at all levels and financial commitment by the government. The importance of learning basic life support (BLS), Basic Trauma Life Support for the common man, and advanced trauma life support (ATLS) for nurses, paramedics, and doctors should be recognized. ATLS/Advanced Trauma Courses for Nurses (ATCN) courses should become a mandatory requirement for a license to do clinical practice.

All citizens must be equipped with two specific abilities, i.e., how to stop bleeding and give cardiopulmonary resuscitation at the point of injury. Primary trauma care must be accessible to the injured within the golden hour by the fastest means. Once the victim reaches the hospital, a non-coercive ecosystem should be put in place whereby they are attended to immediately without any financial or legal hurdles for the attending doctor and their team. India should be able to improve their trauma care systems using affordable and sustainable programs, identifying problems especially related to system issues, developing reasonable corrective action plans, following through on implementing these plans, and evaluating whether the corrective action plan has had its intended consequences.

Trauma care needs to change in favor of honest, taxpaying citizens who should automatically be insured for long-term treatment by a conscious government policy. Similarly, emergency care for below poverty line (BPL) families is adequately covered under the Ayushman Bharat scheme. Developing high-quality and innovative home-grown technology with innovative, low-cost, more durable, and easier-to-repair versions of many medical devices will play a big role in making trauma care affordable for the middle and lower sections of society, the villages, and the hinterland.

The content and context in this white paper are relevant to the current Indian scenario and its projection in the next 10 years. By this time, India is expected to become a firmly established world power that can hold its own. For that to happen, the spread and reach of trauma care across the country in general and enhanced ability to treat injuries due to firearms and explosives specifically must be achieved.

Experts from the Armed Forces Medical Services (AFMS) and the National Academy of Medical Sciences (NAMS) have collaborated to develop this white paper on gunshot and blast injuries (BI) for submission to the Government of India. Implementation of the recommendations has the potential to transform the paradigm of managing firearm and explosive-induced injuries in our country.

INTRODUCTION

War, conflict, crime, and accidents have been omnipresent since the origin of humankind. All diseases may be conquered, but conflict, trauma, and war will remain. This is because neither the desire for dominance, supremacy, and control over resources will ever end, nor will the unexpected ever stop happening. However, the intense nature and severity of injuries due to gunshot wound (GSW), missiles, and explosives are progressively on the rise on account of the easy availability of firearms, a dramatic shift like warfare, changes

in societal behavior as well as the demographic changes occurring in the world. Incidences of wounding, mutilations, and disruption of body parts on account of GSW, missile, and blast injuries (BI) are increasing progressively all over the world, and India cannot remain untouched. Hence, it is time to address the issue substantively before it is too late.

BACKGROUND

- The use of higher-order explosives and indigenous ways of weapon delivery has resulted in unusual and

unconventional forms of injuries both in military and civil life. Hence, India needs a comprehensive policy to address the complex issues related to firearms injuries and those due to explosions. This is so that the military/paramilitary/ police and other members of the security establishments, as well as the civilian population caught in the crime scene/in the crossfire, who are usually unintended victims of collateral damage, are managed comprehensively and as medical, legal and criminal dimensions of the issue addressed.

- The more common wounding agents in modern warfare are artillery, missiles, and bombs, and not GSW, whereas, in terrorist operations, it is the GSW injuries that predominate. In suicide attacks, it is an improvised explosive device that is the most commonly used agent. Hence, the pre-hospital care for the victims must be standardized and incorporated as part of the country's medical/ paramedical/ nursing courses.
- The echelons of care, the objectives and standard of initial care, measures to minimize blood loss and maintain oxygenation, the concept of the primary survey, secondary survey, and triage, followed by treatment, the standard of documentation, in maintaining clarity, brevity and consistency with a uniform protocol, needs to be implemented all over the country. If everybody can speak and interpret all relevant matters and communicate amongst the stakeholders along the same lines, it will eliminate the communication gap to a large extent. Similarly, the medico-legal aspect relevant to the problem has been addressed holistically in the white paper. This white paper will lead to a comprehensive understanding of the problem from the point of view of policy formulation and its implementation in India.

TERMS OF REFERENCE

- To identify the current status of gunshot & BI.
- Identify the deficiencies which need to be addressed.
- To recommend measures for the management of gunshot & BI.

METHODOLOGY ADOPTED

The study was commissioned as a joint study by NAMS and the Armed Forces. The study findings are based on an extensive review of the literature using the databases of Pub Med, Cochrane Library, Google Scholar, various books, journals, and publications, as well as inputs from the manuals used by the Armed Forces. The fields chosen were title, keywords, abstracts, and MeSH (Medical Subject Headings). Extensive discussions and deliberations by team members and the various experts on the subject matter, both in person

and in electronic mode, followed. Extensive inputs based on the experiences of various domain experts were used in critical analysis of the matter. The content and context were analyzed in as much detail as possible, and the inferences obtained were relevant to the current Indian scenario and its projection in the next 10 years. At that time, India is expected to become a recognized world power.

DETAILED STUDY OF THE SUBJECT MATTER

The matter is discussed under the following lines.

- What is the realistic achievement in matters related to managing gunshot and BI that we should aim for the citizens of India in the next 10 years?
- What is the current reality regarding our ability to manage gunshot and BI in India as a country, and how to address the gap in capabilities?
- What measures are necessary for the management of gunshot & BI?

DESIRABLE OBJECTIVES FOR THE NEXT TEN YEARS

- In the next 10 years, India as a whole should be able to become a country where citizens in any part of India should be able to avail facilities of high-quality trauma care, including care for bullet injuries and explosive-induced BI. The aim is to save a maximum number of lives, reduce disability amongst our compatriots, and properly rehabilitate victims so they can remain productive members of society and contribute to the national economy. This, if achieved, will become a symbol of the largest social security cover in the world where no family will go on to face poverty due to the loss of its bread earner.
- To achieve this, all citizens must know enough about the actions to avoid injuries, reduce their impact on occurrence by taking simple measures, access immediate emergency care, and benefit from universal coverage.

To enable this to happen, the following should be aimed for

- (a) All citizens must be equipped with two specific abilities: how to stop bleeding and how to give cardiopulmonary resuscitation at the point of injury.
- (b) Ambulances with medics/paramedics should be able to reach the injured as fast as possible within the golden hour. Alternately, the victim should also be able to reach the nearest trauma care facilities, preferably once the emergency caregiver has controlled his/her bleeding and breathing using the fastest means.

- (c) Once the victim reaches the hospital, he should be attended to immediately by the attending doctor and his/her team without any reservation (without financial or legal hurdles). The hospitals should be protected from financial burdens by providing prompt reimbursement for the treatment.
- (d) A collective national effort, planned but time-bound at all levels, must improve the medical fraternity's and common citizens' abilities to manage GSW and BI.
- (e) The national trauma registry and archiving system, as well as all details regarding gunshot and BI available at the hospital, mortuary, forensic labs, cremation ground, cemeteries, police, etc., should be digitized, networked, and AI-enabled to generate a realistic database so that one can look for patterns and improve outcomes by suggesting action points.
- (f) The financial support to all hospitals should be based on a computer-based, server-secured, and AI-enabled network and from a deliberately and consciously developed national corpus, preferably the consolidated fund of India. It is suggested that all transactions in digital format in the country be charged @ 0.01% as 'trauma care cess, from which the reimbursement to all the echelons giving robust trauma care is provided quickly. The absence of financial support to the hospital, most of which is in a private set-up, combined with the inability of the unknown victim to be in a position to pay until one of his family members could commit to the expected expenditure, is the universal impediment to good trauma care in India and this truth needs to be accepted as we move on as an emerging nation. This needs to change in favor of honest taxpaying citizens who should be automatically insured for treatment and below poverty line (BPL) families who should be covered under the Ayushman Bharat scheme.

THE CURRENT STATUS OF GSW AND BIs - ACTIONS WHICH ARE REQUIRED TO BE TAKEN

Current situation in the country

- GSW and BI are steadily developing into a significant public health problem in India and seem to be following the trends seen in Western nations. This is consistent with the increasing prevalence of firearms and explosives (industrial as well as illegal) in both villages and the cities of India.^{1,2}
- The exact incidence of gunshot injuries in India cannot be ascertained due to a lack of reliable data, with only a few reliable studies being available from the Armed Forces and civil stream in India, which provide some insight into the nature of injuries and outcome.²

- A study from Mumbai reflecting an urban setting found that the injured victim was rescued by a passerby in 43.5% of cases and helped by the police in 89.7% of instances, with the victim in most cases being transported by a taxi or a private car to a hospital without provision of any emergency medical aid on the site of injury. The ambulance was put to use only in 39.3% of cases. This constitutes a very significant limitation in the successful primary management of firearm injuries.³

Effectiveness of ambulance services

- The Emergency Medical Service (EMS) in rural India is rudimentary despite significant leaps in this field in large metros and capital cities, with the second-tier cities fast catching up with the gradual development of robust emergency ambulance services. However, ambulance services usually take patients to a hospital based on the likely affordability of the patient based on first impression. In other words, a trauma victim with doubtful financial viability is usually directly taken by Ambulance services to the Accident & Emergency of a nearby tertiary care super specialty hospital (most are private entities) only when his life is under imminent threat when he usually gets attended with the immediate interventions required to save his life. However, once he is identified as constituting a financial burden, the victim is often transferred out to one of the second-rung nursing homes on the first available opportunity, usually to the detriment of his safety and health. The government needs to come up with a clear policy on financial compensation for all trauma victims. This is because this group constitutes the largest share of preventable deaths all over the world and occurs usually in a young earning population out on the road for work or leisure, and contributes to the nation's economy. Unless this issue is addressed, victims of salvageable critical gunshot injuries in civilian life will, by and large, continue to become disabled or lose life.
- Most state governments and municipalities in the last ten years have made substantial progress in developing their Ambulance services, e.g., 108 Ambulance' which are integrated with call centers and work 24 x 7 x 365 days, and this service is slowly progressing towards even tier 2 towns, which is very encouraging. However, as a nation, we have a long way to go to make these ambulances capable of handling blast and gunshot injuries. As of now, these ambulances can only give oxygen and fluids, and although they have facilities to provide cardiopulmonary resuscitation (CPR) they are not fully geared up to treat GSW/blast injuries. Thus, the lack of optimal ambulance/transport services constitutes an important limitation in handling GSW/BI, and the matter is deliberated below.

Gaps in ambulance services

It is a hurdle in India that needs an urgent solution. Many organizations, including the government, manage Ambulance Services and are supported and facilitated by police, fire brigades, hospitals, and private agencies. The controlling agencies and telephone numbers vary from state to state. This needs to become unitary, learned, and memorized by children from primary school across the country. GSW/BI requires specialized care when being evacuated. However, in a study, only 30 ambulances out of 94 could partially cater for the provision of ATLS. Another important component in the care of these sick patients is a protocol-based treatment, but only 20% of district hospitals were found to have a documented emergency manual, with only 8% of district hospitals having documented policies and procedures for patient transfer.⁴

Ambulance staffing

Most privately managed ambulances lack an adequately trained workforce. Many are contractual staff on short stop-gap contracts, which is due to the absence of any clear regulation regarding the minimum qualification/ experience required to man an ambulance and the lack of regulations on the minimum number of professionals required for manning an ambulance service (medics/paramedics/telephone attendant/on-call roster, etc.). In the suburbs and hinterland, the situation is even more acute.⁵

Lack of adequate equipment in ambulances

Most ambulances are inadequately equipped and ineffective in providing life-saving trauma care interventions during transport.⁶ The impression that stretchers, oxygen, saline, and bandages are enough to run an ambulance service needs to be dispelled.

Misuse of ambulances

Many studies have reported misuse of ambulances. Another glaring fact is that a large majority of ambulances have been found to transport the dead sometimes or other, either due to an absence of hearse vans or organizational pressure, thus making them not available for a medical emergency should a situation arise. This should be made a punishable offense.

Lack of coordination between the ambulance services and nearby health facility

The impending arrival of patients transported to the nearest health facility is usually not communicated to the receiver due to inadequate communication systems and a lack of knowledge amongst bystanders regarding where to take the

victim. Private ambulances constitute the majority share. Air ambulances are operational only in certain large cities, but affordability is a big drawback. Hovercrafts as ambulances in coastal areas are still in their infancy in India but are expected to be leveraged widely in the next decade. Transfer of patients by helicopter is picking up in rugged terrain, and that by drone is on the anvil as the load-carrying capacities of indigenous drones are now more than 80 kg. Hence, drones, as a viable means of patient transfer, especially of injuries by bullets/explosives, are likely to see the light of day as a mainstay in the next 5 years.

PRIMARY CARE

a) Role of primary care physician

Ideally, the primary care physician should become the sheet anchor in initiating the management of firearm-induced body disruption and massive blood loss once the first responder has brought the victim to the primary care facility since the fate of the victim is generally decided in the next 30-60 minutes.⁷ However, in India, the ability of a primary care physician to independently impart trauma care is often suboptimal, primarily due to inadequate attention given to training on aspects of trauma care during Bachelor of Medicine and Bachelor of Surgery (MBBS) and rotating internship training, due to which, although the doctor is reasonably equipped with the theoretical knowledge, he is unable to put the knowledge into practice.⁸⁻¹⁰ This severe limitation in skill level must be addressed by mandatory exposure to lifesaving measures in the ATLS trauma certification program as part of internship training before being granted an MBBS degree by the university or being registered for medical practice in the country by the National Medical Council (RMP status) and revalidation of the presence of this essential ability every five years.

b) Role of paramedics

A competent paramedic helping a casualty doctor meaningfully makes the job of a doctor so much easier. However, in India, paramedics are imparted a fundamental knowledge of trauma care but practically have no experience of it. This is a paradox since they usually are the first responders. However, they learned many aspects of it if they started working in a field related to trauma/emergency care, which is not common. Since paramedics are now attaining specialization directly after leaving school, e.g., in pharmacy, X-ray, health, recordkeeping, skin diseases, psychiatry, nursing, etc., directly without at any stage working in an emergency or a patient ward, they do not learn to handle a sick patient in a ward at all. Hence, the availability of paramedics who could handle the basic emergency requirements of bullet injury has dwindled

further. Therefore, training in BLS and Basic Trauma Life Support (BTLS) courses should be made mandatory as part of the degree and diploma for nurses and paramedics.

c) Role of the common man

The common man is, by and large, unaware of the basics of trauma management and usually is not in a position to help his fellow citizens who have sustained GSW and BI and are in distress. This is unfortunately aggravated by a sense of apathy more visible in roadside injuries, especially roadside crimes, since victims are unknown, and fear of the consequences of getting involved overwhelms the sense of reason and brotherhood. The citizens have to be taught through various awareness programs to be more responsible for their helpless brothers and sisters in distress, and any disregard for reasonable help should be made punishable and implemented by the withdrawal of social benefits. Social scientists, anthropologists, and non government organizations (NGOs) need to help the government in this effort in a substantive way so that citizens become more responsible. The current approach taken by society, the medical fraternity, and the Government toward the problem of treating GSW and explosive BI need to change.

PARTS OF THE BODY DISRUPTED IN A BLAST INJURY

Bullet injuries form a subset of trauma care. It can affect any part/organ of the body from scalp to great toe, i.e. skull and brain, face (maxilla, orbital structures, naso-ethmoid, mandible, dental elements), neck (cervical spine, major vessels, pharynx, esophagus, trachea), chest (heart, lung, aorta, inferior vena cava (IVC), spine and spinal nerves), abdomen (gut, solid organs, vessels and spine/spinal nerves, retro-peritoneum), pelvis (gut, urinary bladder, uterus, prostate, pelvic bones, head and neck of femur), limbs (brachial plexus, vessels, muscles, tendons, bones, joints). Very few doctors can handle all regions of the body competently. The reason is the trade-off, i.e., compartmentalization of the sphere of general competence in the endeavor to achieve a very high level of special competence in particular aspects of a body. This is explained below.

LIMITATIONS IN COMPREHENSIVE TRAUMA CARE DUE TO SUPER SPECIALIZATION

Surgical super-specialty training is primarily organ/tissue-specific, e.g., neurosurgeons & neurophysician treating nerve and brain derangements, urologist & nephrologist treating kidney diseases, medical & surgical gastroenterologist treating gut, liver, and pancreas, cardiologists & cardiac surgeons treating heart, endocrinologists and endocrine

surgeons treat gland disorders, ear, nose, and throat (ENT) specialists treat Ear, nose, and throat, eye specialists are limited to eyes, gynecologists to the uterus, cervix and ovaries and so on.¹¹ By their inherent nature, some super specialty is required to explore all types of anatomical areas, e.g., vascular surgeons, surgical & medical oncologists, plastic surgeons, and trauma surgeons. They can handle problems in multiple areas better but still have limitations.¹² Thus, the arrivals of so many super-specialties have no doubt enabled advanced Medicare but have robbed the general specialists of the opportunities to explore multiple fields of the body and acquire the confidence to handle difficult situations. On the other hand, super-specialists abilities have touched an extraordinary level of excellence compared to the best in the world in handling body parts in their core areas. However, making ATLS certification mandatory, along with the requirement of compulsory work in a recognized trauma center for 5 days every 2 years for all if made mandatory to maintain their license to practice, will increase the talented and accomplished pool of doctors in trauma care, which will be good for the nation in the long term in both war and peace.

IMPACT OF CONSUMER MOVEMENT ON TRAUMA CARE

Pressure by family members of trauma victims to be seen only by a super-specialist once the victim reaches the emergency department combined with misplaced consumer activism, interventions by consumer court, and the consequent fear of prolonged litigation have no doubt taken its toll. Nobody attempting to save a life with an honest effort would like to be labeled as incompetent due to limited available equipment or staff and another organizational resource crunch over which he has no control. The result is disinclination and, over some time, an inability of a general surgeon in general to handle a non-compressible trauma confidently. This has become a significant limitation in the management of trauma in general and has impacted the ability to handle GSW/explosive BI in the hinterland of India, from where a large number of patients are unable to reach well-equipped trauma care centers in time.

CHANGING PARADIGM IN TRAUMA CARE DUE TO WAR AND TERRORISM

GSW/BI in warzones/special operations differ from civilian injuries in many ways in terms of the severity of injuries. However, the number of terrorist attacks and suicide bombers detonating themselves in public have brought home the prospects of sustaining multi-organ trauma in various combinations and of various severity and complexity, a reality, even in civilian life. No one is immune to firearm injury, and it will strike without warning. The wars of the

21st century, especially the Armenia- Azerbaijan war and the Russia-Ukraine war, have also brought home the bitter fact that modern wars are likely to be prolonged affairs. Further deaths will now occur not only in the forward edge of battle area (FEBA) (borders), where the enemy is in eyeball-to-eyeball contact but equally in-depth, as the military targets are being hit by drones and Quadro/Hexi/Octa/Multi/Hybrid copters easily up to 100 km inside the border due to their progressively extended reach. Similarly, the reach of the modern missiles and various forms of guided munitions of our adversary now covers up to almost 1500 km, i.e., practically the whole of our country. Hence, theoretically, all parts of India will constitute part of an extended warzone in a full-scale war. Increased and determined efforts of the enemy to hit valuable strategic targets like parliament, oil refinery, and the stock market in an attempt to break the will of the adversary, especially in urban areas, is a reality and will, beyond any doubt, result in widespread collateral damage. The government has to take cognizance of this and act. Policymakers must carefully frame a comprehensive and realistic policy on this account by constituting a high-powered task force as soon as possible.

IMPACT OF SOCIAL CHANGE ON INCIDENCE OF CRIME

The instability of the social fabric due to the aspirational upwardly mobile population of India may increase the incidence of violent crimes. This may be further fueled by the easy availability of small firearms (indigenous as well as foreign-made), both legal as well as illegal. Hence, a progressive increase in the crime rate is inevitable unless urgent corrective action is initiated. Further, since nobody is insulated from firearm injury without predictability in time and space, social reformers have a big role to play.

HOW TO STRENGTHEN NETWORK AND ACCESS

- Injuries will never fade, even if all diseases are conquered. Gunshot and BI will become more and more destructive as time passes with scattered pellets, clustered shrapnel, and many newer forms of destructive abilities. This requires India to become ready and develop a robust, workable competence-based region-wise chain of trauma care echelon, with information about its working widely disseminated and in real-time leveraged by all citizens using a widely available and free app mandatorily put in all the mobile phones sold in India with video of basic measures along with an interactive option to seek help at the location of the injured as well as to revise intervention measures. This should be combined with a robust network of emergency care ambulances so that victims can reach

the appropriate center as quickly as possible, preferably within the golden first hour. Similarly, all public transport drivers and attendants must be given basic training to stop bleeding and maintain airways as part of a licensing exam. Besides this, by law, they should know the primary and alternate routes to reach the nearest trauma center in their permitted driving area so that no time is lost.

- Multiple applications are available to geo-tag a person's current location. One such application is to be identified/created de novo and exclusively used for trauma care by incorporating this as a non-erasable and mandatory feature for all mobile phones and smart watches sold in India. The application should be developed in multiple regional languages. It should be linked with a voice alert feature, "Help me," in addition to the use of a key/tap, which will activate a "first response" and simultaneously show on the mobile screen the location and identity of the nearest trauma care facility along with access road to reach there as with Google map. The screen on the mobile should also pop up an Alarm button, which, when tapped, should initiate the "Second Response," which does four actions. (a) Emits loud call for help by bystanders (b) Automatically sends an save our souls (SOS) message and a call to the nearest emergency response team along with its designated Ambulance team (c) Activate the camera of the mobile for visual inputs (d) Switch on the current location, so that the electronic medical record (EMR) team can track its location real-time if passer-by has moved him.
- Similarly, the emergency response team should be able to respond quickly and, after a quick assessment, send a message to the higher-echelon trauma care facility so that it is forewarned and render continuous help while in transit. The emergency response team should be able to log on to the local police network for safety requirements and the traffic police for road clearance/diversion measures to avoid losing precious time. Adopting the above, the referral problem is dispensed with as the EMR team is the decider, followed by the trauma care centre.

IMPORTANCE OF COMPLIANCE WITH FIREARM REGULATIONS

- The Indian Firearm Act is one of the strictest Firearm control provisions in the world. No citizen of India has a constitutional right to own a firearm, as is the case in the USA and some other countries. Criteria for approval of a firearms license may be made even more stringent. All weapons with the caliber of .22 and above should need a permit. Similarly, all air guns capable of delivering 20

joules or more of muzzle energy /with a caliber of more than 77 should require a license.

- UP, Punjab, and the state of J&K have the most licenses and the maximum number of illegal firearms. Insurgents in states like Manipur, as well as Left Wing extremists in the state of Chhattisgarh, possess a large number of illegal firearms and improvised explosive device (IED). Mirzapur is considered the biggest hub of illegal weapons. Kodavas are permitted to carry firearms without a license because they are considered born warriors by the British Raj. If this is still in vogue, it needs to change.
- In India, a license for non-prohibited bore weapons (NPBW) (bore refers to the diameter of the bullet) is issued by civil police/ DM/State Govt as applicable and, as per Arm Act 1959 and Arms rule 1962, one can carry it if there is a perceived threat to his life. Only two firearms can be issued on one license, whereas prohibited bore weapons (PBW) like pistol (9mm) and handguns (.38 and .455) are issued by the Ministry of Home Affairs, and only 50 cartridges can be legally issued per annum (max of 30 cartridges at a time). Further, the Indian Arms Act of 1959 prevents any citizen from carrying a self-ejecting pistol or gun. Also, sons/daughters are prohibited from carrying the father's/ mother's firearm. In India, it is not legal to carry firearms in public, although this is violated with impunity. Possession of unauthorized firearms is punishable by imprisonment of 7 to 14 years and a fine. Similarly, whenever the owner dies, his firearm is required to be either transferred or surrendered to local police. No firearms can have more than a 6-inch sharp edge on any end. Firing a gun in the air has been made illegal in some states like UP, and others should also follow suit.¹³ These licensing laws are, thus, sufficient but need to be implemented in letter and spirit. This will require immense political will and concerted effort towards law enforcement.

IMMEDIATE INDIVIDUAL RESPONSE TO BLAST INJURY

Some protective measures can be adopted by citizens in general to avoid injury in the event of a threat by bullet/blast. Citizens may be taught, as part of reflex behavior, to lie down flat on the ground with their head away from the direction of the sound of a bullet/blast (reduces target area and protects head and eyes). They should not panic, but on the first opportunity, they should take cover in the nearest safe location and contact the police using the emergency fast dial on the phone. If they notice any casualty in their vicinity, they should be able to act as per the situation's needs and pull him to a safe zone. Thereafter, the measures to be adopted by

the common man to prevent death within the golden hour (for bullet injuries) and within platinum minutes (for BI) are adherence to the simple and easily followed provisions of basic life support. The same is given below.

BASIC LIFE SUPPORT (BLS): Steps

- (a) Quick initial assessment by the first responder is important. First, check to ascertain the scene's safety and look for debris, shrapnel, and the presence of any malicious intent to harm.
- (b) If the scene is considered safe, tap on the shoulder and speak to the victim loudly to ascertain whether the individual is conscious and responsive.
- (c) Call for professional medical help and an ambulance.
- (d) Stop the bleeding: The first action should be to stop the bleeding by compressing the wound with a clean cloth available next to you and elevating the limb. If the leg is burst and bleeding, apply a cloth tightly proximal to the wound to reduce blood flow.
- (e) Look for a satisfactory chest rise and whether it is equal on both the right and left sides with breathing effort. If present but the patient is unconscious, clean the mouth with a dry handkerchief to reduce the chances of airway obstruction and put the individual in a coma position to reduce the chances of the tongue falling back to obstruct the airway and vomit being aspirated in the lung. An unequal rise in the chest indicates pneumothorax and constitutes an emergency requiring prioritization of the need to reach a nearby hospital.
- (f) Check for evidence of cervical spine injury. Keep a close watch on breathing effort. If the breathing has stopped, immediately initiate CPR after checking the carotid pulse as per the teaching of BLS. If a pulse is present, continue with rescue breathing only. If a pulse is absent, conduct high-quality chest compression (30 times) on the sternum, ensuring adequate chest recoil to fill the lung with air, followed by 02 rescue breaths. Continue the same for at least one hour/ placement on a ventilator, whichever is earlier, continuing to watch for and manage bleeding from the wound simultaneously.
- (g) This CPR is to be continued by a passer-by in rotation (too tiring for a single person) till an ambulance/equipped doctor/ paramedic reaches you.

Note: - Rescue breath is useless if the heart does not carry the blood (oxygen) across to other body parts. Hence, in effect, CPR is a delicate balance between forcing the heart to start from under the ribs while being gentle enough not to puncture it. Hence, this simple CPR+ BLS course is a must for the general public to know and must be incorporated into all First Aid courses properly to attain

the status of 100% informed citizenry. Once inside a hospital, the trauma protocol action needs to be activated.

BASIC TRAUMA LIFE SUPPORT (BTLS)

- BTLS differs from BLS in that it trains the learner to stop the bleeding, assess deformities (abnormalities in the shape of a body part or organ compared to the normal shape), contusions (bruising which in extreme cases may lead to significant blood loss with blood leaking into surrounding tissue), abrasions (may be simple or contaminated with IED debris), puncture/ penetrations (ability to opine that the object did not pass through), perforations (when searched consciously to find whether the object has passed through with an entry and exit wound), burns (extent and degree), lacerations (how deep below the skin and likely underlying structures it could have damaged), tenderness (may be muscle tear or a fracture, etc.), swelling (due to blood collection, expanding hematoma etc.) on a scientific and analytical manner with focus on what to suspect and act accordingly. This involves critical thinking and objective assessment of firearm injuries by looking for clinical presentations other than airway, breathing, circulation, disability & exposure (ABCDE) taught in BLS. The student is also taught to handle immediate post-traumatic shock episode, which occurs on seeing dead bodies and ghastly injuries strewn around in a major blast injury and is, at times, a cause of sudden death on account of a very intense adrenaline surge (Broken Heart Syndrome).¹⁴
- Military surgeons are conversant with the correct approach to treating trauma through their training since the Armed Forces put a lot of effort into training their soldiers and paramedics in BTLS, Nurses in ATCN, and doctors in ATLS. In the last few years, the AIIMS JPN Apex Trauma Centre and some similar institutes have spearheaded the effort to disseminate trauma care knowledge in military and civilian centers. This effort needs to be sustained and expanded as much as possible.

Need for advanced training and teaching

Training (skill development) and teaching (achieving theoretical clarity of the subject matter) are integral to any progressive effort and must be sustained to maintain the gains achieved. The National Board of Examinations has recently begun registering courses in trauma care, although in a very limited manner. Similarly, paramedic training, although done at many institutions, lacks accreditation, a structured review program, or assessments for periodic updates of skills and knowledge in the field of trauma and bullet/BI. Hence, their actions, however well-meaning, get translated into widely

varied and individualized treatment meted out by the first responders, including attending doctors unsystematically (although with good intentions), leading to preventable deaths. This is reflected in the glaring fact that in the Mumbai terror attacks, out of a total of 271 casualties encountered, 175 people (including 9 terrorists) died, 108 were dead after admission (68 due to bullet injuries, 30 due to BI, and 10 had both). Six postoperative deaths were all due to GSW. This indicated that the impact of severe bullet and BI could not be addressed adequately, and potentially salvageable patients could not be operated on within an acceptable time frame.

Role of civil defense volunteers in BLS/BTLS

The members are usually nationalist, motivated, and well-meaning citizens. However, the civil defense forces lack trained personnel to provide BLS or BTLS. This captive and easily identifiable group must be given organized training.

TRAUMA CARE ONCE IN HOSPITAL

- The super-specialist doctors of the country are fully competent to tackle complex trauma concerning their field of expertise. However, only a minuscule proportion of trauma victims can reach well-equipped super-specialized care facilities since such super-specialty centers are all located and clustered in big cities where patients of all types of illness come from villages, rural districts, towns, and tier 2 cities.^{8,10,15,16}
- Those super-specialists who work in the suburbs of cities and smaller towns work by and large in a relatively modest private set-up, which often do not have the technical/ medical equipment and supporting facilities, including trained staff required to treat complex trauma like cardiovascular and lung injuries, complex pelvic or brain trauma, or major abdominal solid organ and large vessel tears, and hence are unable to utilize their available domain expertise fully which often results in preventable death.
- However, general surgeons and orthopedic surgeons form the mainstay of medical professionals available in non-metros, and they are now imparting primary care and conducting definitive surgery in the field of GSW. On receipt of complex firearm-induced trauma, if definitive surgery is not feasible, they try their best and perform damage control surgery and can do a reasonable job provided they have acquired the expertise to treat trauma involving all areas of the body during their postgraduate training or have undergone a course focused on treating complex trauma. This is a critical point since this group of professionals forms the most important intervention echelon in the width and depth of the country and can

save lives in a very significant way by successfully stopping a major bleed, combating shock, and, if required, helping/ transferring the patient to a proper trauma care facility. GSW and BI victims require intensive care unit (ICU) care both at admission and in post-operative care. A survey showed that only 47% of district hospitals (>300 beds) and only 5% of district hospitals (<300 beds) had an ICU of reasonable standard.^{17,18}

TRAUMA CARE CENTERS IN INDIA

- District hospitals in India were designated as level III Trauma Care Centers in the 12th five year plan, catering to an injured's initial evaluation and stabilization. medical colleges & hospitals with bed strength of 300 to 500 were identified as Level II Trauma Centers committed to providing facilities to provide definitive care for severe trauma victims with in-house emergency physicians, surgeons, orthopedic surgeons, and anesthetists. The medical colleges and hospitals with more than 500 beds were planned to have a Level I Trauma Centre to provide the highest level of definitive and comprehensive care for patients with complex injuries. However, this has not been fully realized and highlighted in various reports. Police records give a fair indication of areas with a high number of gun violence. The recommendations of Niti Aayog's report on emergency and injury care at secondary and tertiary level centers in India have, although focused on road accidents in a major way, should also be integrated into the trauma care framework. The local government, at least in urban areas, must be armed with a dynamic strategy whereby, from these areas, the victim of firearm injury can be shifted to a trauma care facility within 30 min.
- As per a Times of India report published in 2017, in Maharashtra, out of 18 trauma care centers, only three were adequately staffed and functional; the rest were either non-functional or partially functional due to inadequate workforce or shortage of infrastructure.¹⁹ Other reports have also flagged the inadequacy of a trained workforce and lack of essential equipment and training.^{8-10,15}
- A report stated that only 33% of district hospitals (>300 beds) had emergency operative services for trauma patients.⁴ In such a scenario, the ability to manage injuries on account of explosive devices, IEDs, bullet injuries, and bomb blasts is a serious question.

BLOOD BANK FACILITIES

The blood bank is an essential component of trauma care. Out of 34 assessed district hospitals, 15 had no blood bank available

24/7, only 4 had an emergency blood transfusion protocol, and only 5 had a massive blood transfusion protocol. Blood banks in larger cities housed as corporate/private entities are doing much better regarding availability and accreditation.

DISASTER MANAGEMENT DRILLS & POLICIES

Mass shootings and BI can easily overwhelm the resources of a normal emergency department, and the conduct of regular drills to face such disaster management provides the opportunity to plan, prepare, and, when needed, enable a rational response in the case of disasters/ mass casualty incidents. Disasters and mass casualties can cause great confusion and introduce inefficiency in the hospital. However, the capacity to cope with such scenarios exists in only about 35-50% of district hospitals. This capacity must be increased in collaboration and coordination with the district, state, and Indian disaster management agencies, railways, civil aviation, National disaster response force (NDRF), military, and paramilitary organizations.

VIEWS OF THE WORLD HEALTH ORGANIZATION ON TRAUMA CARE

- International Society for Trauma Surgery and Intensive Care (IATSIC) is an integrated society within the broader International Society of Surgery and provides guidelines targeted at administrators, ministries, and policymakers under the umbrella of WHO and, from time to time, updates the guidelines for trauma quality improvements program. The report says that 5,800,000 people die of injury every year in this world, with the burden being excessive in low and middle-income countries.
- The WHO guidelines bring out the core essentials of trauma care services, which every person in this world should realistically be able to receive, even in the lowest income setting, and encourage member states to improve their trauma care systems using an affordable and sustainable program, identifying problems especially related to system issues, developing reasonable corrective action plans, following through on implementing these plans and evaluating whether the corrective action plan has had its intended consequences. It has also suggested the creation of a death panel review to identify the factors of care that need to be strengthened and the adoption of a modern quality assurance program, especially focusing on patients who have died of low injury severity scores. WHO also has a designated Department of Violence and Injury Prevention and Disability (VIPD), which issues updates occasionally.
- India needs to form a similar body and leverage its immense advancement in the field of Information technology,

artificial intelligence (AI), and software development capabilities, and aim to create the most extensive database in the field of trauma in the world with GSW and BI being a subset, where records of various agencies, courts, cremation and burial ground, forensic science services, hospitals and medical colleges may be integrated. This will be a big step in improving the care of firearms injuries and forming a robust database, which will be beneficial in achieving a larger purpose of maintaining the country's security.²⁰⁻²²

AVAILABILITY OF AFFORDABLE EQUIPMENT

- Assured and timely availability of technologically and scientifically sound equipment and supplies of medicines and consumables are essential to trauma care. Studies have shown that overall mortality decreased by 15–20%, and preventable deaths were reduced by 50% with improvements in trauma care planning and organization. The development of high-quality and innovative home-grown technology will play a significant role in making trauma care affordable for the middle and lower sections of society.
- Many medical devices used in trauma care, like oximeters and ventilators, need lower costs, more durability, and easier-to-repair versions. Indigenization can decrease costs and increase the availability of a range of equipment. Innovations using disruptive technology will be game changers. This is more important in GSWs and BI, where bleeding control is achievable with minimally invasive procedures.
- In a study by medical colleges/ tertiary care centers, most of the Hi-Tech equipment was found to be mostly imported. Approximately 90–95% of ultrasonography (USG) and computerized tomography scans (CT), considered essential for the last 40 years, are still largely either imported or sold with minimal make-in-India components of key parts. This is very difficult to accept in a country with such a high electronics and computer technology talent pool. This needs to be addressed on a war footing. The import of foreign equipment also poses a challenge for repairs and maintenance. This leads to a significant downtime. Moreover, due to economic reasons and lack of training, cutting-edge technology fails to penetrate the Indian market, and phased-out and refurbished devices are more commonly marketed in the hinterland of India, which are the usually old models phased out from tertiary care hospitals in big cities of India and abroad. Hence, local production emphasizing Make in India is a necessity that can no longer be ignored to increase the availability of these important

technologies and make the facilities available and affordable in middle-level towns and villages of India. Low-investment fields like trauma care in the private sector need low-cost equipment produced in India to succeed for poor people.

- The availability of indigenous ventilators and other lab equipment was made possible during the COVID-19 pandemic with firm government policies. The market size of the medical devices sector in India was estimated to be \$11 billion (approximately ¹ 90,000 Cr) in 2020, but its share in the global medical device market was estimated to be only 1.5%.²¹ This is expected to reach 100 billion USD in the next 10 years as more hospitals come up in the hinterland, causing a loss in foreign exchange. It is time for India to leap forward in the field of manufacture of medical equipment by increasing investment in research and development if we are to achieve a reasonable national aim of 100 billion USD (Rs. 8,500,000,000,000) industry in this sector simultaneously enabling a large number of medical equipment to reach the small towns and villages, thereby taking the level of care in villages much higher. This will be a remarkable feat towards affordable health for all.

REQUIREMENT OF POLICIES AND PROTOCOLS ON CONDUCT OF AUTOPSY

There is a national program for prevention & management of trauma & burn injuries (NPPMT&BI). However, exclusive standard policies and protocols for treating GSWs/BIs are lacking in their role. Most of these victims are treated by in-house protocols of the facilities and are guided by the expertise available in the hospitals. Similarly, there is no policy on the conduct of autopsy. The lack of national policy regarding autopsies has led to significant variations in the number and proportion of autopsies performed at dedicated centers. Autopsy rates seem to vary greatly across cities and regions, as do the proportions of autopsies involving firearms deaths. Imphal, the capital of Manipur, exhibits the highest rate of autopsies on gunshot victims; 42.5 percent of all autopsies were carried out on murder victims, while a lower yet still an impressive proportion involved firearms murder victims. It may be relevant that Manipur is home to the highest firearm murder rate in the country. Whereas Imphal stands out based on its uniquely high recourse to autopsy for victims of firearm murders, a large number of victims in other parts of the country do not undergo autopsy, as a result of which the correct pattern of injuries suffered by GSWs/BI is not reliably available. Hence, a policy needs to be implemented where all GSW/ BIs must be subjected to a "limited postmortem focused on the area of interest. If the postmortem is not done for any reason whatsoever, a whole-body CT scan must be

made legally mandatory prior to burial/ cremation so that the broad nature of the injury and the likely cause of death can be reliably documented.

APPROACH TO THE MANAGEMENT OF GSW AND BI IN THE MILITARY ENVIRONMENT

- In GSW, injuries among individuals using battle protection jackets (BPs), 60% involve extremities. In other instances, 60-80% of injuries involve the chest and abdomen, which constitutes a vast and unprotected target area that cannot be compressed satisfactorily to stop hemorrhage.
- Just as self-care (e.g., packing of shell dressing and use of self-applying tourniquet) and buddy care (like raising legs and applying pressure) are life-saving interventions in battle, informed medical assistance and first aid by passers-by and fellow citizens in civilian life can be of immense use in stopping bleeding due to GSW. Hence, citizens must be trained to use belts/ rope/scarf/pieces of cloth torn out from worn fabric for tourniquets & packing wounds with clean cloth to stop the bleeding. Similarly, wider availability of individual first aid kit (IFAK) in all motorized vehicles (@1 kit per passenger) may be made mandatory so that any vehicle owner can use it in an emergency while transferring a victim to the hospital.

COMBAT SCENARIOS

- In the Korean War, which lasted over 3 years, out of 40 lakh casualties, 20 lakh were civilians, indicating the brutality of the war. In the ongoing Ukraine-Russia War, which has now touched 600 days and counting, the total number of casualties due to bullet injuries and explosive action has already crossed 3,50,000 with about 56,000 killed in action (KIA) and about 2,50,000 wounded in action (WIA) indicating a 15-17% KIA rate in the larger context, out of which about 20% were collateral damage i.e., civilian death (9444) which is noteworthy and since most of the death occurred in cities and towns (denser population), must be taken seriously. Only about 15% of soldiers could return to join the battle (RTD-returned to duty), causing a severe shortage of troops ready to fight again, one of the lowest rates of RTDs compared to previous wars. Further, about 85% were either maimed or were dead, which is one of the highest in modern warfare. This is alarming in a war showing no sign of stopping, with many more likely to be affected in the same proportion. This extraordinarily high rate is due to the large number of explosions due to higher generation weapons with much more destructive power, i.e., missile/rocket/drone/aircraft/tank actions conducted

up to 300-400 km inside the border and in urban areas. India has a much higher urban population density than Ukraine or Russia. If we as a country have to face a similar situation, our death rate of the civilian population would be many times higher. This new normal will likely be reflected in any future conventional conflict between India and its adversaries. Hence, we must be prepared for it.

- Firearms and explosives kill or maim the victims either intentionally or accidentally. The immediate concern is death, either due to blood loss due to the inability to breathe or due to the major disruption of organs in any of the three cavities of the body. i.e., cranial, chest, and abdominal cavity, when the extent of loss becomes incompatible with life. Associated bone, nerve, vessel, muscular, and maxillofacial disruptions may contribute to death in an immediate time frame, although by themselves, they may not be the cause of death. However, it may result in disability in the long term. Bala et al.²³ (2008) reported in a study of 181 patients with abdominal trauma after a terrorist bombing attack amongst the civilian population in Israel who required laparotomy on admission to Hadassah Hospital Jerusalem, Israel, in the 5-yr period from 2000 – 2005, there were injuries to multiple body regions in 87.5% of cases, with shrapnel being the leading cause. In the same hospital, the pattern of thoracic injuries consequent to suicide bombing attacks resulted in 52.7% of the patents sustaining lung contusions and 45.5% of victims requiring tube thoracostomy, reemphasizing the requirement of all medics and paramedics to be trained to perform the relatively simple procedure of needle thoracostomy and tube thoracostomy on-site as part of BTLS.
- The approach to the problem differs in battlefield, rural, and urban settings since the type of injuries and the availability of facilities to manage the trauma are variable. However, the basic principles of staging casualty care remain the same. These are explained in detail in the succeeding paragraphs.
- It is paradoxical that, upon the least trained falls, the most important responsibility is saving lives and managing bullet injuries since the best position to become the first responder is usually the bystander. But suppose the first responder fails in his duty. In that case, the responsibility of the first response falls on the primary care doctor to whom the victim is taken, but after paying a heavy price, i.e., loss of precious time when a victim continues to bleed. Hence, correct decision-making by the bystander is the most important factor that impacts the survival of an individual facing severe blood loss and organ disruption within the golden hour and, at times, within the platinum 10- 30 minutes. Hence, it is necessary to form robust

guidelines for casualty care at all levels in a large country with a diverse topography like India, where the barriers to timely care are different for plains, hills, deserts, jungles, islands, hinterlands, heartlands, and border areas due to different time taken to cover the same distances by road /foot/ boat. Similarly, the problems of managing battle casualties in war and conflict zones (both civilians and armed forces) and managing crime scene casualties (both police and civilians) are different and need to be addressed carefully.

TACTICAL COMBAT CASUALTY CARE (TCCC) PROTOCOL

- TCCC covers three major aspects of the standard of care for modern battlefield/ terrorist operations. These are:
 - (i) Care Under Fire (CUF)
 - (ii) Tactical Field Care (TFC)
 - (iii) Tactical Evacuation Care (TACEVAC)
 However, it must be appreciated that these guidelines are not a substitute for sound clinical judgment.
- The medico-legal, forensic, and investigation angle to the issue is gaining importance, and it is time we put special attention to this aspect so that the culprits do not get away. Fear of getting caught/identified and punished is essential in reducing crime. Education & awareness programs from the school level & adoption of personal protective measures to minimize impact, e.g., lying down on the ground in civilian life on the sound of gunfights, and the adoption of special measures amongst police and armed forces will also reduce the injury rate. The broader use of surveillance cameras and an increased number of well-equipped forensic science laboratories in every district will become a deterrent to crime to some extent.
- Future threats, advances in firearms and explosives, and newer and more ingenious methods to inflict damage need to be weighed closely and factored in a structured and sustained manner as a state policy. Corrective measures need to be instituted continuously with periodic up-gradation. Training and adoption of the Massive Hemorrhage Airway Resuscitation Circulation Hemorrhage and Head Injury Everything else (MARCHE) protocol, along with widening the training network in BLS/ATLS/ATCN as a mandatory component of life skill training from early schooling days is important.
- A clear doctrine of optimal usage of casualty care resources is required for casualties occurring in remote areas. It is essential to move the life-saving elements to the point of incident'. Putting undue emphasis on quickly shifting to nearby hospitals to save a life over that of securing vital elements, i.e., respiration, bleeding, and spinal stability, is to be discouraged. Hence, there is a need to invest heavily in Far Forward's casualty care if preventable death is to be reduced & specific action is initiated towards this before evacuation by road/air. This is essential to prevent delayed medical intervention and improve survival.
- Once a patient reaches a primary care echelon, doctors and nurses must possess higher-order skills in 10 areas, and all items required to achieve this must be available on the ground. This applies to both civilian and military environments.
 - (a) Ability to intubate a patient
 - (b) Ability to place intra venous (IV) drips & central line & manage shock
 - (c) Ability to place a thoracostomy needle and chest tube
 - (d) Ability to pack the abdomen and place a binder to stop an ongoing bleed
 - (e) Ability to pack an open bleeding wound by hemostatic dressing and apply a tourniquet correctly
 - (f) Ability to stabilize spine and limb
 - (g) Ability to do percutaneous tracheostomy and cricothyroidotomy in maxillofacial injuries with flail jaw and tongue fallback
 - (h) Ability to catheterize/do suprapubic percutaneous cystostomy
 - (i) Ability to relieve pain without undue sedation.
 - (j) Ability to safely transfer the victim to the next trauma care echelon
- The structure and quantum of medical support must be flexible and pegged with population concentration, limitations of reach due to terrain constraints, and the anticipated intensity of combat/ terrorist damage. Further, once given, the evacuation request should materialize by a clear algorithmic approach to a non-threatening sector/ area with a better trauma care facility. This facility may be a military/civilian hospital (private/public) and must be integrated into the war planning. The Nation fights modern wars as a whole approach with armed forces, paramilitary, airlines, ship industry, industrial complexes, Indian Space Research Organisation (ISRO), National Technical Research Organisation (NTRO), and Defence Research and Development Organisation (DRDO), and the role of more than Indian 1,00,000 doctors, nurses, and the citizenry must be clearly defined to fight the threats faced by an emerging power who aims to redefine the world order.
- Interaction between civilian Medicare set-ups and military organizations in peacetime as part of the national effort needs to be expanded and the capabilities of each other leveraged. These organizations, which form the sheet anchor of medical care in India, must integrate in a major way and incorporate the private sector in the effort.

MANAGEMENT OF GSW AND BI

Basic features of explosion and BI

Higher order explosives (HOE) like Tri Nitro Toluene (TNT), C-4, Semtex, Nitroglycerine, Dynamite, and ammonium nitrate fuel oil (ANFO) produce supersonic blast waves that cause direct damage, e.g., Lung rupture, Gastrointestinal (GI) perforation and hemorrhage, ear damage by rupture of tympanic membrane, disruption of the middle ear, rupture of the globe of eye as primary damage due to direct impact of blast wave. Secondary injuries may occur due to the effects of projectiles, i.e., damage may occur due to flying debris and fragments, which can lead to penetrating/blunt injuries and fractures in any part of the body, and tertiary injuries as the individual gets thrown by the blast wind, leading to head injury, visceral injuries, fracture, and traumatic amputations. All of the above and also the impact of other mechanisms/circumstances can lead to asphyxia/crush injuries/burns/sudden aggravation of existing medical conditions termed as quaternary injury. Low impact explosions (LOIE's), e.g., pipe bombs, Molotov cocktails, and gunpowder, have a much lesser blast effect.

Primary injuries

- **Blast lung:** It is diagnosed by a clinical triad of apnea, bradycardia, and hypotension and confirmed by the characteristic butterfly pattern on Chest X-ray. It may also present as dyspnea, cough, hemoptysis, and chest pain. A chest tube is recommended to be placed prophylactically before transfer by air or before general anesthesia.
- **Blast ear:** - It may present as sudden tinnitus deafness or ear bleeding due to Tympanic membrane perforation, as vertigo or otalgia, or a different combination of the above. Sudden deafness may occur, requiring the written mode of communication in an otherwise normal individual.
- **Abdominal injury:** - A containing bowl may perforate, and solid organs may rupture, e.g., liver/spleen/testes. Acute presentation may be as severe pain in the abdomen of sudden onset or unexplained hypotension/ hypovolemia and, after 24 hours, may present with signs of peritonitis and, after another few days, with signs of sepsis. Hence, an element of suspicion must be there to diagnose this in an otherwise normal bystander near a blast injury reporting to a doctor.
- **Brain injury:** - Mild traumatic brain injury (MTBI) (concussion) without any direct blow to the head may present as headache, fatigue, poor concentration, lethargy, depression, anxiety, insomnia, and other symptoms of post traumatic stress disorder (PTSD). This must be kept in mind since there are no overt injuries.

Non-primary injuries

- Any organ/tissue may be injured. Hence, the clinical presentation may be of an unconventional pattern. This may be
 - As visible in a penetrating trauma,
 - As features of blunt trauma with or without inspection findings
 - As air embolism presenting clinically as stroke, MI, acute abdomen, blindness, deafness, spinal cord dysfunction or claudication
 - As burn injuries
 - As acute renal failure
 - As compartment syndrome with tense, painful/ anesthetic/pulseless limb
 - As features of carbon monoxide (inadequately burnt coal)/cyanide (burning plastic) poisoning if the incident occurs near ammunition storage points and presents as confusion, headache, difficulty in breathing, cyanosis, etc.

Important points in management

- All medics and paramedics should be mandatorily trained in trauma life support courses as part of their Degree/ Diploma/Certificate program and learn the MARCHE protocol.
- Recognizing a gurgling sound in the throat as an impending airway obstruction and the importance of placement in a coma position (recovery position) as a reflex behavior amongst citizens cannot be overemphasized. The ability of students in schools to demonstrate BLS capability should be rewarded with additional marks from Class VIII onwards as recognition of a very important skill level.
- Ability to stop the bleeding, insert I-Gel, secure IV lines, give fluids, splint fracture, tie a pelvic binder, and insert a needle (in second intercostal space) to decompress a pneumothorax does not require a great amount of training in an aware, intelligent, confident and the rising Indian population. This can become part of Class Xth, XIth, and XIIth curriculum and be practiced on interactive mannequins available as a Make in India product. This has been validated to be an achievable skill among interested non- Medics with no formal training in medicine.

MARCHE PROTOCOL

All doctors, nurses, and paramedics must become competent in resuscitation techniques and follow a standard protocol to minimize omissions of vital steps in caring for the injured. This may be combined with a checklist to ensure and reduce unintended errors.

M (Massive Hemorrhage): Stop the bleeding by application of hemostatic dressing (chitosan/kaolin based dressings) and tourniquet and Inj Tranexamic Acid 1gm IV over 10 minutes in the event of massive bleeding and, if required, repeated hourly to a maximum of 8 hours.

An (Airway): Perform head tilt, chin lift, and jaw thrust maneuver to open the airway, insert the Naso-Pharyngeal airway, suck out the oral cavity clear of secretions to prevent aspiration, exclude spine or pelvic injuries, and place the victim in the recovery position. In extensive maxillofacial disruptions, using naso-pharyngeal airway (NPA)/ innovative gel (IGe)/endotracheal tube (ETT) is not usually feasible. Hence, training in cricothyroidotomy in manikins/ simulators is important so a person can replicate it in real life.

R (Resuscitation): Needle decompression by 18G or 16G intricate or BT needle in the triangle of safety [with the arm abducted, anterior axillary fold (lateral edge of pectoralis major) & posterior axillary fold (lateral edge of latissimus dorsi) diverges as it descends from the apex of the axilla. Its intersection with a horizontal line at the level 5th ICS (level of nipple in males)] forms a triangle. A needle introduced at the upper border of ribs within this triangle saves the life of a tension pneumothorax patient exposed to GSW/ nearby explosion by converting it technically into an open pneumothorax. Similarly, the insertion of a chest tube (ICD) to treat hemothorax (3rd leading cause of death) should be a mandatorily acquired ability for medics, nurses, and paramedics.

The ability to perform this simple procedure along with CPR and stoppage of bleeding should be validated every 5 years and linked with the renewal of a license to practice. Suppose the victim does not have a good breathing effort. In that case, inserting a supraglottic airway like i-Gel is uncomplicated. It is life-saving when combined with ventilation by a self-inflating bag with oxygen and an peripheral oxygen saturation (SPO2) monitor. Any doctor who cannot do this simple action should not have the right to do clinical practice.

C (Circulation): Rising pulse and falling blood pressure (BP) are signs of impending shock, especially if accompanied by intense sweating. They indicate the need to infuse IV fluids to maintain BP at 70 - 90 mmHg systolic (permissible hypotension) until bleeding is controlled. Attempting to elevate the BP beyond 90 mm Hg by infusion of extra fluids may restart a bleed and hence should be avoided in a field situation. A blood transfusion may be required if blood loss is assessed to exceed 1 liter.

H (Hypothermia/Head Injury): Keep the hypothermic patient warm to reduce the chances of coagulopathy and hypothermia. Treat hypothermia energetically to avoid the

lethal triad of hypothermia, coagulopathy, and acidosis in polytrauma by the use of thermal blankets and warm air. In a patient with a head injury, instead of Glasgow Coma Scale (GCS), the Alert Verbal Pain Unresponsive score is easy to comprehend for a common population, i.e.

A: Alert

V: Response to verbal commands

P: Response to pain

U: Unresponsive

Head Injury patients should be maintained at a 30° head-up position using blankets and pillows or by lifting the head end of the stretcher. This reduces venous pressure and ensures good venous drainage.

E [Everything else (M-PHAAT-D)]:

M: Monitoring: - Pulse, BP & SPO2

P: Pain Management: - Using Paracetamol/ Tramadol/ Morphine

H: Head to Toe examination: - To confirm/exclude additional injuries

A: Address all wounds

A: Antibiotics: - Broad-spectrum antibiotics + Metronidazole

T: Tactical evacuation preparation: - To reduce the time from injury to surgery.

D: Documentation of the care given: - Provide the subsequent treating team with useful information.

GENERAL CONSIDERATION IN PRE-HOSPITAL AND REMOTE FIELD SETTING

- A normally breathing and fully conscious patient of GSW/BI with a pulse of less than 110/ min and BP of more than 90 mm Hg systolic, and absence of diaphoresis (who is not sweating profusely) needs only the bleeding to be controlled as an immediate measure. Clear mentation + systolic BP > 70mmHg indicates ≤30% blood loss, and here, IV fluid should be withheld in field conditions as it may lead to re-bleed/ hypothermia. Hence, only once the person reaches a hospital, a normal BP should be achieved by giving 1 to 1.5 liters of hydroxyethyl starch (HES) or Ringer's Lactate in an adult to achieve a systolic BP of 90 mmHg and conduct surgery planned.
- Application of a tourniquet to control a bleeding wound is generally done 3 inches (10 cm) above the bleeding site, preferably on a single bone, and if it is inadequate to control bleeding, tie another one above it. The junctional tourniquet is of immense value when bleeding from the axilla or inguinal area occurs. Similarly, hemostatic dressing

applications are always to be accompanied by adequate pressure to be effective and, if inadequate, may either be topped with a second compression dressing or replaced with a larger one. Inflatable Target Compression Devices are a new addition to the armamentarium to stop bleeding and should be available in all trauma centers. Explosion-induced Traumatic amputations are often associated with multiple and multi-organ injuries. They, hence, are usually accompanied by hemorrhagic shock due to massive blood loss, needing fluid and blood replacement at the earliest, in addition to all the measures given above.

- (c) Pure head injury with intracranial bleed presents with bradycardia (slow pulse) and hypertension (high BP). If there is altered mental status with evidence of head injury, but the radial pulse is found to be fast (tachycardia) but weak (hypotension), it should be assumed that there is a second site of bleeding (chest/abdomen/limb) which needs to be searched for. Hemostatic dressing can be either Celox Gauze, Chito Gauze, or quick clot (there is no clear evidence of one being better or worse than the other). Mark all tourniquets at the time of application with a permanent marker. Limb bleed is compressible bleed & torso bleed is noncompressible, which must be kept in mind. A tourniquet can be applied to arms and thigh (single bones) at 250 mm Hg or 50 mm Hg over systolic BP, whichever is higher, for up to 2 hours safely. It must be emphasized that pressure above venous pressure and below systolic arterial pressure increases the bleeding rate from torn veins/venules, and hence, raising the pressure above systolic pressure is very important.
- (d) Some important points are:
- Bandage may mask bleeding due to capillary wick action and hence to be applied only when bleeding has been controlled by applying direct pressure & splint application.
 - Do not remove bullet/shrapnel unless confirmed to be away from critical vascular structures on X-ray/ USG, lest it leads to restart of an earlier controlled bleed. It is better addressed in the operation theater.
 - Limb elevation stops pure venous ooze.
 - Compress the artery proximal to bleed for 10 minutes until it stops bleeding, and gently clamp a vessel if it is visible. There should be no temptation to explore a wound in a state of hemostasis.
 - Explosion-induced fracture to be splinted to reduce bleeding and pain
 - Once the patient is stabilized, wash wounds gently and dress them to reduce contamination
 - Avoid wound debridement in field conditions to reduce the chances of uncontrolled bleeding.

- (e) Respiratory distress in an upper torso trauma merits needle thoracostomy and, if confirmatory, needs to be followed up with a chest tube. Any open/sucking chest wound should be treated by applying a vented chest seal immediately and, if not available, a non-vented chest seal with one side open keeping a close watch.
- (f) If possible, insert a urinary catheter and seek transfer to a higher facility. Hypothermia is avoided by removing wet clothes and covering them with blankets and warmers. The explosion may have led to penetrative eye injury. Do not put a pressure patch here; instead, cover it with a rigid eye shield and transfer it to a higher center. Explosion-induced burn injuries are common and are to be treated along standard guidelines, as are fractures due to the off effect. Keep in mind the possibilities of chemical/thermal injuries to the airways of the lung, especially when an explosion is sustained in a closed room since this patient is likely to have chemical pneumonitis and may have to be intubated early.
- (g) Safe Intubation can be ensured by adhering to the presence of essential items using a simple checklist, as per SOAP ME, in the ambulance and emergency department.
- S: Suction machine with preferably a Yan Kauer tip
O: Oxygen cylinder, Bull Nose fitting, Bains Circuit, Ambu Bag
A: Assortment of NPA, oropharyngeal airway, supraglottic airway (laryngeal mask airway, iGel), ETT Masks, bougie and Stylets
P: Neutral Position, especially if spine injury is suspected
M: Medication: Ketamine/Etomidate, succinylcholine/Rocuronium, Phenylephrine, Atropine, Adrenaline
E: Equipment: Video Laryngoscope, Multiparameter Monitor, preferably with EtCO₂, Cricothyroidotomy set, percutaneous tracheostomy set, Standard Tracheostomy set, and Endotracheal tubes are mandatory items in an emergency department.
- (h) Once resuscitated, as far as possible, use fresh whole blood to replace blood lost since it has sufficient levels of 2-3 diphosphoglycerate (2,3-DPG) & does not have the problems of hypothermia, acidosis, hyperthermia, and high cytokine levels. The inotrope of choice to treat hypotension in combat trauma is noradrenaline, except in high spinal injury with Bradycardia where dopamine is preferred. If a second Inotrope is required, Vasopressin should be added. Use dextra ethyl starch solution as an interim measure if blood is not available to treat shock.
- (i) Urine output is a good marker of organ perfusion. When arterial blood gas analysis (ABG) is used, base deficit & lactate level are the markers of adequacy of resuscitation. Serial hemoglobin is required to assess the need for blood transfusion to reach 8-10 gm %, and once this is achieved,

scale back the fluid/blood to avoid pulmonary edema/ adult respiratory distress syndrome (ARDS).

- (j) Thus, the ten main essentials for saving lives are:
 - (i) Triage
 - (ii) Management of difficult airway (MODA)
 - (iii) Avoidance of the lethal triad of Hypothermia Coagulopathy & Acidosis (HCA Syndrome)
 - (iv) Prevent ACoTS – Acute Coagulopathy of trauma shock
 - (v) Damage control resuscitation (DCR)
 - (vi) Damage control surgery (DCS)
 - (vii) Excellent Pre-hospital Care & resuscitations
 - (viii) Robust Transfer facility
 - (ix) Excellent post- operative Critical care management
 - (x) Rehabilitation of injured
- (k) In injuries sustained in remote areas, the severity and lethality factors are much. The evacuation to even a basic trauma care center is usually delayed due to administrative constraints, rugged terrain, hostile environment, snowbound/jungle/desert/marshy areas, and facilities to treat surgical trauma being located far off, necessitating provision of house & On site management within the golden hour. The positive aspects are that the injured soldiers are generally young, healthy, and have a good physiological reserve; hence, if proper intervention is done within the golden hour, chances of survival increase substantively. Therefore, all efforts should be made to plan timely interventions.
- (l) If any evacuation is expected to take a long time, it is better to stage it with periodic re-assessment and corrective actions. Communication (telephonic/ Internet-based App) helps guide interim treatment and plan safe casualty evacuation (CASEVAC). Decide who will accompany the wounded casualty based on competency requirements. If the time to transfer to the nearest hospital is more than 1 hour, administer Inj TXA (Tranexamic Acid) 1gm (100 mg/ml) intra venous/intra osseous over 10 minutes repeated hourly for up to the next 8 hrs. It works by stopping blood clots from being broken down.
- (m) Special points for Ships: Care for merchant ships under pirate attack at high seas has to be given closest to the site of the operation/ incidence, including damage control surgery at sea before evacuation to a unit/ hospital with bigger holding capacities and better capabilities. In ships with closed compartments, explosions lead to shrapnel injuries. In the absence of safe zones in the sea, the possibility of casualties being carried out is limited. Hence, moderately advanced life-saving facilities must be provided, considering replenishment is impossible at high sea. Therefore, self-aid buddy care (SABC) has

special importance, emphasizing 15 minutes of direct pressure, tourniquet, suction, IV access, and needle chest decompression until doctors can attend to the victim.

GENERAL CONSIDERATION IN HOSPITAL MANAGEMENT OF BULLET AND BI

- A hospital where a bullet/ blast injury patient has arrived must always be in a state of readiness to receive them. The hospital's critical care team on call must be on the premises when the patient arrives. Hence, it will be of great value if the information on impending arrival is transmitted to the nearest trauma hospital well before by a centralized web-based helpdesk. The various actions expected are as given below
- (a) Confirm readiness for combat trauma anesthesia using a carefully prepared checklist.
 - (b) The ATLS/MARCHE protocol is to be followed as given above. The main points for consideration are
 - Wide bore IV access + Hb level + Grouping and cross matching
 - Extended Focused Abdominal Sonography in Trauma (FAST):
 - Check for Fluid/Blood in
 - o Peritoneum
 - o Pericardium
 - o Pleural cavity
 - Start broad spectrum Antibiotic cover, e.g., by triple drug-Cefotaxime+ Amikacin+Metronidazole
 - Relieve pain and anxiety with Opioid + Non steroidal anti inflammatory drug (NSAID) combination
 - Regional anesthesia/blocks for targeted pain relief
 - Vasopressors & fluid resuscitation to treat hemorrhagic shock
 - Inj TT 0.5ml if immunization status is not known
 - (c) Prioritize in the event of a mass casualty and decide
 - Who has more chances of survival
 - Who will give some more time for intervention
 - Who will eat away more time at the cost of more lives
 - Who can be evacuated only by critical care team & who can go by standard ambulance or a passenger vehicle with citizen paramedics?
 - If early total care (ETC) is planned: Intervene on day 1 (Silver Day) only if the patient is stable hemodynamically and has normal respiratory rate, temperature, urine output, coagulation profile, and lactate levels.
 - If DCS is contemplated, ensure that a backup primary critical care facility is available to transfer patients out by patient transfer unit (PTU)/critical care air transfer team (CCATT) quickly if necessary.

DAMAGE CONTROL RESUSCITATION

- (a) **Effective hemorrhage control** with restricted volume replacement strategy, enough to ensure critical organ perfusion, indicated by a permissive hypotensive state of systolic BP of 70-90 mmHg (MAP 50-60 mmHg) till major bleeding due to gunshot/explosives has stopped, ensures clot integrity and obviates dilutional coagulopathy, hypothermia, and acidosis. However, in traumatic brain injury, MAP of >80 mmHg is recommended. Tranexamic acid loading dose of 1gm over 10 minutes followed by maintenance infusion of 1gm over the next 8 hours is recommended whenever bleeding cannot be controlled.
- (b) **Anesthetic considerations:** Maintain a neutral position by removing only the front half of the Philadelphia collar while intubating when performing RSI. In field situations, the patient should not be paralyzed unless ventilation with a bag and mask is possible. Avoid drugs like Propofol & Thiopentone for induction since they can cause hypotension in a bleeding patient. Hence, Ketamine and Etomidate remain the drugs of choice for induction, and succinylcholine to induce muscle paralysis. Algorithm for damage control resuscitation is as given in Figure 1.
- (c) Remember to secure the ETT/Tracheostomy well against dislodgement during transport and watch for a drop in BP following intubation.

DAMAGE CONTROL SURGERY (DCS)

- Indicated ongoing bleeding in a severely injured victim who is progressing to hemorrhagic shock. Damage control intervention in compressible areas (limbs) may be done if ischemia is imminent. e.g., to restore femoral/brachial blood flow. Similarly, one may be required to intervene in inaccessible major organ injury needing interim intervention to buy time for a definitive surgery once the patient stabilizes.
 - Ketamine remains the mainstay for induction, and thereafter, a volatile anesthetic agent can be used for the continuation of anesthesia.
 - Rapid sequence intubation with readiness for cardiac arrest and resuscitation is a key element.

- Attempt laryngoscopy and intubate
- If unsuccessful place SGA device and intubate using it
- If unable to place SGA device continue facemask ventilation to gain time and attempt once more once saturation improves
- If still unsuccessful do a cricothyroidotomy and continue ventilation
- Once situation under control consider tracheostomy
- If the patient is fully conscious and is not in threat of choking-consider extubation

Figure 1: Algorithm for damage control resuscitation. SGA: Supraglottic airway.

- Stop the bleeding: If direct pressure for 5 minutes fails to stop rapid hemorrhage, it indicates an arterial injury or large venous rent.
- Once the bleeding is under control, aim to achieve permissible normotension (systolic BP of <100 mm Hg)
- Monitor volume status by maintaining urine output at 0.5 ml per kg body weight
- Do not attempt extubation after DCS for 24-48 h until the decision to conduct or not conduct a relook surgery is taken if the patient is in a definitive care set-up. If the care required is beyond the hospital's capability, transfer the patient to an intubated state.
- Keep patients warm by using fluid warmer 'and forced air warming system'
- While evacuating, ensure the correct complement of medics/ paramedics, emphasizing maintaining a lung-protective ventilatory strategy.
- Scalp bleed is best stopped by running and locking vertical mattress suture guided by everting the skin edge with a hemostat.
- In the case of open head injury with skull fractures, the loose fracture fragments of the skull should never be pushed into the brain by compression and should be removed. Place petroleum medicated gauze, with a wide dressing over it, with gentle pressure, till the patient reaches the neurosurgical center in a 15° head position.
- In all major injuries, a self-retaining Foley catheter is placed to monitor urine output once the patient's vitals are stabilized.
- Pelvic injuries are to be managed by placing a pelvic binder/ bed sheet/large towel at the level of the greater trochanter and securing it with tight knots/pin/stitch
- Pain relief reduces systemic response and preserves victims' morale. This can be achieved by Injecting Paracetamol 1 gm, Tramadol 100 mg, and Morphine 3 mg, repeated for 6-8 hours. Nerve blocks are very useful for pain relief and must be used whenever feasible to help reduce the requirement for opioids and other sedatives.
- Limit DCS's aims only to control bleeding to save lives and salvage limbs. Stabilize after that and transfer. Defer repair of anatomical lesions. Aim to restore physiology instead.
- Amputate nonviable limb with vascular injury. Use temporary shunts for emergency vascular repair.
- Laparotomy, if done, pack to stop bleeding with the safe application of clips and use a vessel sealing device, with no attempts to attempt ETC, which should be left for the higher center.

- Special attention is required if
 - o Age greater than 70 years (higher risk due to age and co-morbidity)
 - o Systolic BP less than 90mm Hg (impending shock)
 - o Base deficit ≥ 6 (Acidosis)
 - o PTT > 40 sec or INR > 1.4 (Coagulopathy)
 - o GCS ≤ 8 (severe functional/anatomical brain compromise)

Timeline to intervene

- o Day 1: Only DCS to restore physiology.
- o Day 2-4: Only a second look procedure since the body is Hyper-inflamed.
- o Day 5-10: Definitive procedure (window of opportunity)
- o Day 10-20: State of immune suppression, no intervention
- o Day 20 onwards: Secondary reconstructive surgery.
 - After surgery, keep the patient warm, restore volume deficit, prevent coagulopathy, give ventilatory support (if required), and monitor well.
 - As a thumb rule, do not remove the abdominal pack for 48 hours unless compartment syndrome sets in. DCS is unsatisfactory and is a cause of concern due to insufficient initial control of spillage from the gut or if signs of infection set in. In such circumstances, it is prudent to re-examine under controlled settings, change packs, achieve hemostasis, decontaminate, and make a feeding jejunostomy/gut diversion. A check X-ray is necessary to confirm the removal of the old abdominal pack.
 - Desperate re-exploration in coagulopathic, acidotic unstable patients is to be attempted only in higher centers and never in mass casualty situations, where it is better to concentrate on the salvageable.

DCS for chest injury

Thoracic Injuries due to blasts and firearms need quick interventions

- If voice is normal, any chest injury with difficulty in breathing is a candidate for needle decompression followed by chest tube insertion.
- Distended neck veins in the presence of hypotension and clear breath sounds indicate cardiac tamponade and merit an emergency pericardiocentesis (preferably USG /FAST guided), followed by transfer to a higher center.
- Hemothorax merits tube thoracostomy. Blood >1500 ml or flow rate of > 300 ml per hour merits thoracotomy and non-anatomic stapling of lung & blood transfusion to save life.

- Open pneumothorax needs a one-way flap seal on the wound, followed by tube thoracostomy at another site on the same side, after which the original wound may be closed by a tight suture followed by planned transfer.
- Flail chest: - Assume co-existing underlying pulmonary contusion.
Control pain by non-narcotic drug or by block (intercostal/paravertebral) and even epidural analgesia if feasible. Signs of desaturation merit intubation and evacuation.

DCS for thoraco-abdominal injuries

Any bullet injury below T4 (nipple level) merits evaluation for abdominal injuries.

Abdominal trauma

- (a) The most important decision is whether to operate in a remote area or a forward surgical center. This is done by balancing one's ability with the limitations of the facility and the possibilities of a safe evacuation. The decision should be based on appreciating the limitations of the facility's diagnostics, the limitations of the facility for supportive care, and the probability of safely transferring a patient within a specified time limit to a higher center.
- (b) Bullet/ penetrating injury between the nipple and pubic symphysis in front and from the tip of the scapula to the sacrum behind indicate retroperitoneal/intraperitoneal injury.
- (c) Focused Assessment with Sonography in Trauma (FAST) is very beneficial in the absence of which diagnostic peritoneal aspiration (DPA), i.e., Four Quadrant Tap 'should be done in field conditions and, drawl of 10 ml or more Frank' blood from any one quadrant constitutes an indication for early laparotomy. If the facility is unavailable, it merits transfer by the fastest means to a higher center.
- (d) FAST indicating a lodged bullet outside the peritoneal layer can be extracted, avoiding a full laparotomy provided DPA is negative and no free gas under the diaphragm and hemoperitoneum is excluded.

Laparotomy

In Laparotomy for trauma, the general guidelines are: -

- Midline full incision under broad-spectrum antibiotic cover.
- Pack all four quadrants while searching for injuries.
- Stop the bleeding: Clamp/staple/stitch on sighting the fresh bleed under direct vision.
- Reassess an unstable patient continuously and consult senior colleagues whenever possible.

- Visualize all solid organs and hollow viscus.
- Right/left medial visceral rotation, to expose retro-peritoneal injuries, to be attempted only if the experienced surgeon is present and avoided as far as possible in a field condition.
- Complete surgery within 1 hour (patient is usually unstable).
- If necessary, avoid post-operative abdominal compartment syndrome by temporarily closing the abdomen with a mesh or plastic bag (Bogota bag) and placing an NG Tube and urinary catheter to reduce intra-abdominal pressure.
- Retro-peritoneal gas indicates duodenal or colonic injury and may be sutured/drained/diverted based on competence level.
- Pancreatic injury – Don't disturb unless bleeding actively.
- Rectal bullet injury may be associated with pelvic fracture fragments. Packing in a field situation is safer. Later, it can undergo primary repair with a proximal loop colostomy.
- During DCS for abdominal injury, the steps are:
 - o control hemorrhage
 - o check the extent of the injury
 - o control contamination (resection/washing)
 - o do therapeutic packing and close temporarily

Liver injuries

Once confirmed by FAST, operate only if unstable; otherwise, transfer to a higher center. If compelled to open as part of DCS, pack the liver, spray hemostatic fluids on the bleeding surface, plus give Tranexamic Acid (TXA) (intravenous). Transfer blood if the situation permits. Definitive surgery should be done only in higher centers.

Splenic injuries

Once confirmed by FAST, splenectomy is only if there is ongoing bleeding—no role of splenic conservation in GSW injuries.

Head injuries

Gunshot penetration may be accompanied by bleeding from multiple orifices (ear, nose, and mouth). In contrast, the blast effect on the brain may present subtly as cognitive dysfunction, inattention, loss of concentration, reaction time delay, and posture imbalance. The important points are

- Look for mentation and diaphoresis; the presence of hypotension indicates a second injury other than the brain since isolated closed head injury presents as hypertension.

- Assume cervical spine injury and apply a Philadelphia-type collar. Examine the scalp for entry/exit wound.
- Intubate to correct hypoxia, infuse to correct hypovolemia
- Gently examine the scalp for loose fracture fragments, and after gently washing with saline, place a sterile drape.
- Do not pack ear/nose/throat in an ongoing bleed to prevent intracranial collection of blood. Take an AP and Lateral X-ray, including Cervical Spine
- Quickly conduct CASEVAC except in life-threatening extradural haematoma (EDH)/subdural haematoma (SDH). Do emergency craniotomy to avoid a decorticate/decerebrate state.
- While planning evacuation, the general principles are:
 - o Unconscious – intubate and transfer thereafter.
 - o Wide decompressive craniectomy, before transfer in desperate situations, enables survival and enables the opportunity for definitive treatment in a higher center later. Preserve the loose cranial segment in the saline/abdominal pocket.
 - o Critical care team must accompany evacuation.

Pelvic injuries

Check for entry/exit of the bullet's path and make a calculative guess.

- o Make only one careful attempt to assess the mechanical stability of the pelvis by compression and distraction. If unstable, apply a pelvic splint.
- o Watch for leg length discrepancy, scrotal/labial swelling, ecchymosis, and abrasion, suggesting pelvic ring injury
- o Per rectal/Genito, the urinary exam rules out/confirms the presence of a compound fracture. X-ray (AP view) + FAST confirms blood/gas in the peritoneum.
- o If blood in meatus/urine - FAST guided suprapubic cystostomy is a simple option
- o Possibilities of retroperitoneal hemorrhage and coagulopathy to be kept in mind and may require transfusion of blood and blood products.
- o Pelvic binder/bed sheet tied tightly at the trochanter level/placing sandbag/bean bag at the trochanter level/lying in lateral decubitus with injured side down & ankles tied (internally rotated femur) helps reduce bleeding. An external pelvic fixator may be applied on transfer to a higher center. In desperate uncontrolled arterial bleeding, stop the bleeding by the retroperitoneal pack with a suprapubic incision.
- o On laparotomy, if you see a controlled retroperitoneal hematoma, never open it. Just do a diversion colostomy if necessary.

FRACTURE AND ASSOCIATED SOFT TISSUE INJURIES

- Dictum is delayed primary closure of the contaminated wound
- Bullet-induced open fractures in field condition should only be splinted, with a close watch for neurovascular deficit and onset of compartment syndrome
- Blast injury-induced fracture needs irrigation and debridement and the application of cast/slab with a window/external fixator.
- Pain on passive extension, tense edematous limb, and loss of sensation in the first webspace in the foot are signs of impending compartment syndrome and merits fasciotomy.
- Mangled extremities due to rip-off limbs (when at least three out of the four, amongst soft tissues, bones, nerves, and vessels, are damaged) with ongoing hemorrhage merits consideration for amputation as a part of DCS & DCA
- Warm ischemia time of more than 6 hours merits consideration for amputation of limb at an appropriate level as a life-saving measure.
- The guiding principle is Always saving a life over limbs whenever possible.
- Use of loupe magnification, good lighting, and tourniquets helps visualize tissue better
- Whenever in doubt, excise muscles, fascia, and loose bones but conserve skin.
- Since collaterals may maintain distal perfusion, it does not exclude major vascular injury in the limb but gives some more time to respond. One must watch out for an expanding hematoma, which may be addressed by a temporary shunt using plastic IV tubing/drain tubes/reversed vein graft interposed if expertise exists. Heparinize only if there is no other threat of uncontrolled bleeding.
- Nerve transactions should be marked by colored, non-absorbable sutures for easier identification by the surgeon later.
- Dressing of wounds should be done with sufficient pressure to stop the bleeding. However, toes and fingertips should remain exposed whenever uninjured to continuously assess the vascularity.
- Amputation: - Clinically reddish-brown urine in a dead limb 'indicates Myoglobinuria with impending ARF and weighs in favor of a decision towards amputations.

SURGICAL CONTROL OF VESSEL BLEED

- (a) Temporary shunt should always be attempted in major vessel injuries, failing which quick ligation and control of

bleed become necessary to save a life. Advanced training to approach proximal subclavian vessels through midline sternotomy/anterolateral thoracotomy/clavicle head resection is uncommon, but if present, it is very valuable in a remote location where an endovascular facility is unlikely.

- (b) To save a life, the vessels which may be ligated without a major deficit in a GSW & BI are:
 - (i) Vein: - External Jugular (both sides), Internal Jugular (one side), Brachiocephalic, Infra renal IVC, left renal, Internal Iliac, subclavian, mesenteric, Tibialis anterior/Tibialis Posterior/Peroneal.
 - (ii) Arteries: - Digital, radial/Ulnar (one of two), external carotid, Brachial distal to profunda brachii, internal iliac, profunda Femoris, hepatic artery.

LABORATORY AND IMAGING SUPPORT

- (a) Complete blood count (CBC), serum electrolytes, blood sugar, renal function test (RFT), liver function test (LFT), creatinine phospho kinase (CPK), and blood lactate are desirable tests that require making available. Prescreened blood and blood products are preferable, but if not feasible, fresh whole blood is to be used after testing for Human Immunodeficiency Virus (HIV)/Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV), syphilis, and malaria (preferably by card-based test) as per National Aids Control Organisation (NACO) guidelines along with blood grouping and cross-matching. Temperature criteria for the preservation of kits must be carefully maintained.
- (b) Hand-held X-ray and USG with convex sector/curvilinear transducer is a valuable tool for detecting bullet fragments/splinters, pneumothorax, hemothorax, fractures, hemoperitoneum, and torn/damaged solid organs.
- (c) FAST: Uses 3 to 7.5 MHz curvilinear/sector transducer. USG performed within 5 minutes of arrival in the presence of an overwhelming number of casualties due to bullet/explosion/ BI is an extremely beneficial test to diagnose the problem of hemothorax/pneumothorax/haemo-haemo-pneumoperitoneum in an unstable patient. The standard views to be taken care
 - Longitudinal right upper quadrant - To look for fluids in perihepatic/subphrenic/Morrison's pouch
 - Longitudinal left upper quadrant - To look for fluids in peri-splenic, splenorenal, and subphrenic areas
 - Suprapubic view- To look at the pouch of Douglas
 - Transverse Subxiphoid view- To look at Mediastinum and pleural space for hemothorax)
 - Right and left lateral view - To look for fluid at right and left paracolic gutters

- General view- To detect solid organ injuries
- During an ultrasound examination, assuming the Trendelenburg position helps transfer fluids to the upper Quadrant and the Anti-Trendelenburg position to the pelvis gives a better diagnosis window.
- E- FAST: - Higher frequency linear transducers used with dual probes of 3-3.5 Hz and 7-12 MHz are now available in the market and used to diagnose Pneumothorax better by detecting
 - o Absent pleural sliding
 - o A line more numerous than normal and placed unevenly
 - o Absence of B lines
 - o Signs on M-mode ultrasound barcode or stratosphere sign.
- IVC diameter evaluation to assess hypovolemia: Using a subxiphoid approach with a transducer in sagittal orientation, the IVC diameter 2 cm below the Cavo Atrial junction is measured. IVC collapsibility >12 to 15% indicates volume depletion levels and the requirement to step up fluid/blood.
- Solid organ injury: - Look for
 - o Subcapsular collection in the Liver/Spleen
 - o Heterogeneous appearance of liver/spleen parenchyma – indicates bleeding/injury/ damage
 - o Echogenic area within the liver/spleen parenchyma suggests laceration.

MEDICO-LEGAL ASPECT OF GSW AND BI

- GSW/BI in a combat scenario are treated with implied consent for emergency care in a combat zone. However, legally valid consent is important for elective interventions.
- Identification of death in war zones should be carefully done ethically and morally.
- Even a bullet-infected patient has the legal right to autonomy and self-determination enshrined within Article 21 of the Indian Constitution and can refuse treatment unless the intervention is labeled emergency.
- Informed refusal also forms an important part of informed concern, and a patient may choose for intervention only in a higher center. Hence, legally valid consent is important. However, in a tactical combat scenario, only implied consent is sufficient, provided an imminent threat to life or limb exists.
- When GSW/explosive blast injury gives you some time for a second opinion, it may be taken if required.
- Death in combat zone/terrorist operations/civilian life merits clinical autopsy/Medico-legal autopsy after clearance by military/ police/UN observers, and records of it are required to be kept in safe custody

- Victim of bullet injury may wish to make a dying declaration. In such circumstances, the magistrate of the enemy country is intimated. When he cannot come, the MO may record the Dying declaration after certifying the soundness of mind in the presence of 2 witnesses whose signatures are affixed to the document. A video of the dying declaration may be recorded if in a hospital.
- The personal effects of the victim should be disposed of correctly.
- Radiographs, Fingerprints, and basic dental data must be recorded and matched to establish identity.
- In war injuries, the international code of medical ethics, laws of armed conflict, and the International Convention on Human Rights (Geneva Convention) should be followed, and matters of conflicting loyalty should be addressed.

RECOMMENDATIONS OF TASK FORCE GROUP

The key recommendation of the white paper is as given below:

Policy formulations, facility improvement training, education, and awareness programs on medical aspects should be targeted

(i) To address the issues related to lack of the lack of data about gunshot & BI:

Problem: How many cases of gunshot or BI are treated in civil and armed forces hospitals in a year? No data is available since there is no trauma, gunshot, or blast injury registry.

Recommendations: Eminent institutes may be entrusted with establishing a well-funded, well-staffed independent department. There is a need to develop countrywide Trauma registries to know the exact number of gunshot injuries and BI, age group, occupation, gender, causes, circumstances, nature of firearm/explosives used, part of the body affected, high-risk areas, high-risk groups, and so on. Only then will the pattern and likelihood become apparent.

(ii) To address the issue of insufficient knowledge amongst citizenry about the 'First response' to gunshot & BI.

Problem: Action taken within the first 30 minutes to stop bleeding and maintain respiration usually decides whether the victim will live. However, most of the victims do not reach the nearest trauma centers within this time. Often, patients are taken by bystanders/ good Samaritans without any measures to stop the bleeding or secure the airway due to a lack of knowledge about how to do it. Every year, a large number of precious lives are lost unnecessarily.

Recommendations: All children from the school level be taught how to stop bleeding from a wound and how to give CPR by the periodic practice of First Aid from class VIII onwards, teaching them the basics of Life Support (BLS)

in class VIII and IX, and making BTLS a compulsory part of Class Xth exam. Unskilled and untrained citizens could easily perform this in a trial setting. Hence, all citizens of India should know this and should not be left to medics and paramedics to whom a victim does not reach soon enough

(iii) **To address the issues related to the quality of Patient management:**

Problem: There is no fixed protocol followed in managing patients with gunshot wounds or BI in the majority of hospitals. In most tertiary care level hospitals in civil setup, super-specialists work on contracts and are available only on calls. In many hospitals, patients are managed locally according to the system in vogue. The surgeon managing thoracic injury may not be comfortable managing an abdominal or vascular injury. There is a scarcity of trained and experienced surgeons who are capable of analyzing the patient as a whole and who can understand the deranged physiology of the patient due to simultaneous injury to the multiple anatomical regions of the body, be it thoracic, abdominal, vascular injury or head injury and take a quick decision when to operate and when not to operate.

Recommendations: We need to shift patient management from a based to a holistic approach by ensuring that all diploma holders, graduates, postgraduates, and post-doctoral medics and paramedics must be trained in BTLS and ATLS, which needs to be incorporated as part of their educational qualification and validated by an independent agency. Once in a hospital, trauma management should be based on an established protocol and checklists, which, when followed, should provide reasonable protection from litigations. Further, all surgeons (including superspecialists) must conduct a minimum of 10 life/limb surgeries in a trauma center every 2 years as part of renewing their licenses. The specific issues about educational standards, certification, continuing education, and evaluation requirements for doctors involved in trauma care are yet to be fully addressed, and the time has come for a high-powered team of experts cum policy makers to deliberate on it and evolve a National Policy on the matter linked to license to practice.

(iv) **To address the issues related to lack of Rehabilitative services**

Problem: There is a lack of knowledge on the socio-psychological impact of gunshot injury and blast injury on the survivor and their families. PTSD (Post-traumatic stress disorder) is characterized as failure to recover after experiencing a terrifying event. This brings back memories of the trauma accompanied by intense emotional (flashbacks) and physical (pain, trembling) reactions due to heightened reactivity to stimuli, anxiety, or depressed mood and has a long-term impact on the

psyche of the victim. They need expert counseling but are currently counseled by amateurs in the field.

Recommendations: The apex medical institutes must initiate focused research in the field and train a subset of psychiatrists and Clinical Psychologists in the field of PTSD. GoI may consider the establishment of Rehabilitation Centers focused on rehabilitating Trauma Victims with a broad mandate to interact with intergovernmental agencies.

(v) **To address the issue of financial compensation for the trauma care providers**

Problem: Trauma victims, on many occasions, reach the emergency department as unknown and hence not in a position to pay for the services on arrival. However, the hospital is required to commit his resources immediately

Recommendations: The government has to develop a financial compensation policy for all trauma victims. This is because they constitute the largest share of preventable deaths all over the world and in a young earning population out on the road for work and leisure, thereby contributing to the nation's economy. Unless this issue is addressed, victims of critical firearm injuries in civilian life will continue to die by and large.

(vi) **To aim for a modern, well-equipped, well-networked ambulance service manned by ATLS-trained staff in all parts of India.**

Problem: Most state governments and Municipalities in the last 10 years have made substantial progress in developing their Ambulance services, e.g., 108 Ambulance which are integrated with call centers and work 24 X 7 X 365 days, and this service is slowly progressing towards even Tier 2 towns, which is very encouraging. However, as a nation, we have a long way to go to make these ambulances capable of handling Blast and GSW injuries; as of now, these ambulances can, by and large, give oxygen and fluids and have facilities to provide CPR.

Recommendations: Most of the ambulance services are not geared up to treat bullet/BI. The emergency ambulance services are required to be fully equipped with a certified staff proficient in BLS and ATCN/ATLS. Similarly, the ambulances are required to be equipped with trauma care products like a tourniquets, hemostatic dressing, resuscitation equipment, needle thoracostomy, tube thoracostomy, spine stabilizers, volume expanders, modern splints, along with AI-based interactive help modules, and GPS enabled patient-friendly modern vehicle.

(vii) **To introduce robust training in trauma care as part of the Medical, Nursing, and paramedical curriculum.**

Problem: Medical, Nursing, or Paramedical curriculums do not provide structured training in Trauma care. Hence, doctors, nurses, and paramedics' ability to manage bullet injuries is generally inadequate.

Recommendations: Basic management of bullet/ blast injury should become a compulsory element of all certificate programs, degrees, and diplomas in medicine, paramedical, and nursing education, with regular mandatory refresher training to maintain currency (online or offline or both in combination). ATLS for doctors and ATCN for Nurses and paramedics should become compulsory parts of the license to practice.

(viii) **All out efforts to be made to reduce the availability of illegal firearms**

Problem: Illegal manufacture of weapons, possession of illegal weapons as well as illegal usage of legal weapons is common in India, instilling fear and hesitancy in the mind of the general public. Whenever a citizen is forced to hold himself from his honest contribution towards his nation due to fear of certain elements of the society and those working covertly to weaken a nation's will, that nation can never rise to its true potential. All policymakers must give very high importance to this matter and address it.

Recommendations: All-around efforts should be made to reduce the availability of illegal firearms. A license should only be given when one has attained age 25, provided one clears a well-organized psychological test assessed by an experienced psychologist and can provide a valid reason for its requirement. This should be a mandatory prerequisite in even applying for a license for firearms, with legal provisions to monitor the owner's conduct in a continuum.

(ix) **All trauma centers should be well-staffed with competent medics**

Problem: Trauma centers should be managed by doctors, nurses, and paramedics with special trauma competence. This has been primarily diluted in most centers due to the non-availability of an adequate number of fully qualified certified staff.

Recommendations: Formal education and specialty training in emergency medicine, trauma surgery, and critical care are desirable (but not mandatory) attributes for personnel involved in trauma care, but is a mandatory requirement to expertly handle the disruption of the body due to bullet/explosive since it involves a different dimension of anatomical and physiological avalanche where time is in premium, i.e., quality of intervention in the platinum 10 – 30 min decides the fate of 50% of victims. However, such training is unavailable at most Medical/Paramedical training institutes. This needs to be addressed using advanced trauma simulators in training and a one-year internship in a higher-level center.

(x) **Records held by all stakeholders in crime management must be integrated into a shared database**

Problem: In India, various stakeholders concerned with bullet and BI, which constitute the maximum mode of crime, are not integrated.

Recommendations: It is suggested that all Police Stations, Medical Colleges, and District Hospitals where medico-legal postmortems are held and the associated Forensic lab, as well as the criminal courts, be integrated and a centralized database formed so that accurate, valid, and reliable data can be recorded. This may be considered a very critical repository of databases. All planning and policies can be made accurately if the integration is done correctly.

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-Sd-

Air Vice Marshal

Tanmoy Roy VSM

Chairman, NAMS-AFMS Joint Task Force

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Task Force Report

NAMS task force report on cervical cancer

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EXECUTIVE SUMMARY

Cervical cancer is an important public health problem in India, being the second most common cancer among women. Despite efforts at a national level, the disease burden, with an age-standardized incidence rate of 17.7 and age-standardized mortality rate of 11.2 per 100,000 women years, remains well above the target incidence of 4 per 100,000 women years proposed by the World Health Organization as the goal of the cervical cancer elimination initiative. There is a wide variation in disease incidence across the country, ranging from 4.1 per 100,000 women in Dibrugarh, Assam to 27.7 per 100,000 women in Papumpare, Arunachal Pradesh.

Women living in hard-to-reach communities and those with a poor socioeconomic status (SES) carry the major burden of the disease, which is almost always diagnosed in advanced stages. The cervix is easily accessible for screening, and health care workers can be trained to perform visual inspection with acetic acid (VIA) and to collect cervical samples for cytology and human papilloma virus (HPV) testing at the community level. Transition to HPV testing has been proposed since this is the most sensitive test; this has the added advantage of self-sampling. Lack of treatment facilities leads to loss to follow-up. The screen-and-treat strategy is being actively promoted now. Women living with HIV (WLHIV) are a high-risk, vulnerable group that needs special care in this regard.

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Central to the problem remains a lack of knowledge and awareness which leads to poor screening and vaccination uptake even where they are available, accessible, and affordable. Developed nations with vaccination and screening programs in place have already achieved or are on their way to achieving elimination. Till recently, vaccine cost remained a major challenge in India. This can now be addressed by the development of an affordable indigenous HPV vaccine and more vaccines are in the pipeline.

Despite the emphasis on increasing cancer centers and training facilities over the last decade, these are still far from adequate for our population. This further exacerbates the problem and leads to a poor outcome. The introduction of subspecialty training programs in gynecologic oncology has been initiated, but there is still a vast unmet need. Newer advances in chemotherapy and immunotherapy have a promising role, especially in recurrent disease, but here also, availability, accessibility, and affordability remain the key issues. More emphasis is needed on providing palliative care.

Task force members reviewed the published literature and data pertaining to all aspects of the problem of cervical cancer in India and developed a consensus on the following key observations and recommendations, taking into consideration the health care services and the varied social–cultural–economic contexts across the Indian landscape:

Policy

- Introduction of universal HPV vaccination for schoolgirls by the age of 14 years in the National Immunization Programme for primary prevention of cervical cancer. Introduction of gender-neutral vaccination in due course.
- Nationwide comprehensive screening policy for women aged 35–50 years, outlining goals, timelines, and responsibilities across sectors, aligning with global standards and transition to HPV testing.
- Advisory body dedicated to cervical cancer prevention activities at central and state levels which will create a registry, provide the necessary guidance and approvals to initiate/ escalate vaccination and screening activities, and follow the outcomes.
- Coordination with National AIDS Control Organization (NACO) to introduce screening services for WLHIV at anti-retroviral therapy (ART) centers.
- Increase the investment in cancer care infrastructure and training of oncology professionals.
- Upscaling of radiation facilities, i.e., one radiation therapy (RT) machine per 1 million population; every RT center should have brachytherapy services.
- Ensuring an uninterrupted, affordable supply of quality-assured screening tests, treatment devices, essential chemotherapy drugs, etc.
- Making cancer a notifiable disease and strengthening the cancer registries and linkages.
- Intersectoral coordination with the Ministry of Education for integration of cervical cancer education into the school curriculum.
- Intersectoral coordination with the Ministry of Information and Broadcasting to develop educational programs and awareness messages for radio and television, including embedding some of these messages into popular television serials, etc.
- Financial protection for the treatment for cervical cancer through insurance policies.

Services and Training

- Vaccination
 - Allocation of funds for all the necessary arms of the implementation of vaccination, including infrastructure and equipment, human resources, transport, IEC and communications, etc.
 - Strengthening cold chain capacity, vaccine distribution, reducing vaccine wastage, and improving staff training.
- Screening
 - Fund allocation for infrastructure and equipment, transport, referrals, and follow-up.
 - Ensuring a continuous supply of affordable and high-performance screening test and screening devices.
 - Optimization of human resources by training and utilization of ground-level Accredited Social Health Activist (ASHA) workers.
 - Strengthening the health information system to track and screen positive women and minimize losses to follow-up, e.g., by linking the Aadhar card.

- o Integration of newer innovations like self-sampling, portable colposcopes, and artificial intelligence (AI) into screening.
- o Training and re-training of doctors and paramedical workers for screening and treatment.
- o Robust quality assurance system using key performance indicators.
- Oncology workforce and infrastructure
 - o Surgical training of gynecologic oncologists in medical colleges and tertiary centers in performing radical hysterectomy and providing holistic care.
 - o Capacity-building through training of pathologists, radiologists, medical physicists, and oncology nurses.
 - o Improving opioid availability at cancer centers; training of oncologists and palliative care staff for prescribing and titrating opioids.
 - o Integration of home-based models of palliative care into primary health care.
- Development of nation-specific guidelines for cervical cancer treatment.

Education and Awareness

- Establishing departments of preventive oncology at all medical colleges to upscale capacity-building.
- Education and mobilization of communities. Health promotion through behavioral change with the involvement of community, civil society, community-based organizations, media, etc., as included in the strategy of National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases & Stroke (NPCDCS), now renamed National Programme for Prevention & Control of Non-Communicable Diseases (NP-NCD) in 2023.
- Involvement of schools and parents in vaccination efforts.
- Bringing the preventive activities under one umbrella and enhancing public private partnerships to support vaccination programs, screening and awareness campaigns, improving linkages to secondary and tertiary facilities, and patient navigation and follow-up.
- Awareness and educational activities through survivor groups to reduce cancer stigmatization.

Research

- Strengthening collaboration among various cancer centers for trials and formation of cervical cancer-specific research groups.
- Selection of patients for less radical surgery.
- Radiation treatments with fewer fractions.
- Rational and pragmatic trial designs for chemotherapy addressing the needs of our population, e.g., additional chemotherapy cycles post concurrent chemoradiation and less toxic, low-dose, and low-cost options like metronomic chemotherapy.
- Facilitating the development of generic chemotherapy and immunotherapy.
- Implementation studies to understand vaccine hesitancy, and impact of screening and the factors which could alter the uptake and outcomes.

INTRODUCTION

Cervical cancer is the second most common cancer affecting Indian women. Two-thirds of women present with locally advanced disease despite it being a preventable cancer. Countries lacking an organized human papilloma virus (HPV) vaccination and screening program carry the major burden of the disease. Women in rural areas without adequate literacy and knowledge about cervical cancer are the ones who are the most affected. Despite efforts to combat cervical cancer, disparities in access to diagnosis and treatment persist. This highlights an urgency to address resource inequities in cancer care.

Cervical cancer is one of the few cancers which has a long premalignant phase and can thus be prevented by appropriate screening and timely clinical interventions. Various barriers, such as lack of manpower, infrastructure, and funding, as well as socioeconomic and cultural barriers have been impediments to the screening efforts. The national program for screening of common cancers (2016) proposed screening by visual inspection with acetic acid (VIA).¹ However, to implement an effective, organized screening program in a large population, alignment with global standards is mandatory. Persistent infection with high-risk types of human papilloma virus (hr HPV) has been shown to be the necessary cause

of cervical cancer. The World Health Organization (WHO) calls for the elimination of cervical cancer recommends HPV vaccination of 90% of girls under 15 years, screening by HPV test of 70% of women at 35 and again by 45 years, and treatment of 90% of lesions.² The long-term promise of HPV vaccination is increasingly evident in countries that included the vaccine in the national program a decade ago.^{3,4} However, the immediate focus is needed for fortifying resources to diagnose and manage preinvasive and invasive cervical cancer cases. Addressing shortages in radiation and chemotherapy facilities, especially in smaller towns and rural regions, is pivotal for optimal cervical cancer care.

Raising awareness about cervical cancer, its causes, risk factors, and prevention is a cornerstone of the initiative. Public health campaigns should target communities, schools, workplaces, and media outlets to disseminate accurate information and dispel misconceptions. Government can play a pivotal role in policy formulation, funding allocation, and program implementation and collaboration among various stakeholders. This is imperative for the successful implementation of the initiative. A robust monitoring and evaluation system is required for tracking progress and identifying areas requiring improvement.

Challenges to be addressed include financial constraints, limited health care infrastructure, cultural barriers, vaccine hesitancy, and outreach to marginalized populations. The elimination initiative by WHO has the potential to save countless lives and significantly reduce the burden. By harnessing the collective efforts of governments, organizations, health care professionals, and communities, we can pave the way for the elimination of this preventable disease among our women and achieve the WHO targets in this regard by 2030.

The present report, under the auspices of the National Academy of Medical Sciences (NAMS), India, discusses the means and measures to address the problem of cervical cancer more coherently and effectively.

BACKGROUND

Medical professionals can play an important role in eliminating cervical cancer, the second most common cancer among women in India and a preventable one. The NAMS, India has taken the initiative by constituting a task force on cervical cancer with the objective of developing a white paper to be submitted to the Government of India for improving the health intervention activities in the area of cervical cancer. This white paper discusses the burden of cervical cancer in India and offers a roadmap for policymakers to address this issue more effectively with the help of medically oriented

interventions. It will help various stakeholders to address the problem of cervical cancer in the Indian population.

OBJECTIVES

The main objectives of the task force are:

1. To identify the current status in the area of cancer cervix.
2. To identify the deficiencies which need to be addressed.
3. To provide recommendations and future directions for making improvements in the field of cervical cancer.

METHODOLOGY

The task force members reviewed the published literature and data pertaining to cervical cancer in India. The initial working draft was circulated among the task force members, and comments were sought. Further modifications were made to the document based on the inputs received from the experts. They then developed a consensus on the key observations and recommendations, taking into consideration the health care services and the varied socioeconomic contexts across the Indian landscape.

CURRENT STATUS

Disease burden

India has a population of 511.4 million women aged 15 years and older who are at risk of developing cervical cancer, which accounts for 18.3% of all cancers^{5,6}. It has been estimated that there were 127,526 newly diagnosed cases of cervical cancer and 79,906 reported deaths in 2022. Although the age-standardized incidence rate of cervical cancer has decreased substantially by 53.25% from 33.8 in 1990 to 18.0 in 2022, it is still the second most common cancer and a second most common cause of death due to cancer among Indian women [Figure 1a-1b and Table 1].⁶

According to the report of the National Cancer Registry Programme (2012–2016) of the Indian Council of Medical Research, Papumpare district has the highest incidence rate of cervical cancer (27.7) in Asia [Figure 2a]. Cervical cancer is the leading type of cancer among women in Barshi Rural (AAR 15.3), Osmanabad and Beed (13.1), Mizoram (23.2), Tripura (9.8), Nagaland (9.3), Pasighat (20.3), and Cachar District (15.3). A significant decrease in the incidence rates has been observed in 10 population-based cancer registries (PBCRs), although an increase has been reported in some states [Figure 2b].⁷

Table 1 depicts the summary of the disease burden in India.

The median age at diagnosis is 50 years. It has been observed that the disease burden is negligible before the age of 30 years⁵ [Figure 3].

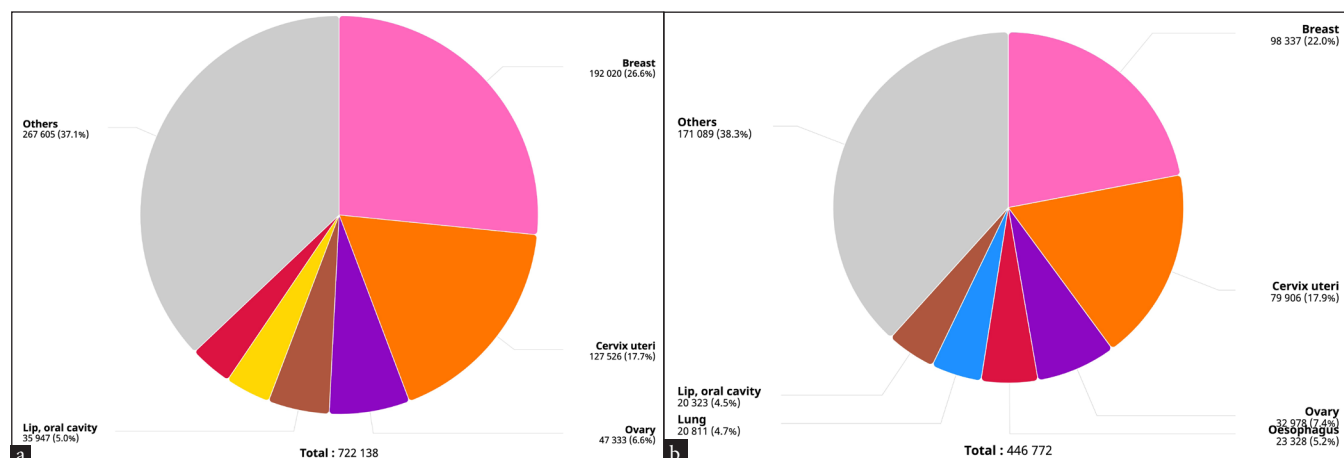


Figure 1a-b: Pie chart depicting annual incidence and mortality from cervical cancer in 2022. Source: Global Cancer Observatory (<http://gco.iarc.fr>).

Table 1: Burden of cervical cancer in India

	Incidence	Mortality
Annual number of new cases/deaths	127,526	79,906
Crude rate	18.9	11.8
Age-standardized rate	17.7	11.2
Cumulative risk, 0–74 years (%)	2.0	1.3
Ranking of cervical cancer (all ages)	2nd	2nd
Ranking of cervical cancer (15–44 years)	2nd	2nd

Source: <https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21834>

Risk factors for cervical cancer and HPV genotypes in India

Risk factors

There are many known risk factors associated with the development of cervical cancer. Persistent hrHPV infection is the strongest risk factor, and it usually occurs in a background of other coexisting factors, as it is necessary but not sufficient. In India, about 5.0% of women in the general population harbor HPV 16/18 infection in the cervix at any given time, the two most common oncogenic types globally; 83.2% of all

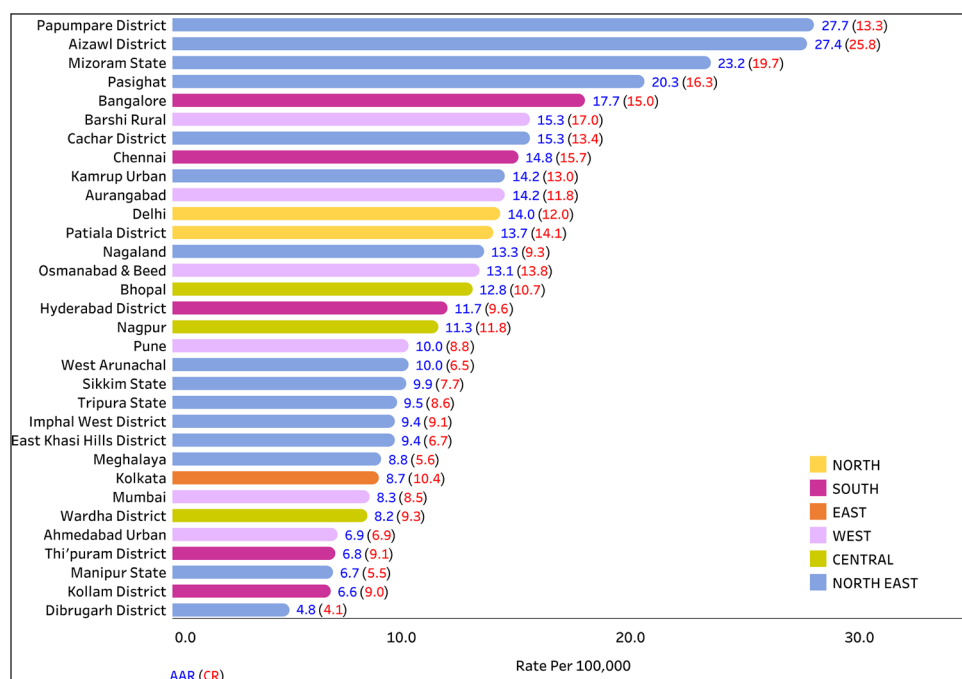


Figure 2a: Comparison of age-adjusted incidence rates (AARs) of 28 population-based cancer registries under the national cancer registry programme. Source: https://ncdirindia.org/All_Reports/Report_2020/default.aspx.

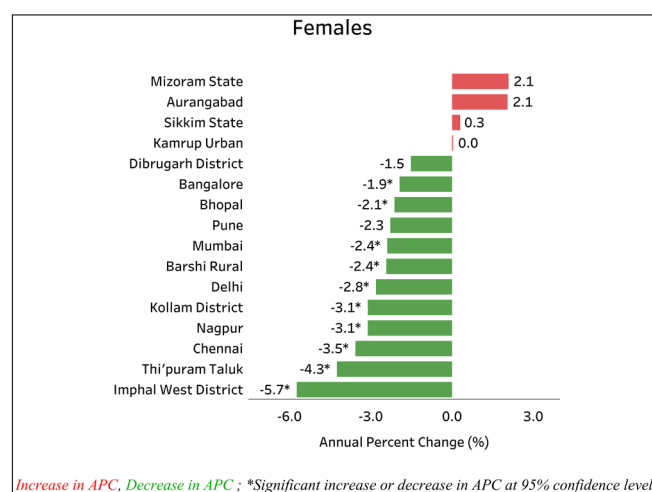


Figure 2b: Annual percent change (APC) in Age adjusted incidence rate (AAR) over the time period. Source: https://ncdirindia.org/All_Reports/Report_2020/default.aspx.

invasive cancers are HPV 16 or 18 positive, which is higher than the global average of 70%.⁵

The SES largely determines the risk of developing cancer cervix and plays a major role in survival too, as it is linked to multiple other risk factors. Approximately 85% of women with cervical cancer lives in a low middle-income country (LMIC). Directly related to the SES is the educational background. A population-based study conducted in south India showed that patients from a lower educational background have poor survival, and this was at least partially explained by having a more advanced disease at the time of diagnosis.⁸ Early age at

marriage and onset of sexual activity, multiparity are other correlates linked with SES that are well-known risk factors in our population.⁹

Poor genital hygiene may be an indirect risk factor leading to genital infections, which can act as cofactors in the development of preinvasive lesions, according to a prospective study conducted in Kerala in 1999.¹⁰ Pelvic inflammatory disease due to various other factors, such as nutrition, immunity, and multiple sexual partners, increases the risk of cervical cancer. Coexistence of *Chlamydia trachomatis* and HPV 16 can increase the risk of cervical cancer.¹¹

Tobacco smoking and coinfection with Human Immunodeficiency Virus (HIV) have been identified as established cofactors, whereas herpes simplex virus type-2 (HSV-2), immunodeficiency, and certain dietary deficiencies are other probable cofactors.¹²

Prolonged use of oral contraceptive (OC) pills is a risk factor for cervical cancer. The relative risk in current users increased with increasing duration of OC use: use of OCs for 5 years can double the risk of cancer.¹³

Lack of awareness among women about the signs and symptoms of cervical cancer adds to improper utilization of screening services. In a knowledge, attitude, and practices (KAP) survey done in South India, the common symptoms of cancer cervix, such as intermenstrual bleeding and foul-smelling discharge, were reported by only a third of the patients. Similarly, the association of younger age at coitarche and marriage, as well as the increased risk with multiple

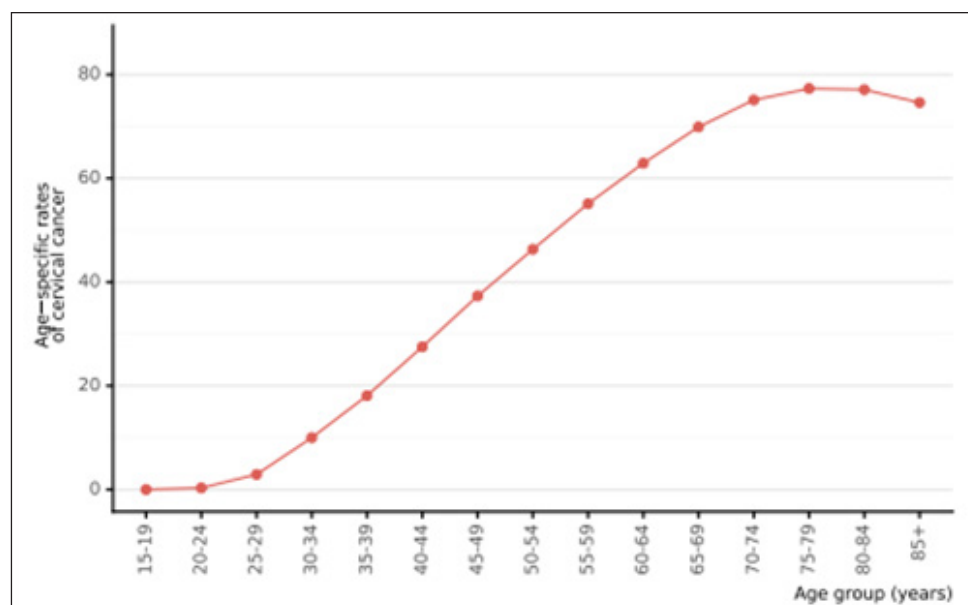


Figure 3: Age-specific incidence rates of cervical cancer in India (estimates for 2020). Source: <https://gco.iarc.fr/today>.

sexual partners leading to repeated HPV infections, was known to only about a fifth of the population interviewed.¹⁴

The first rural cancer registry was set up in 1987 at Barshi with a population of 0.4 million in western Maharashtra. Apart from the usual registry methodology, there was regular community interaction to educate on the warning signs of cervical cancer and motivate individuals to seek early medical attention. To overcome the adverse conditions in the rural areas, the registry adopted case finding in the community itself. The registry investigators visited the villages at least twice a year to identify the cases. Screening clinics were also set up in villages. The registry activity increased awareness in the population ($P < 0.01$), increased the frequency of early cervical cancers by more than twofold during the past 16 years, and significantly decreased the relative risk of death (HR 0.7 [0.5–0.9]). According to the latest National Cancer Registry Programme (NCRP) data, there has been a significant decrease in age adjusted rate (AAR) over the time period, although carcinoma cervix still continues to be the leading cause of cancer among women in Barshi. This emphasizes the role of community awareness and education apart from the ongoing risk factors to be an important unmet area.¹⁵

HPV genotypes in India

In a meta-analysis including nine studies from India, the overall HPV prevalence was 12.0% in women with normal cytology/histology. The reported HPV-16/18 positivity was 78.9% in women with invasive cancer (87.7% in North and 77.2% in South India), 61.5% with high grade squamous intraepithelial lesion (HSIL), and 30.8% with low grade squamous intraepithelial lesion (LSIL). There was no difference in the overall HPV prevalence in cervical cancer between North and South India ($P = 0.063$). However, HPV-16 and HPV-45 appeared to be more prevalent in North India ($P = 0.018$ and 0.013 , respectively), and HPV-35 in South India ($P = 0.033$). Various high-risk HPV genotypes found among Indian women included types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59^(16,17).

Worldwide, HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases. In India, these two types are found in 83.2% of cervical cancers and in 28.2% and 62.8% of low-grade cervical lesions (LSIL/cervical intraepithelial neoplasia (CIN1)) and high-grade cervical lesions (HSIL/CIN2/CIN3/CIS), respectively. Other high-risk types categorized as probable/possible carcinogenic types are HPV 26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85, and 97.⁵

In the latest report by the Catalan Institute of Oncology/ International Agency for Research on Cancer based on

various Indian studies, among 511.4 million women at risk for cervical cancer, about 5.0% are estimated to harbor cervical HPV-16/18 infection at a given time.⁵

Current status: HPV vaccination and screening

HPV vaccination and cervical cancer control

Vaccines against HPV genotypes 16/18 have been available since 2006 and have been recommended by WHO since 2009. Quadrivalent vaccines include low-risk HPV genotypes 6/11 as well. Since 2018, a nonavalent vaccine has been introduced that targets five additional hrHPVs, namely, 31/33/45/52/58.

HPV vaccines have been progressively introduced in many national immunization schedules and are presently included in the program in 130 countries. However, several studies and international agencies have reported that both vaccine introduction and coverage achieved are still suboptimal. In 2016, it was estimated that HPV immunization programs targeted only 12% of young adolescent females worldwide, and only 6% of girls aged 10–20 years had been vaccinated by end of 2014.¹⁸ The National Technical Advisory Group on Immunization (NTAGI) has recommended the inclusion of HPV vaccine in the Indian national program.

Given the highly effective and cost-effective prevention strategies available and the growing inequalities worldwide, WHO proposed a cervical cancer elimination strategy that includes scale-up of HPV vaccination to 90% of adolescent girls by 2030. This target is aligned with the Immunization Agenda 2030 and the sustainable development goals (SDGs) agenda (SDGs 3.4 and 3.b.1). HPV vaccination is the most cost-effective strategy to prevent cervical cancer in LMICs.¹⁹ Vaccination, screening, and treatment of preinvasive lesions are the pillars of WHO's cervical cancer elimination strategy.

HPV vaccines currently available in India

- 1) Gardasil [Merck Sharp & Dohme (MSD)] – Quadrivalent HPV vaccine, licensed in India in 2008, targets four HPV genotypes, high-risk types 16 and 18, and low-risk types 6 and 11.
- 2) Gardasil 9 (MSD) – Nonavalent HPV vaccine, licensed in India in 2022, targets nine HPV types, including high-risk types HPV 16/18/31/33/45/52/58 and low-risk types 6/11.
- 3) Cervavac [Serum Institute of India (SIIL)] – Quadrivalent indigenous HPV vaccine, licensed in 2023, targets four HPV genotypes, high-risk types 16 and 18, and low-risk types 6 and 11.
- 4) The bivalent vaccine Cervarix Glaxo Smith Kline (GSK) for HPV 16/18 is presently not available.

HPV vaccine recommendations and efficacy

Dosage recommendations of various professional organizations and committees have been revised from time to time based on emerging information from various large studies and trials. Thus, there is a dichotomy between the vaccine dose recommendations on the product literature as licensed and that which is recommended for current practice.

The original guidelines for three-dose schedules at all ages were changed to two-dose guidance by WHO in 2018 for girls aged 9–14 years. In its latest position paper published in December 2022,²⁰ WHO now recommends the following:

- A one- or two-dose schedule for girls aged 9–14 years.
- A one- or two-dose schedule for girls and women aged 15–20 years.
- Two doses with a 6-month interval for women older than 21 years.

This has enormous implications, especially for LMICs, where there is a potential to improve coverage rates by increasing availability, decreasing costs, and improving logistics. The primary target of vaccination is girls aged 9–14, prior to the start of sexual activity. The minimum interval between the first and second dose should be 6 months. Immunocompromised individuals should receive at a minimum two doses and where possible three doses.

The vaccination of secondary targets such as boys and older females is recommended where feasible and affordable. Previously, there were shortages in the global HPV vaccine supply, but with the increasing availability of new vaccines and improved capacity of older vaccines, this is now set to change.

In June 2022, the NTAGI recommended the introduction of HPV vaccine in the Universal Immunization Programme in India with “a one-time catch-up for 9- to 14-year-old adolescent girls followed by routine introduction at 9 years”. This was based on the Indian evidence on the effectiveness of a single dose of HPV vaccine. In the India IARC trial, a multicenter, prospective, cohort study on vaccine efficacy against persistent HPV 16/18 infection at 10 years, after one, two, and three doses of quadrivalent HPV vaccine in girls, a single dose of HPV vaccine was found to provide similar protection against persistent infection from HPV 16 and 18, to that provided by two or three doses.²¹

Evolution of Indian data, the India IARC trial, and evidence leading to the recommendation for a single dose of HPV vaccine

In a cluster-randomized trial initiated in 2009, the investigators originally aimed to compare the immunogenicity, frequency of persistent HPV infection, and cervical precancerous lesions caused by vaccine-targeted HPV types after vaccination with two doses of quadrivalent vaccine on days 1 and 180 compared with three doses on days 1, 60, and 180. Suspension of recruitment and vaccination in 2010 due to events unrelated to the study led to some vaccinated girls receiving fewer than the planned number of vaccinations by default. As a result, the authors reanalyzed the data as an observational cohort study. The primary outcomes were immunogenicity in terms of L1 genotype-specific binding antibody titers, neutralizing antibody titers, antibody avidity after vaccination for the vaccine-targeted HPV types 16, 18, 6, and 11, and incident and persistent infections with these HPVs. Analysis was per actual number of vaccine doses received.

Of the 21,258 eligible girls in 188 clusters, 17,729 girls were recruited from 178 clusters before suspension. Four thousand three hundred and forty eight (25%) girls received three doses, 4979 (28%) received two doses on days 1 and 180 or later, 3452 (19%) received two doses on days 1 and 60, and 4950 (28%) received one dose. Immune response in the two-dose HPV vaccine group was noninferior to the three-dose group (median fluorescence intensity ratio for HPV 16 was 1.12 [95% CI 1.02–1.23] and for HPV 18 was 1.04 [0.92–1.19]) at 7 months, but was inferior in the two-dose default (0.33 [0.29–0.38] for HPV 16 and 0.51 [0.43–0.59] for HPV 18) and one-dose default (0.09 [0.08–0.11] for HPV 16 and 0.12 [0.10–0.14] for HPV 18) groups at 18 months. The geometric mean avidity indices after fewer than three doses by design or default were noninferior to those after three doses of vaccine. Fewer than three doses by design and default induced detectable concentrations of neutralizing antibodies to all four vaccine-targeted HPV types, though at lower concentrations after one dose.

Cervical samples from 2649 participants were tested; the frequency of incident HPV 16, 18, 6, and 11 infections was similar irrespective of the number of vaccine doses received. The testing of at least two samples from 838 participants showed that there were no persistent HPV 16 or 18 infections in any study group at a median follow-up of 4.7 years (IQR 4.2–5.1). Hence, it was concluded that the short-term protection afforded by one dose of HPV vaccine against persistent infection with HPV 16, 18, 6, and 11 is similar to

that afforded by two or three doses of vaccine and required further assessment.²²

In addition, the authors proposed that the two-dose recommendation of HPV vaccine could be expanded to girls aged between 15 and 18 years to reduce program cost and improve compliance. This was based on the subgroup analysis of 1795 girls aged 15–18 years receiving two (1–180 days) and 1515 girls of the same age receiving three (1–60–180 days) doses. Immunogenicity outcomes in 15- to 18-year-old two-dose recipients were also compared with the 10- to 14-year-old three-dose (N = 2833) and two-dose (N = 3184) recipients. At seven months, the 15- to 18-year-old two-dose recipients had noninferior L1-binding antibody titers against vaccine-targeted HPV types compared to three-dose recipients at 15–18 years and at 10–14 years of age. Neutralizing antibody titers at 18 months in 15- to 18-year-old two-dose recipients was noninferior to the same age three-dose recipients for all except HPV 18. The frequency of incident infections from vaccine-targeted HPV types in the 15- to 18-year-old two-dose recipients was similar to the three-dose recipients.²³

Subsequently, the WHO recommendation has supported off-label single dose of HPV vaccine to reduce programmatic costs, mitigate supply shortages, simplify logistics, and allow more LMICs to introduce the vaccine. Hence, the durability of protection offered by a single dose becomes extremely important. In this respect, the authors conducted a study to determine whether single-dose recipients had sustained immune response against targeted HPV types at 10 years post-vaccination and whether this response was superior to the natural antibody titers observed in unvaccinated women. The antibody response observed over 120 months showed stabilized levels 18 months after vaccination for all four HPV types. Although the HPV type-specific (binding or neutralizing) antibody titers after a single dose were significantly inferior to those after three doses of the vaccine [lower bounds of geometric mean titer (GMT) ratios < 0.5], they were all significantly higher than those observed in unvaccinated women following natural infections (GMT ratios: 2.05 to 4.04-fold higher). Hence, a durable immune response in single-dose recipients of HPV vaccine at 10 years post-vaccination was confirmed.²⁴

HPV vaccination coverage

In 2016, a multidisciplinary expert group constituted by the Secretary, Department of Health Research and the Director-General, Indian Council of Medical Research (ICMR) reviewed the available evidence globally regarding immunogenicity

and efficacy, adverse effects, cost-effectiveness of the HPV vaccines and recommendations of WHO for the introduction of HPV vaccine at the country level. The group recommended that adolescent girls aged 9–13 years should be vaccinated with two doses of the HPV vaccine.²⁵

Following this, an HPV vaccination program for school girls was launched in New Delhi on National Cancer Awareness Day (November 7, 2016), which vaccinated nearly 1200 girls. Simultaneously, the Government of Punjab initiated a well-planned campaign in two districts, vaccinating girls of Class 6 with 98% and 99% coverage in phase 1 and 2, respectively. In 2018, Sikkim became the first state to launch a state-wide program in which 25,284 school girls aged 9–14 years were vaccinated with 97% coverage.

In an evidence-based impact projection study, HPV transmission model (EpiMetHeos) was adapted to current Indian data on sexual behavior, HPV prevalence, and cervical cancer incidence; assuming a 90% vaccination coverage in girls aged 10 years, HPV vaccination could effectively reduce the prevalence of HPV16/18 infection by 97% in 50 years with the age-standardized incidence rate falling below the threshold for the elimination of 4 per 100,000 women years. This study also concluded that in girls aged 11–20 years, single-dose vaccination along with catch-up was more protective than two-dose vaccination without any catch-up, resulting in a decrease of 39%–65% versus 38% in lifetime risk of cervical cancer.²⁶

At present, cost issues have played a major role in limiting the outreach of the available vaccines. Serum Institute of India Pvt. Limited (SIIPL) has developed and tested an indigenous quadrivalent vaccine, Cervavac, which will be affordable and is likely to be included in the national immunization program in the coming years.

Status of cervical screening

There are presently three accepted modalities of screening, namely, cytology, HPV testing, and VIA. While cytology has been the oldest method of cervical screening, established in the 1940s in the developed world, it has been seen to be effective only when performed with good-quality assurance and with repeated rounds of screening, as it has relatively poor sensitivity of about 55%.²⁷ Its greatest strength lies in a high specificity which makes it better as a triage tool. Its widespread use is limited by the lack of resources in terms of laboratories and trained personnel. In India, it is available in cities and larger hospitals and medical colleges but, even there, there are limitations to the numbers that can be done. In a recent cross-sectional multicentric study conducted at

tertiary care institutes across India, among the eligible women only 24.8% received screening. Availability of screening kits was limited to 10–25 Pap/HPV tests per day. VIA and HPV testing were offered only at certain centers. Colposcopy and treatment facilities were optimal at all centers (data under publication).²⁸

VIA has sensitivity comparable to Pap smear but poorer specificity. It has the advantage of immediate results and the ability to be incorporated into a screen-and-treat program. While this makes it a suitable screening method for LMICs, the high false-positive rate means many women will be referred unnecessarily for triage, or be over treated in a screen-and-treat program. Repeated rounds of training for quality control, as well as linkages to secondary level facilities are necessary for scaling up coverage and adequate treatment.

HPV tests have the highest sensitivity with reasonable specificity and are presently the preferred choice for screening. They also have the best negative predictive value. This is the basis for the WHO recommendation to transition to HPV tests with a goal of screening 70% twice in their lifetime, by age 35 and again by age 45 years. However, it is essential to have validated tests with quality control; otherwise, there will be a large number of false positives and negatives.²⁹ Point-of-care HPV tests will be useful in the screen-and-treat strategy. Self-sampling is emerging as the sampling type of choice under WHO's recommended self-care guidelines. While both DNA and RNA tests are being used in screening, self-sampling is presently recommended for HPV DNA tests only. Tests are also available that have partial HPV genotyping which works as an inbuilt triage. HPV-positive cases that are HPV 16/18 positive can be considered for a screen-and-treat approach.

For HIV-positive women, the WHO recommends using HPV DNA as the primary screening test rather than VIA or cytology, along with triage after a positive screen. In these women, screening should start at 25 years and the recommended screening interval is 3–5 years.³⁰

Linkage of screening with treatment is essential to prevent cervical cancer. A screen and treat approach has been recommended by WHO. For HIV-positive women, the screen, triage, and treat approach is recommended.

In 2016, MoHFW released the Operational Framework for the Management of Common Cancers under the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases & Stroke (NPCDCS), renamed National Programme for Non Communicable Diseases (NP-NCD) in 2023.¹ VIA was implemented as the test of choice for screening women between 30 and 65 years of age, with specific guidelines for the screen-and-treat approach. However, several barriers have been observed in implementation. A

pilot study conducted at Silchar, Assam, in 2018 found a lack of human resources, overburdening of the existing staff, and difficulty in motivating the community for screening as the top three challenges in implementation.³¹

The National Family Health Survey (NFHS-4) 2015–2016 reported that 22% of women have undergone cervical screening in India, and the majority of the districts fall in the range of 10–20% coverage. As per the 2021 India factsheet of WHO, the coverage of cervical cancer screening is only 3.1%^{32,33}. Another study conducted in 2020 in South India revealed that only 14.3% had at least one-lifetime pelvic exam, and 7.1% had undergone cervical cancer screening.³⁴ The higher percentage reported here maybe due to the fact that responders may have perceived speculum exam or even a pelvic exam of any sort, most likely related to antenatal and pregnancy care, as cervical cancer screening. The recent NFHS-5 data are also in line with the WHO data, where the percentage of women who have ever undergone cervical cancer screening in India is 1.9% (2.2% in urban areas and 1.7% in rural areas) [Figure 4].

Andhra Pradesh, Bihar, Jammu and Kashmir, Telangana, and West Bengal have more rural women participating in cervical cancer screening than those in urban areas. The women living in the urban regions of Mizoram, Himachal Pradesh, Kerala, and Maharashtra have a significant number of women undergoing a screening test for cervical cancer. The practice of cervical cancer screening is close to insignificant in Nagaland, Ladakh, and Gujarat.³⁵

The Tamil Nadu government conducted successful pilot programs and subsequently rolled out a cost-effective and operationally feasible large-scale cancer screening program. The pilot project was started in Chennai Corporation in 2005, and scaled to a district-level pilot in February 2007 by the World Bank that supported the Tamil Nadu Health Systems Project. State-wise scaling up in 16 districts in 2012 was later extended to the remaining 16 districts in 2013.³⁶ The main components included a cost-effective VIA-based screening strategy with a screen-and-treat approach, mass awareness campaigns, self-help groups to reach the community, trained personnel, diagnostic and treatment services at all levels with assured linkage between the facility centers, interdepartmental coordination with school education and labor welfare departments, data analysis, quality assurance with intensive monitoring, and supervision and online reporting system by the health management information system. By 2016, 81% of the target population was screened with 3.3% positivity rate. However, the positivity rates, compliance with colposcopy, and CIN detection rates were far lower than had been seen in a cluster-randomized trial in Tamil Nadu by IARC, in which

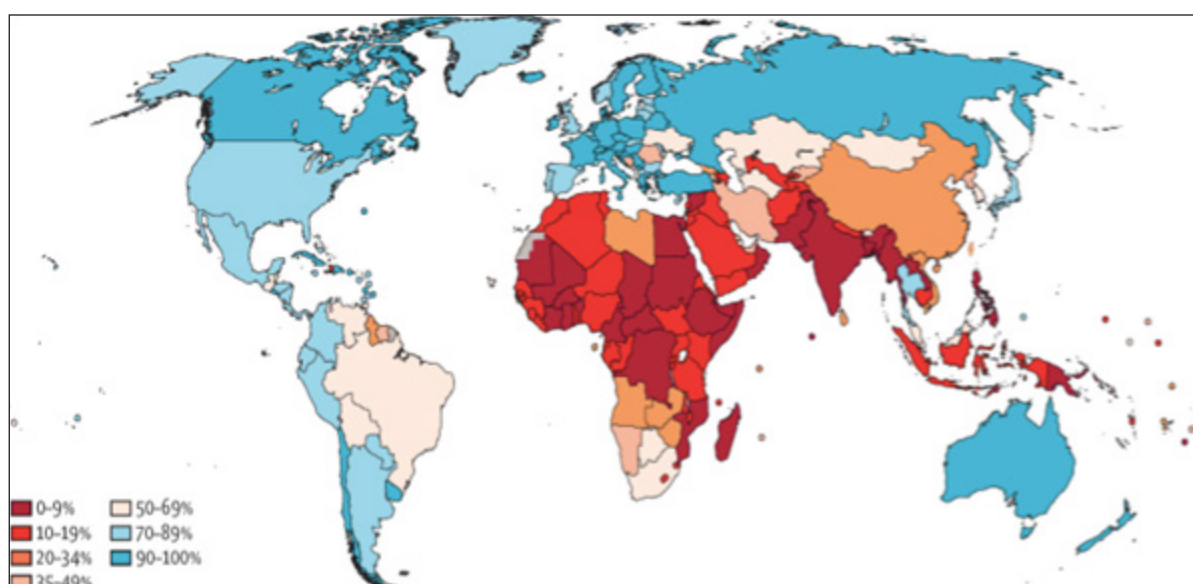


Figure 4: Countrywise ever in lifetime cervical cancer screening coverage in women aged 30–49 years. Source: <https://hpvcentre.net>

VIA-based screening showed a reduction in incidence by 25% and mortality by 35% over a follow-up period of 7 years.³⁷ In another cluster-randomized study conducted in Mumbai to investigate the efficacy of VIA performed by primary health workers in reducing cervical cancer mortality showed a 31% reduction.³⁸ However VIA screening, requires good training and sustained quality assurance to be an effective method to prevent cervical cancer in developing nations.

The poor specificity of VIA (53.3%) is a major drawback; evidence suggested the use of adjunctive tests like addition of HPV testing to VIA to increase its specificity (95.4%). This approach had the potential to reduce referral rates without compromising the sensitivity.³⁹ Subsequent studies suggested that a single round of HPV testing may be a more effective strategy in reducing the incidence and mortality. In the cluster-randomized trial conducted in rural India to measure the effect of a single round of screening by testing for HPV, cytologic testing, or VIA, authors found a significant reduction in the numbers of advanced cervical cancers and deaths by using a single round of HPV testing.⁴⁰ Another study to evaluate the effectiveness of VIA, Pap, and HPV testing in a cervical cancer screening program in a periurban community in Andhra Pradesh concluded that HPV testing had higher sensitivity (100%) and specificity (90.6%) compared to cytology (sensitivity=78.2%; specificity=86.0%) and VIA (sensitivity=31.6%; specificity=87.5%). The authors also suggested that potentially 87.6% of underlying cases of CIN3 and cancer may have been missed due to program failure.⁴¹

HPV testing has been recommended by WHO as the primary screening modality, and the development of rapid, point of care HPV tests along with the choice of self-sampling has the potential to make it the future screening modality. A cross-sectional study to examine the concordance between HPV by Hybrid Capture 2 (HC2) and polymerase chain reaction (PCR) on self-collected vaginal and physician-collected cervical samples showed that the concordance between HC2 and PCR was 90.9% for self-samples (kappa=63.7%, 95% CI: 55.2–72.2%) and 95.3% for physician-collected samples (kappa=80.4%, 95% CI: 71.8–89.0%).⁴²

Presently, indigenous HPV tests have been developed and efforts are ongoing for validation by international standards so that these can be included in the national program with confidence.

Status of surgical facilities in the country

Surgery for cervical cancer

The type and extent of surgery for cervical cancer is determined based on the FIGO stage of the tumor – the size, histological type and extent of tumor, desire for future fertility, and any comorbidities. Table 2 shows the various surgical procedures that may be performed for the management of patients with cervical cancer.

Radical surgery is the preferred treatment modality for early stage cervical cancer. However, due to lack of a population-based screening program in the country, only a small proportion (generally less than 10%) of women with cervical

cancer present in the early stage and are candidates for radical surgical resection. However, this is expected to change with increasing implementation of screening programs. Open abdominal route is the current standard of care for radical hysterectomy for cervical cancer. In a randomized controlled trial of open versus minimally invasive surgery (MIS) for cervical cancer, the rate of disease-free survival (DFS) at 4.5 years was 86.0% with MIS and 96.5% with open surgery. The hazard ratio for disease recurrence or death from cervical cancer in the MIS group was 3.74 (95% CI 1.63–8.58), a significant difference that remained after adjustment for age, body mass index, stage of disease, lymphovascular invasion, and lymph node involvement. MIS was also associated with a lower rate of overall survival (OS) (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77–20.30). A higher proportion of vault recurrences occurred in the open surgery group (43%, as compared with 15% in the MIS group), and all nonvaginal vault recurrences occurred in the MIS group. This was a new pattern of recurrences in the peritoneal cavity seen only in the MIS group and subsequently confirmed by several other reports as well.⁴³ Subsequent to these findings, MIS is contraindicated due to poorer oncological outcomes compared to the open surgical route and should not be offered outside a clinical trial setting.

The hypothesis to downsize the tumor in patients with locally advanced cervical cancer (LACC) by the use of neoadjuvant chemotherapy (NACT) to make the disease amenable to radical surgery has fascinated researchers for decades and has been investigated in two large trials^{44,45}. A phase III randomized controlled trial was conducted at Tata Memorial Centre, Mumbai to evaluate the role of NACT

followed by radical hysterectomy in patients with LACC. Six hundred and thirty-five patients with International Federation of Gynecology and Obstetrics (FIGO) stage (2009) IB2, IIA and IIB, squamous cell carcinoma of the cervix were randomized to NACT-surgery ± adjuvant treatment or concurrent chemoradiation. Results of this trial showed inferior DFS with the NACT surgery compared to the standard concurrent chemoradiation. At a median follow-up of 58.5 months, five-year DFS was 69.3% in NACT-surgery and 76.7% in the chemoradiation arm ($P=0.03$). There was no difference in OS between the two treatment groups. Similar results are shown in a recently published, multicenter trial conducted by European Organisation for Research and Treatment of Cancer (EORTC). Results of these two large trials do not support the use of NACT and radical surgery in patients with LACC, and concurrent chemoradiation remains the standard of care for these patients. Currently, radical surgery is recommended only in patients with low-risk FIGO 2018 stage IB1-2 and stage IIA1 disease.⁴⁶ The likelihood of the need for adjuvant radiation in more advanced tumors increases the morbidity from combined modality therapy as well as places additional burden on the health system.

Evolution of gynecologic oncology specialty in India and its current status

The recognition of the subspecialty of gynecologic oncology as an independent discipline in India is relatively recent. In the year 2011, the Medical Council of India (MCI) approved the Magister Chirurgiae (MCh) in gynecologic oncology as a 3-year comprehensive training program. The course was first started at the Tata Memorial Hospital (TMH), Mumbai, with a single student per year. As a result of persistent, proactive

Table 2: Various surgical procedures performed in patients with cervical cancer

Procedure	Indications
Large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP)	Diagnostic procedure; treatment of high-grade intraepithelial neoplasia (CIN 2–3)
Cold knife conization	Diagnostic procedure; fertility-sparing procedure in stage IA1 disease
Type B and C1 (nerve-sparing) radical hysterectomy + pelvic lymph node dissection/sentinel lymph node biopsy	Stage IA2–IB1
Type C2 radical hysterectomy + pelvic lymph node dissection	Stage IB2
Radical trachelectomy + pelvic lymph node dissection/sentinel lymph node biopsy	Stage IA2–IB1, fertility-sparing procedure
Ovarian transposition	Ovarian function preservation prior to pelvic radiation in young patients
Pelvic exenteration	In select patients with stage IVA/recurrent disease
Urinary/bowel diversion procedures	Palliative procedures

actions, both from various academic centers and regulatory bodies, within a span of 12 years, there has been an exponential increase in the number of seats and training centers across the country; currently, 11 centers provide training opportunities to 28 students per year [Table 3].

Further, augmentation to the subspecialty of gynecologic oncology occurred with the approval of Doctorate of National Board (DrNB), and Gynaecologic Oncology by the National Board of Examination (NBE) in 2019. At present, 16 students per year across 11 centers can enroll in this course [Table 4].

Admission to these courses is through superspecialty national entrance and eligibility tests (NEET), followed by an online counseling, conducted by the Directorate General of Health Services, New Delhi.

The ability to perform a radical hysterectomy and pelvic lymph node dissection defines a gynecologic oncologist. However, the optimum surgical management of a patient with cervical cancer requires not only surgical skills and training but also an understanding of disease biology, preoperative evaluation to assess suitability for surgery, a detailed knowledge of the surgical anatomy of the pelvis, management of perioperative complications, and postoperative adjuvant treatment planning. The above-mentioned training programs are conducted by academic centers with adequate clinical workload and infrastructure and a well-designed, structured curriculum.

Table 3: Institutions offering MCh gynecologic oncology in India

S. No.	Name of Institute, City	No. of Seats Per Year
1	Acharya Harihar Regional Cancer Centre, Cuttack	2
2	All India Institute of Medical Sciences, New Delhi	5
3	AIIMS, Rishikesh	2
4	Amrita Institute of Medical Sciences, Kochi	2
5	Christian Medical College, Vellore	3
6	Dr. Bhubaneshwar Borooah Cancer Institute, Guwahati	2
7	Gujarat Cancer & Research Institute, Ahmedabad	4
8	Kidwai Memorial Institute of Oncology, Bengaluru	3
9	Regional Cancer Centre, Thiruvananthapuram	2
10	St. John's Medical College, Bengaluru	1
11	Tata Memorial Centre, Mumbai	2

Table 4: Institutes offering DrNB gynecologic oncology in India

S. No.	Name of Institute, City	No. of Seats Per Year
1	Apollo Hospitals, Bannerghatta Road, Bengaluru	1
2	Chittaranjan National Cancer Institute, Kolkata	2
3	Dharamshila Narayana Superspeciality Hospital, Delhi	2
4	Fortis Memorial Research Institute, Gurgaon	1
5	Lakeshore Hospital and Research Centre, Kochi	1
6	Mahavir Cancer Sansthan & Research Centre, Patna	2
7	Medanta, The Medicity, Gurgaon	1
8	Rajiv Gandhi Cancer Institute and Research Centre, Delhi	1
9	Sri Shankara Cancer Hospital and Research Centre, Bengaluru	1
10	Tata Medical Centre, Kolkata	2
11	Vardhaman Mahaveer College and Safdarjung Hospital, Delhi	2

During training, students get to learn complex surgical skills as well as comprehensive multidisciplinary management of gynecological cancer patients, including basic principles and techniques of systemic therapy, radiation therapy (RT) and palliative care, and preventive gynecologic oncology. The development of surgical skills is a continuous process that evolves over several years. Continuous practice, mentorship, regular appraisal, and learning new surgical skills are ongoing processes throughout a surgeon's professional career.

With the establishment of the subspecialty of gynecologic oncology in the last decade and the availability of trained gynecologic oncologists in many cities, the proportion of cervical cancer patients undergoing surgery by a gynecologic oncologist is steadily increasing. However, considering our huge population, heterogeneity, and wide disparities in health care resources and still limited availability of gynecologic oncologists in most parts of the country, a substantial proportion of patients with cervical cancer undergo surgeries by a nongynecologic oncologist; including general gynecologists, general surgeons, and surgical oncologists. The latter, during their training as surgical oncologists, undergo rotation in gynecologic oncology. However, evidence suggests that outcomes of gynecologic cancer patients are better when managed by specialists trained in gynecologic oncology compared to those managed by generalists.^{47,48}

Besides MCh and DrNB training programs, there are several university-recognized fellowship courses offered by various cancer centers across the country. The Association of Gynaecologic Oncologists of India (AGOI) accredits gynecologic oncologists to conduct fellowship programs (<http://www.agoi.org/educational-activities/fellowship>).

Inappropriate surgical management of patients with cervical cancer in India

Despite clear guidelines on the indications of radical surgery for invasive cervical cancer, a considerable number of women still undergo inadequate or improper surgery in the country. The incidence of cervical cancer diagnosed after inadvertent simple hysterectomy has been reported to be 5–15%. In a retrospective analysis of 768 patients with cervical cancer presenting to the Tata Memorial Hospital from January to June 2019, 87 patients (11.3%) had inadequate surgery prior to presentation: simple abdominal hysterectomy in 77 patients (88.5%), vaginal hysterectomy in 5 patients (5.7%), and subtotal hysterectomy in 6 patients (6.9%). Forty-one patients (47.1%) had residual disease at presentation (unpublished data). Several factors have been identified to be responsible for inadequate/improper surgery including lack of routine screening for cervical cancer, inadequate diagnostic workup prior to surgery, limited availability of dedicated cancer centers equipped with surgical and radiation oncology facilities, deliberate hysterectomy for grossly invasive cancer, misreading of pathology results, errors at the colposcopic examination, etc.⁴⁹ A study from Northeast India found that failure to perform preoperative Papanicolaou smear, incomplete evaluation of cervical intraepithelial neoplasia (CIN) on cervical biopsy, and negative Papanicolaou smear accounted for 75% of the patients undergoing inappropriate simple hysterectomy. The study also showed a significant delay in referral to an oncology center after inadvertent simple hysterectomy; 23% (12/52) patients were referred more than 100 days after hysterectomy.⁵⁰ Inadequate or improper surgery adversely affect patients' survival. Patients with residual or recurrent vaginal cancer after surgery for cervical cancer have modest outcomes with chemoradiation and with significant treatment-related toxicity.^{51,52}

Improper surgery in patients with invasive cervical cancer can be avoided by implementation of universal screening for cervical cancer and optimum management of screen positives. A thorough preoperative evaluation of patients should be done before scheduling for a “benign hysterectomy.” If a gross cervical lesion is visualized, irrespective of the cytology report, a biopsy must be mandatory prior to hysterectomy, and timely referral to an oncology center with all clinical details and biopsy tissue should be made so that treatment can

be started at the earliest. One of the key strategies to decrease the morbidity and mortality from cervical cancer is to further strengthen the subspecialty of gynecologic oncology.

Status of radiation facilities in the country

In India, the majority of patients present in locally advanced stages, where surgery plays a limited role. The specialty of RT has progressed rapidly over the past two decades with the development of more sophisticated planning and delivery techniques. The introduction of computer technology and imaging has galvanized the practice of RT, and advancement in RT techniques has yielded improved clinical outcomes with reduced toxicity.

RT can be used in different settings for the management of patients with cervical cancer: (i) as definitive therapy for curable patients, (ii) as adjuvant therapy for operated patients to prevent locoregional recurrence, and (iii) as palliative therapy for alleviating the distressing symptoms in patients with advanced incurable disease.

The radiotherapy centers in India have either teletherapy facilities alone or both teletherapy and brachytherapy facilities. Currently, India has approximately 704 teletherapy machines (Linear Accelerator 544, Telecobalt 160), 22 advanced therapy machines (7 Gamma knife units, 22 Tomotherapy machines, 10 Cyber knife machines, and 2 proton beam therapy centers). Every year, around 40 external beam therapy units are added and 15 units are decommissioned, bringing the total number of new units to 25 per year.

Brachytherapy remains an integral portion of the RT treatment of cervical cancer. It can be used in different settings, viz., intracavitary, interstitial, and combined intracavitary and interstitial. Cervical cancer patients treated without brachytherapy experience compromised survival outcomes. The modern high-dose rate (HDR) remote after-loading brachytherapy machines are gradually replacing low-dose rate (LDR) units as these have several advantages. Presently, the number of remote after-loading brachytherapy units in India is around 325. Of these, about 280 are HDR after-loading units, and around 50 are LDR units. It is emphasized here that every RT center must have brachytherapy services so as to impart comprehensive treatment to cervical cancer patients.

As per the Directory of Radiotherapy Centres (DIRAC) data, Western Europe and North America have more than three teletherapy machines per 1 million population, while India has less than 1 machine per 3 million population [Figure 5]. This is grossly inadequate as per the WHO recommendations.

Apart from the gross inadequacy of RT facilities, the distribution of centers is also heterogeneous. Most of the RT

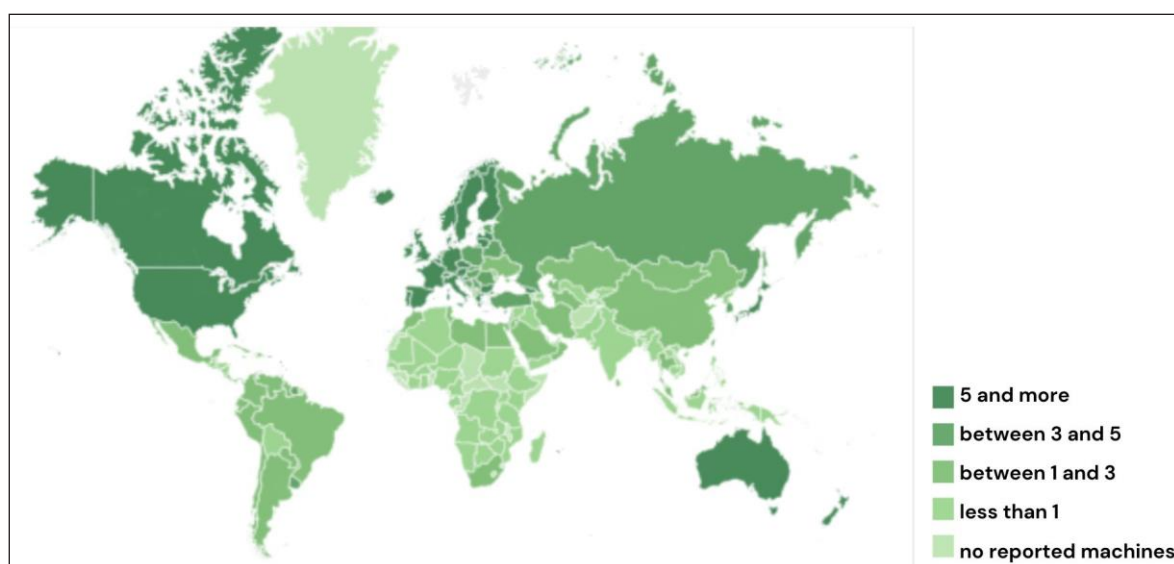


Figure 5: Global map of radiotherapy machine distribution. Source: The IAEA Directory of Radiotherapy Centres (DIRAC) <https://dirac.iaea.org>. Accessed on Nov 9, 2024. IAEA: International Atomic Energy Agency.

centers are concentrated in large metropolitan cities like Delhi, Mumbai, Kolkata, Chennai, Bengaluru, and state capitals while rural areas with a major burden of cancer cervix do not have RT machines in their vicinity. This can be attributed to the factor that RT machine installation and usage requires technically trained staff as well as good infrastructure. Also, quality assurance is pivotal in running a RT center. In terms of brachytherapy equipment, the state of affairs is even more dismal [Figure 6]. Not every teletherapy center has a brachytherapy machine and even when a brachytherapy machine is available, centers are not able to utilize it optimally due to a lack of expertise and unavailability of accessories along with other logistic and regulatory issues.⁵³

Recent reports also suggest that the high costs incurred on travel to distant centers leads to noncompliance. A study performed at a rural cancer center indicated that over 60% of patients were noncompliant citing difficulties in travel. These patients had to travel a distance of more than 100 km from home to hospital.⁵⁴

We need one RT machine per million population for adequate RT services. In its 2023 report, Directory of Radiotherapy Centres (DIRAC) has included India along with the poorest Sub-Saharan African countries.⁵³ The health care policy in the future must include galvanizing more RT resources in order to meet the required infrastructure. Distribution of medical colleges are now at par across the Indian geography. But, not all medical colleges have a radiation oncology department. Population data of cancer incidence and prevalence are now available to enable decision-making; an initiative should be

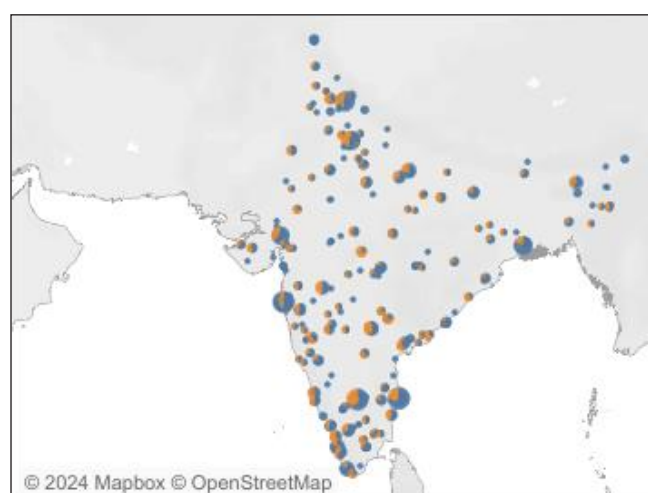


Figure 6: Distribution of radiotherapy equipment in India. Source: The IAEA Directory of Radiotherapy Centres (DIRAC) <https://dirac.iaea.org>. Accessed on Nov 9, 2024. IAEA: International Atomic Energy Agency.

taken to earmark geographical areas where RT center along with other cancer treatment facilities can be installed.

Status of systemic therapy and gaps

Early-stage disease is managed through surgical approaches, while the standard of care for locally advanced yet nonmetastatic cases involves concurrent chemoradiation. Nonetheless, relapses remain common even with post-curative treatments. The incidence of relapse rises with advanced stages, with nodal positivity emerging as an independent adverse prognostic indicator. The -year survival rate for patients in stages IIIC and IVA dwindles to a mere

15–20%. In advanced stages, the majority of relapses manifest systemically, significantly constraining the success rate of salvage therapies. Systemic treatments, encompassing chemotherapy, targeted therapy, and immunotherapy, are employed for these cases. Despite these efforts, post-relapse treatment options are limited, resulting in many patients eventually succumbing to the disease.

Outcomes from NCRP data from 2012 to 2016 show that in 60.0% cases, the clinical extent of the disease was locoregional. Localized disease was seen in 32.8%, whereas distant metastases were observed in 5.1% cases. A high proportion of patients with cancer cervix uteri underwent chemotherapy plus radiation (localized 49.8%, locoregional 56.6%, distant metastases 46.7%, and stage unknown 38.3%). Radiotherapy alone was the second most preferred treatment for cervical cancer. Only 7.7% patients with clinically localized cancer cervix uteri were treated with surgery [Table 5].⁷ This highlights the need for strengthening the availability of systemic therapy options.

Current systemic therapy options

For locally advanced cases: concurrent chemotherapy with cisplatin, coupled with radical radiotherapy is now the standard of care.

For metastatic and relapsed cases, the following options are in use:

1. *Chemotherapy*: The standard first-line treatment typically involves paclitaxel and carboplatin. However, responses are usually short-lived, and progression is inevitable.

2. *Targeted Therapies*: These include anti-angiogenic drugs such as bevacizumab, which, when combined with chemotherapy, have demonstrated improved survival rates in studies.⁵⁵

3. *Immunotherapy*: Recent advancements in immune therapeutics have led to the increased use of anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PDL-1) blockers as the standard of care in various cancers, including cervical cancer.⁵⁶ While these drugs have shown promise, their use remains limited due to high costs.

Existing gaps

1. *Locally Advanced Cervical Cancer*: FIGO Stage IIIC and Stage IVA patients have a discouraging -year survival rate of 15–20%. A significant proportion of relapses in advanced stages manifest systemically, hampering the efficacy of salvage therapies. This highlights an unmet need to enhance outcomes within this subset of cervical cancer patients. Recent studies evaluating the addition of extra chemotherapy cycles to standard concurrent chemoradiation did not yield positive results. Therefore, there is a need for more rational and pragmatic trial designs to address this gap.

2. *Recurrent and Metastatic Cases*: Efforts should be directed toward researching less toxic therapies, such as exploring low-cost options like oral metronomic chemotherapy, evaluating low-dose immunotherapy, and facilitating the development of generic immunotherapies. Encouraging global pharmaceutical companies to expand compassionate access programs to Indian patients and conducting clinical trials in India would also be beneficial.

Collaborative efforts

The formation of cervical cancer specific research groups dedicated to novel preventive approaches and the promotion of research for developing low-cost, less toxic, and efficient therapies are necessary.

Table 5: Number (n) and relative proportion (%) of types of treatment according to the clinical extent of disease

Treatment	Localized only	Locoregional	Distant metastasis	Unknown
	N %	N %	N %	N %
Surgery	592 7.7	318 2.3	10 0.8	41 7.9
Radiotherapy (RT)	1935 25.1	4356 30.8	442 37.1	172 33.1
RT+chemotherapy	3842 49.8	8005 56.6	556 46.7	199 38.3
Systemic therapy	340 4.4	689 4.9	133 11.2	57 11.0
Multimodality*	995 12.9	682 4.8	42 3.5	46 8.9
Palliative care	18 0.2	83 0.6	7 0.6	4 0.8
Surgery	592 7.7	318 2.3	10 0.8	41 7.9
Total	7722 100	14133 100	1190 100	519 100

*Multimodality includes the combination of surgery and/or radiotherapy and/or systemic therapy. Source: https://ncdirindia.org/All_Reports/Report_2020/resources/ NCRP_2020_2012_16.pdf

Inadequacies in Indian data underline the necessity for collaboration between academic institutions to foster data collection, aggregation, and analysis aimed at identifying specific issues.

Molecular research

Advancements in molecular research are needed that could potentially yield significant insights for developing newer effective therapies for cervical cancer management.

Current health programs and national guidelines on screening and management

Ministry of Health and Family Welfare (MoHFW) has taken numerous steps over the years to control this preventable cancer at the national level.

The National Cancer Control Programme (NCCP) was launched in 1976 with the aim of strengthening tertiary care institutions and to improve holistic care for cancer from prevention to palliation. Subsequently, in the late 1990s, the priorities were redefined, and the program aimed at primary and secondary prevention, which included health education, awareness about the disease, and screening using cytology (Pap smear) to prevent the disease. This was practically feasible at the ground level by the launch of the Modified District Cancer Control Programme (MDCCP).

In 2010, NCCP was integrated with the NPCDCS, renamed as National Programme for Non-Communicable Diseases (NP-NCD) in 2023. It was rolled out in 21 states, initially under noncommunicable disease (NCD) clinics in community health centers (CHC). Beyond this, there is the tertiary care cancer centers (TCCCs) scheme, the aim of which is to strengthen/set up state cancer institutes (SCI) and TCCCs to provide comprehensive cancer care. Under the NPCDCS program, VIA was recommended for all women between 30 and 59 years of age by healthcare workers, and protocols were made for the management/referral of VIA-positive cases for colposcopy and further treatment as and when required.¹ Training of health care professionals on VIA/colposcopy and on ablative methods were also part of this program. In 2016–2018, MoHFW developed the mobile technology platform for cervical cancer screening, which helped in the implementation and continuous monitoring of the screening program in each state.

With the increasing need for cancer-screening guidelines in India, ICMR's National Institute of Cancer Prevention and Research (NICPR), Noida, formulated national cancer screening guidelines in 2013. Based on this, VIA was considered as an effective screening strategy in countries like

India, where resources for cytology are scarce. Subsequently, it was included in the NPCDCS program and implemented in all the states to the last mile involving grassroots workers like village health nurses and Accredited Social Health Activist (ASHAs).

In 2018, the Federation of Obstetric & Gynaecological Societies of India (FOGSI) developed resource-stratified Good Clinical Practice Recommendations (GCPR) or screening and management of screen-positive cases by stratifying the healthcare system into good-resource settings and low-resource settings. This helps clinicians to choose the appropriate method of screening based on available resources and individual preferences.⁵⁷

In 2019, the National Cancer Grid, a consortium of more than 180 cancer institutions in India, which aims to provide evidence-based guidelines on the three most common cancers in India produced population-based screening strategies for breast, cervix, and oral cavity cancers. VIA is considered as a viable option of screening women aged 30–65 years one to three times in their lifetime.⁵⁸

The Department of Health Research has released a health technology assessment for early diagnosis of cervical cancer. Based on this, screening is the major cornerstone in the prevention paradigm, and it suggests VIA every 5 years as the most cost-effective screening method in the context of India presently.⁵⁹

DEFICIENCIES TO BE ADDRESSED

Gaps in the implementation of screening and awareness activities

Various barriers, including the health system, provider and community-related socioeconomic and cultural issues, have slowed down the screening efforts in developing countries [Figure 7].

Health system

The national guidelines for screening of common cancers, including cervical cancer, were introduced in 2016, but they still face several lacunae in terms of implementation. India introduced and scaled up VIA-based programs with varying levels of organization and performance. Case studies have shown that program organization rather than a choice of test may determine the success of a screening program.⁶⁰ Due to the simplicity of VIA, it was possible to build infrastructure, increase numbers of trained health care personnel, and develop a system of multilevel coordination within the health system. However, after more than 7 years, the number

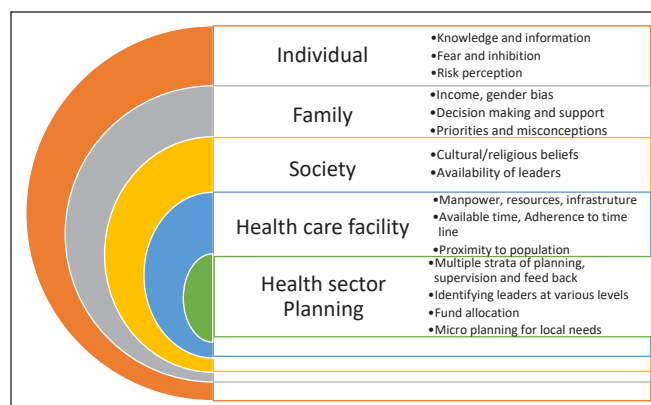


Figure 7: Barriers in cervical cancer screening.

of women screened remains very low (~3%). A major reason for this could be a lack of political will and the absence of a dedicated advisory body for prevention activities at various levels. Shifting of priorities in health care with a focus on the increasing burden of cancer is required. The major lacunae faced are fund allocation, human resource building, infrastructure, and equipment. Furthermore, communities have poor access to the health care system, which increases the gap even further. Implementation of simple screening algorithms and ensuring an affordable and continuous supply of high-performance screening test will help achieve the goal.

Provider

Rigorous training and retraining of health care workers at primary and secondary levels for performing VIA and maintaining quality control, as well as timely referral and treatment of positive cases is still lacking. There are no fixed protocols or a dedicated facility for cervical cancer screening at health care centers. Continuous supply of affordable screening test kits is a challenge faced at many places. The screening test chosen, i.e. VIA, lacks high sensitivity and is dependent on human resources and, therefore is not able to meet community needs. HPV DNA testing kits, along with point of care (POC) tests have performed far better, but their availability is a major issue at present. Women who are screened positive face difficulties in reaching referral centers or getting treatment, and this leads to high losses to follow-up. There is no database or health information system to track these women. The option of self-sampling is still on a research basis, although it has the potential to reduce the burden on health care workers and mobilize women who are not willing for a pelvic exam. Regular outreach camps in difficult terrains are still lacking.

Community

The major problem highlighted in several studies remains a lack of awareness regarding this preventable cancer among the population who are at risk. There are several sociocultural aspects leading to women not prioritizing screening. One of the reasons could be that cancer is not considered a curable entity. Information, education, and communication regarding the causes, and primary and secondary prevention through audiovisuals in the native language could help in reaching to the masses, but they are nonexistent at present. The social structure of a community generates a lot of myths and misconceptions regarding mass screening in camps, leading to poor turnover. Fear and inhibition, along with loss of daily wages incurred, gender bias, and cultural beliefs, add to the problem.

HPV infection, being a sexually transmitted disease, often leads to the general public questioning the screening due to social reasons. The inclusion of ground-level healthcare workers in dispelling myths and addressing the needs of the community with an understanding of its social structure is a necessity.

Figure 8 depicts the major gaps to be addressed at these three levels.

Mitigating the gaps

While implementing a nationwide policy, the program should address the needs of the local population. The attitude

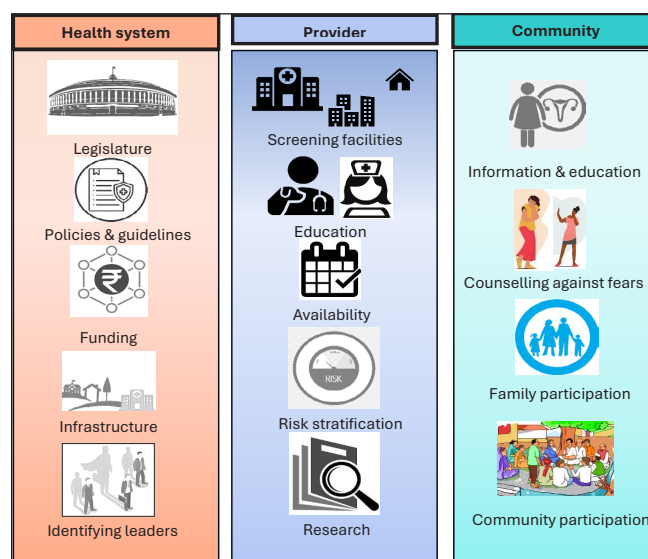


Figure 8: Major gaps to be addressed at the level of health system, provider, and community.

of women who undergo screening defines the direction of the rest of the people in their locality. The feedback from the women who are undergoing screening, to a great extent, influences the others. Hence, educating and screening every woman who enrolls for screening, keeping her confidence intact, and promoting her as an ambassador for the cause will amplify the outcome. Training and including the local women to be part of the team for screening will promote screening by increasing familiarity among the local population and also will help to get feedback.

The planning should be done separately for program managers, healthcare workers, and the targeted population. Time and resources invested in pre-implementation field work and microplanning will help to increase the percentage of women screened. Legislature directing employers to screen women undergoing medical examination during induction into a job or undergoing medical review is the need of the hour.

Follow-up of women undergoing screening and informing them of their results adhering to the timelines will motivate them. The screening team should also convey the management plan for screening-positive women when the reports are conveyed. The delays in management after conveying the positive screen test report will bring more apprehension and attrition. A facility to triage or treat should be available near the screening setup. Reducing the number of visits from screening to treatment is mandatory.

We need implementation studies to understand the impact of screening and the factors that alter the uptake and outcomes of screening. The implementation studies will help to pick up the positive aspects, drop the negative ones, and change the strategy when required.

Population-based data on screening, i.e., the number of women who have undergone screening, the method used, and their follow-up cum referrals, are not available. Creating a nationwide registry for screening linked with a permanent identification number like an Aadhar number may help to understand the ongoing activities, planning, and implementation.

Innovations in the areas of newer screening methods, triage tests to deliver treatment at the same visit, identifying risk factors for the increase in adenocarcinomas of cervix, identifying risk factors in new generations with changing family patterns, development of portable colposcopy, incorporation of artificial intelligence into screening, self-screening methods, using molecular markers for screening, innovating new ways for understanding the KAP, new methods for information-education and counseling (IEC) activities, designing and testing a population-based screening registry,

and training for undergraduate medical students in screening activities are still awaited. The existing screening algorithms need field implementation trials in a large population cohort.

Allocation of funds for cancer prevention research will help to increase the number of research activities in this area of study.

Transition to screening by HPV DNA testing (including POC tests and self-sampling)

Despite the plethora of screening tests [high-risk HPV DNA/Nucleic Acid Amplification Test (NAAT)/mRNA tests, VIA, Liquid-Based Cytology, and Pap Test] being available, the acceptance of these tests is largely influenced by accessibility to health care facilities, socioeconomic status, and awareness. Only tests validated by international standards that have clinical sensitivity rather than analytical sensitivity should be used.

HPV DNA testing has higher sensitivity (96.1% vs. 53.0%) but lower specificity (90.7% versus 96.3%) when compared to cytology. Several multicentric trials have established that primary HPV testing provided about 60–70% greater protection against invasive cervical carcinomas as compared to cytology.⁶¹

WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screen-and-treat/screen-triage and treat approaches among both the general population of women and those living with HIV (strong recommendation with moderate certainty evidence).³⁰ HPV mRNA tests are also available, but these are not recommended for use in self-sampling.

Self-sampling

HPV testing can be done on provider- or self-collected samples. Although many commercially available hrHPV kits (cobas®, BD Onclarity™, Aptima®) are available for screening, only COBAS 4800, 6800, 8800, and BD Onclarity are Food and Drug Administration (FDA) approved for primary cervical cancer screening. Unfortunately, in many countries, especially LMICs, standard cervical cancer screening tests are not universally or even widely available, and hrHPV primary screening is limited due to cost and logistics issues. Women may feel shame and embarrassment due to personal or sociocultural reasons, and in such circumstances, self-sampling can circumvent the hesitancy in treatment-seeking behavior. Self-sampling can help in reaching women residing at the last mile.

A meta-analysis of 18,516 female participants from 24 countries across 5 continents showed that 65% women

preferred self-sampling over physician sampling; the reasons quoted were ease of use, not embarrassing, privacy, comfort performing self-sampling, ability to sample on their own, and convenience.⁶² In another study, authors noted that hrHPV assays based on PCR were equally sensitive on self-samples as well as clinician samples to detect preinvasive lesions (CIN2+ or CIN3+). Also, self-sampling by mailing the kits to women's home address generated a much higher response rate as compared to physician sampling. There was a 12% reduction in sensitivity for the detection of CIN2+ when self-sampling was compared with clinician-collected samples, but this was only seen when testing was performed using hybridization signal-based assays (example: Digene HC2 assay). It is interesting to note that this reduction in sensitivity was not seen when HPV testing was performed using amplification-based methods such as PCR.⁶³

In a study among rural women in India evaluating the acceptability of self-sampling on a five-point Likert scale on parameters like ease, privacy, and discomfort, it was observed that self-sampling was significantly preferred over physician sampling. They used the HC2 test to process both sampling techniques, and it was found that there was a substantial level of concordance between the two methods (Cohen's kappa – 0.73, 95% CI: 0.34, 1.00).⁶⁴

Point of Care (POC) testing

POC testing overcomes limitations like cost, processing time, and laboratory infrastructure and facilitates the screen-and-treat approach in a single visit. They are highly efficacious in LMICs and high-risk HIV populations where women with positive HPV DNA test can be counseled and offered further evaluation to assess their eligibility for thermal ablation/cryotherapy on the same day. Widely used and commercially available tests include:

1. CareHPV (Qiagen): Based on chemiluminescence technology, this qualitative test provides test results within 3 hours.
2. Xpert HPV (Cepheid Diagnostics): This includes DNA extraction, amplification, and detection using PCR technology in integrated cartridges and provides reports as HPV16, HPV18/45, or other hrHPV (31, 33, 35, 52, 58; 51, 59; 39, 56, 66, 68) positive within 60 minutes.
3. Truenat (Molbio Diagnostics, Goa, India): This detects four hrHPV types: 16/31, 18/45 via a microchip-based real-time PCR assay; test results are available in 60 minutes. Now a modified version with 8 types is undergoing international validation testing. It has HPV 16/18 in one channel and HPV 31, 33, 35, 45, 52, 58 in the other.

Partial genotyping in these tests provides an in-built triage method. Other POC tests are currently under development. Various studies have validated the use of POC tests on self- and physician-collected samples in community settings. A study conducted in South Africa evaluated the diagnostic accuracy of Xpert HPV (five channel reporting – HPV type 16; HPV types 31, 33, 35, 52, or 58, or more than one of these types; HPV types 18 or 45, or both; HPV types 51 or 59, or both; and HPV types 39, 56, 66, or 68, or more than one of these types) in detecting CIN 2+ and higher lesions in HIV-positive and HIV-negative populations. Sensitivity in HIV-negative women for all channels was 88.7% (95% CI 83.1–94.3) while specificity was 86.9% (95% CI 83.4–90.4). In HIV-positive women, sensitivity was higher 93.6% (95% CI 90.0–97.3), but specificity was lower 59.9% (95% CI 54.1–65.7) as compared to the general population.⁶⁵

An Indian study evaluated the diagnostic value of a POC, test Truenat, which detects four hrHPV genotypes (16, 18, 31, and 45), using HC2 as a reference test. Of 615 cervical samples, 78 (12.7%) women were found to be hrHPV DNA positive by HC2 and 49 (8%) by Truenat. Keeping in mind the limited genotype testing offered by Truenat, its sensitivity and specificity were found to be 97.7% and 98.9%, respectively.⁶⁶

Is POC testing really the way forward in LMICs where the screen-and-treat/single-visit approach is technically more feasible than the two-visit approach? To evaluate this, a modeling study evaluated the monetary benefit from a single-visit approach as compared to a two-visit approach in three LMICs (India, Nicaragua, and Uganda) using a mathematical simulation model of the natural history of HPV and cervical cancer. Outcomes included health benefits measured as a reduction in lifetime risk for cervical cancer incidence and lifetime costs. Screening at least three times in a lifetime at 30, 35, and 40 years with a two-visit vs. one-visit strategy at a lost to follow-up (LTFU) rate of 10% had a similar reduction in rates of cervical cancer: 62.0% vs. 65% in India, 66.0% vs. 68.8% in Nicaragua, and 67.4% vs 70.1% in Uganda. But as LTFU increased with the one-visit strategy, the reduction in cancer risk remained stable in each country, while with the two-visit approach, it diminished substantially. Also, as LTFU increased, reducing the number of clinic visits (shifting from two-visit to one-visit strategy) was found to be cost-effective.⁶⁷

In the last two decades, there have been consistent efforts to develop low-cost indigenous POC devices. In the field settings of primary health centers, the only available light source is generally a tungsten bulb emitting yellow light attached to a torch or examination light. An ideal light source with certain magnification was a highly desirable requirement for visual inspection under magnification of the cervix. A portable, user-friendly, low-cost device (US\$160 per piece, AV

Magnivisualizer), which has a complete spectrum of visible light (white light) and interchangeable magnification, has been launched by the Government of India for widespread use. A study to evaluate the device showed better sensitivity to detect precancerous lesions of the cervix compared with VIA (83% vs 54%) without loss of specificity. The authors concluded that the AV Magnivisualizer may be useful in settings where colposcopy facilities do not exist.⁶⁸

Improvement of referral system; training primary and secondary health care workers

The referral system from the place of screening to the place of management plays a vital role in every aspect. The staffing needed to manage screen-positive women appropriately necessitates decentralizing and bringing management interventions to or near the screening sites. Multiple referrals lead to attrition in the number of patients availing of the proper treatment.

India's primary health care system focusing on reproductive and child health activities are in four tiers: subcenters (SC), primary health centers (PHC), community health centers (CHC), and district/sub divisional hospitals. Community health centers implement national health programs which are involved in cancer prevention. The operational framework for the prevention of cancer guides all four tiers to participate in cancer prevention activities.

Observations from the District Level Household and Facility Survey (DLHS-4) suggested that there was significant heterogeneity in facility readiness for cancer screening in all four tiers of the healthcare system. Infrastructure and staffing were the substantial barriers to screening.⁶⁹ Experience from the past clearly shows that implementation strategies for cervical cancer screening should be at multiple levels, including a diverse set of stakeholders planning screening and treatment. Task-sharing strategy allocating responsibilities to peripheral health setups needs vigorous preimplementation activities, which will increase the knowledge, motivation, and leadership among peripheral workers. Figure 9 shows the key components of improving the referral system.

Manpower

While many states have succeeded in initiating task shifting and have a pool of trained manpower, the practice of frequent transfers results in loss of expertise in many instances. Increasing the manpower at peripheral setups with a clearly defined job description is ideal, to keep a high quality of screening and management activities. Manpower calculations should be dynamic with provision to increase the number based on future escalation of the program. The provision of patient coordinators who can facilitate the referral pathway

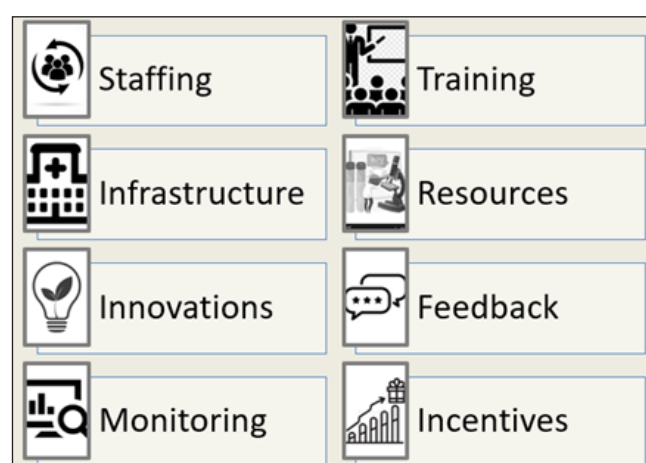


Figure 9: Components of improving the referral system.

and help clients to access services at the referral centers will improve participation rates.

Training

Ongoing training and refresher training of manpower is essential for quality assurance. Training centers at district levels with fixed training calendars and participation of already trained staff in ongoing training activities will increase the confidence to deliver the expected services. Structuring a training module for every level of care involved in cervical cancer screening and management with specified goals and referral guidelines will help to standardize the quality of care. Staff also needs to be trained to handle digital platforms. Recruitment of manpower or agencies to manage social media and other mediums of communication and data collection, which will improve IEC activities and capture data on KAP, will provide future directions to the program.

Data management and tracking

Ensuring smooth communication channels between primary and secondary care facilities will allow for timely patient information and records transfer. Developing software programs enabling monitoring and follow-up of medical records from the peripheral centers will improve the quality of service. Electronic medical records will help identify the gaps and delays in the referral system.

Innovations

Testing and including newer treatment methods like thermal ablation and other contemporary screening and treatment strategies at peripheral setups will help to facilitate the services provided. Including innovations like portable colposcopes at screening setups will help to strengthen the referral system by avoiding unnecessary referrals/undertreatment. Including

telemedicine, teleconsultation, and tele-mentoring facilities will reduce the number of visits for women undergoing screening. Ongoing learning programs through telemedicine will gradually increase the capacity of peripheral setups and help in task-sharing. Incorporating artificial intelligence (AI) for diagnosing and AI algorithms for deciding on management will reduce referrals.

Incentives and motivation

The performance of the referral system at every level should be encouraged by recognizing their work and motivating them with incentives. Monetary rewards, awards, and other incentives for excellence in work can improve performance.

Community participation

The role and contributions of ASHA workers in providing health care in the periphery are significant. Including ASHA workers, community activists, local leaders, and NGOs as part of the referral system and utilizing their services where and when required will bring better outcomes.

Continuous quality improvement

Monitoring the ongoing screening, referral, and training activities through various channels is mandatory for quality improvement. Regularly collecting feedback from the target population and healthcare workers will improve the referral system.

Introduction of HPV vaccine in the national program

The inclusion of an affordable prophylactic HPV vaccine into the national immunization program can significantly alleviate India's cervical cancer burden. Addressing vaccination-related myths and stigma through mass awareness campaigns is vital to boost acceptance rates. HPV vaccination offers safe and effective protection against HPV infections that lead to cancer, marking a crucial step toward eliminating cervical cancer.

Global experiences with HPV vaccination

Several countries have already integrated HPV vaccines into their national immunization programs, leading to a decline in the prevalence of high-risk HPV infections and early-stage cervical cancer cases. By examining these global experiences, India can learn from both successes and challenges encountered during vaccine implementation. Australia, Canada, the United Kingdom, several European countries, Rwanda, Malaysia, and Bhutan have integrated HPV vaccination into their immunization programs, leading to a decline in HPV infections and related cancers.

Australia's school-based HPV vaccination program, initiated in 2007, has demonstrated a remarkable reduction in HPV prevalence, signaling the vaccine's effectiveness. A decline in cancers has been reported from Nordic registries and from the UK. Similarly, Rwanda's proactive approach to nationwide vaccination campaigns has shown the potential for high coverage rates, which is essential for achieving population-level protection.

Measures for a successful introduction in the national immunization program

1. Policy and Advocacy: Efforts must be made to advocate for the inclusion of HPV vaccines in the national immunization program. Policymakers, healthcare professionals, and advocacy groups need to collaborate to build a robust policy framework for vaccine integration.

2. Vaccine Accessibility and Affordability: Ensuring that HPV vaccines are accessible and affordable to all eligible population is crucial.

3. Health Care Infrastructure and Training: The successful implementation of HPV vaccination requires a well-established health care infrastructure and adequately trained health care personnel. Strengthening health care facilities and providing training for health care professionals are essential steps in this direction.

4. Addressing Vaccine Hesitancy: Vaccine hesitancy remains a challenge in many regions. To gain public trust, it is essential to address concerns related to vaccine safety, efficacy, and potential side effects through targeted communication and education campaigns.

5. School-Based Vaccination Programs: Incorporating HPV vaccination in school-based programs can reach a large number of eligible girls and ensure widespread coverage.

6. HPV Vaccination and Equity: It is crucial to address equity concerns to ensure that HPV vaccination reaches all eligible populations regardless of SES, geographic location, or cultural beliefs. Special attention should be given to marginalized communities to prevent further disparities in cervical cancer prevention.

7. Monitoring and Surveillance: A robust monitoring and surveillance system is essential to evaluate the impact of HPV vaccination on cervical cancer incidence and to detect any potential adverse events.

8. Communication and Awareness: Effective communication and awareness campaigns are vital to inform the public,

health care providers, and policymakers about the benefits of HPV vaccination and cervical cancer prevention. Tailored messages and culturally sensitive approaches can help maximize vaccine uptake.

In conclusion, the introduction of HPV vaccination in India's national immunization program holds tremendous potential in reducing the burden of cervical cancer. However, several deficiencies need to be addressed to ensure successful integration and equitable access to the vaccine. By learning from global experiences and developing evidence-based strategies, India can take significant strides in combating cervical cancer and improving women's health nationwide.

Improving access to radiation and chemotherapy

India's oncology community acknowledges acute shortages of vital resources even for fundamental cancer management. The scarcity of radiation and chemotherapy resources disproportionately affects vulnerable populations, particularly rural areas. These therapies are not only crucial for LACC management but also offer palliative care for those with incurable disease. The key barriers are:

- 1) **Geographical disparities:** The concentration of treatment centers in urban areas creates an imbalance in access, leading to delayed or inadequate care for those living far from medical facilities.
- 2) **Infrastructure deficits:** The shortage of equipped radiotherapy and chemotherapy centers further exacerbates the problem. Insufficient facilities and outdated equipment hinder the delivery of timely and effective treatment, thereby affecting patient outcomes.
- 3) **Financial constraints:** Cervical cancer treatment can be financially burdensome, and many patients face difficulties in affording the costs associated with radiotherapy and chemotherapy. High out-of-pocket expenses, coupled with limited health insurance coverage, deter patients from seeking appropriate care.
- 4) **Lack of awareness:** A lack of awareness about cervical cancer and its treatment options among the general population and health care providers leads to delayed diagnosis and treatment initiation. This contributes to the advanced stage at which many patients are diagnosed, making treatment less effective.
- 5) **Health care workforce shortage:** There is a shortage of trained oncology health care professionals, including radiation oncologists and medical oncologists, which impacts the capacity to deliver radiotherapy and chemotherapy services to the growing number of cervical cancer patients.

Allocating resources to establish comprehensive treatment facilities in underserved regions can bridge the existing gap in cervical cancer management. The potential strategies for addressing these barriers include:

- 1) **Policy reforms:** Government policies can be used to increase investment in radiotherapy and chemotherapy infrastructure, expand access to affordable cancer care, and raise awareness about cervical cancer.
- 2) **Infrastructure development:** New radiotherapy and chemotherapy centers can be established in rural areas, and existing facilities can be upgraded with modern equipment.
- 3) **Health care workforce training:** Scholarships, training programs, and incentives can be offered to attract more students to study oncology and to encourage qualified professionals to work in rural areas.
- 4) **Public awareness campaigns:** Public awareness campaigns can be used to educate the general population and health care providers about cervical cancer and its treatment options.

Apart from the mentioned challenges and strategies, the lack of comprehensive data on cervical cancer cases and treatment outcomes hampers our understanding of care deficits and effective interventions. Robust data collection and research initiatives are vital to guide evidence-based strategies for better access to radiotherapy and chemotherapy for cervical cancer patients in India. Collaborative efforts between health care institutions, government bodies, and research organizations can strengthen a national cancer registry, enhancing our understanding of the disease landscape. Investing in cervical cancer research is essential for identifying innovative and culturally appropriate diagnostic and treatment approaches tailored to suit resource-limited countries like India.

Research can also help in identifying cost-effective interventions without compromising quality, reducing the financial burden on patients and health care systems. Research can inform strategies to improve treatment delivery, minimize interruptions, and manage side effects, enhancing patient experiences. It is also the need of the hour to develop nation-specific guidelines for cervical cancer treatment. These guidelines should be based on a comprehensive understanding of disease prevalence and treatment responses within the Indian context, ensuring consistent and high-quality care. Evaluating the effectiveness of telemedicine and mobile health units is also essential to improve care in underprivileged areas. Insights can expand these initiatives to reach underserved populations.

Palliative care

Cervical cancer is associated with severe morbidities, painful course, and difficult deaths. It is the most common cause of death from cancer amongst economically poor women. These women suffer from a high prevalence of malodorous discharge, excessive bleeding, severe abdominal pain, sexual dysfunction, and urinary fistulas in advanced stages. These disabling physical symptoms have a significant impact on the psychosocial and emotional well-being of these women. Since the disease is more prevalent amongst the poor socioeconomic strata, cost-effective interventions are necessary.

Appropriate management using oral metronidazole, oral morphine, antidepressants, and laxatives can significantly improve the quality of life of these women. Less than 1% of India's population has access to palliative care.⁷⁰ Opioid availability for pain management is scarce, with poor availability of trained staff for prescribing and titrating the medication. The excruciating pain significantly affects the life of both the patient and the caregivers. Palliative care specialists can adequately and safely provide pain management to these women. The availability of these pain-relieving medications, along with appropriate training of the specialists for pertinent management is an essential component of palliative care in these women.

Women with advanced cervical cancer usually visit the emergency room in uremia secondary to ureteral obstruction due to various causes. Decompression of obstructed ureters using ureteral stents or percutaneous nephrostomy (PCN) is a management option. Though seen as an emergency "life-saving option" by the physician and the patient, the decision should be based on clear communication about the prognosis, benefits, and burdens of this intervention.⁷¹

Palliative radiotherapy is a cost-effective intervention to reduce vaginal discharge, bleeding, pressure effects, and nociceptive pain caused by pelvic and para-aortic disease. Simple and safe regimens, though are still not conceptualized well.

Palliative care is essential for women with advanced cervical cancer, but it is usually administered when curative treatment is no longer feasible. There is growing evidence that early integration of palliative care (EIPC) with ongoing oncological management can significantly improve the quality of life (QoL) for these women.⁷²

In conclusion, the suffering of women with advanced cervical cancer, an illness mainly of the poor, has been ignored by scientific research with no established mechanisms and protocols for providing palliative care to these women. The collaborative effort of researchers, public health officials,

oncologists, gynecologists, and primary care providers should be the basis of palliative care in these women.

RECOMMENDATIONS FOR WAY FORWARD

Implementation of WHO's cervical cancer elimination initiative

In 2018, the Director General of WHO, Dr. Tedros Adhanom Ghebreyesus, issued a call for action to scale up prevention, detection, and treatment to finally eliminate cervical cancer as a public health problem. In 2020, WHO's member states responded to the call, passing a historic resolution with specific target goals through the World Health Assembly. On November 17, 2020, WHO launched the three-pillar strategy. The resolution and the strategy established clear targets to achieve by 2030:

1. HPV vaccination coverage – 90% of girls are fully vaccinated by HPV vaccine by 15 years of age.
2. Screening – 70% of women are screened by a high-performance test by the age of 35 years and again by the age of 45 years.
3. Access to treatment – 90% of women with pre-cancer were treated and 90% of women with invasive cancer were managed.²

Now, implementing the cervical cancer elimination initiative involves a multifaceted approach encompassing vaccination, screening, treatment, awareness, and collaboration among stakeholders.

HPV vaccination

Central to the initiative is the widespread availability and administration of HPV vaccine. The initiative requires strong partnerships with governments, international organizations, and pharmaceutical companies to ensure affordable and equitable access to these vaccines, particularly in low-income countries. Educational campaigns are essential to dispel myths and ensure public acceptance of vaccines. Based on the WHO data available, by the end of 2022, the number of manufacturers with licensed HPV vaccines and production capacity has also increased rapidly. India developed its own indigenous quadrivalent HPV vaccine (Cervavac, SIIPL) in September 2022. The Indian government is planning to roll it out in the government sector in three phases for 9- to 14-year-old girls in the near future. With this three-phase strategy, 68 million girls in India would have been vaccinated, and a further 11.2 million girls aged 9 years will be targeted for routine HPV vaccination year.⁷³

Based on the latest evidence, WHO/SAGE issued recommendations on the possibility for adolescents up to age

20 years to receive a single dose, which can reduce cost and increase flexibility to reach higher coverage.²⁰ Since the Call to Action, 141 countries have introduced the HPV vaccine into their national schedule, and 59 countries have a single-dose policy.

Screening

It is of utmost importance to develop organized screening programs for systematic screening, treatment, and follow-up of screen-detected women. Cervical cancer screening programs using cost-effective tests and simple algorithms should be implemented for the early detection of precancerous conditions and cancers. These programs should prioritize accessibility, especially in rural and underserved areas. To enhance screening efficiency, innovative approaches like self-sampling kits can empower women to take control of their health. Integration of screening into existing health care services can maximize the initiative's reach. Due to the lack of manpower, infrastructure, quality control, and financial resources, high-quality cytology and HPV screening may not be feasible for wide-scale implementation of the cervical cancer screening program in LMICs. Visual screening tests, i.e., VIA/VILI should be adopted till a low-cost/POC reliable HPV test becomes available.²⁵ VIA can be performed by trained doctors and paramedical staff, with adequate training and quality assurance. Adequate knowledge and training of the health care workers is essential before the implementation of the screening programs. Medical camps with VIA as a screening tool can be conducted in rural/slum areas. Looking to the future, WHO is supporting innovation for the next generation of POC testing and artificial intelligence based screening, which holds exciting potential to further improve quality, reduce costs, and increase access.

Treatment

Diagnosed preinvasive and invasive cases must be promptly treated to prevent disease progression. The initiative requires investments in health care infrastructure, ensuring that health care facilities have the necessary equipment and skilled personnel for accurate diagnosis and effective treatment. This may involve training health care professionals, enhancing laboratory capabilities, and ensuring the availability of treatments like cryotherapy and thermal ablative methods. With recommendations on the use of portable, battery-powered thermal ablation devices to treat precancerous lesions, WHO has also been supporting countries to phase out cryotherapy. In doing so, WHO supported reduced access pricing for thermal ablation products. Collaboration with medical institutions and professional bodies is essential to ensure standardized treatment protocols. For the management

of invasive cancers, WHO has the capacity to strengthen and scale up services and provide guidance for procuring radiotherapy devices. WHO deployed clinical experts to help train surgeons and oncologists, established new partnerships on diagnostics and radiotherapy, and brought together professional societies to further build capacity in LMICs.

Awareness and education

Public health campaigns should target communities, schools, workplaces, and media outlets to disseminate accurate information and dispel misconceptions. The involvement of local leaders, women's organizations, and community health workers can facilitate culturally sensitive conversations. Sex education that addresses HPV transmission and cervical cancer prevention should be integrated into the school curriculum. Sikkim, a state in northeast India that has successfully rolled out HPV vaccination, reached 97% of the target population in its initial campaign. This success is because of good education about the benefits of the HPV vaccine and good communication with the teachers, parents, and health care workers before the vaccine rolled out. This approach holds the same with the other two pillars of WHO strategy as well.

Collaboration among stakeholders

The successful implementation of the initiative relies on collaboration among various stakeholders, including governments, international organizations, health care providers, NGOs, pharmaceutical companies, and communities. Governments play a pivotal role in policy formulation, funding allocation, and program implementation. El Salvador is the first country in Central America to reach WHO's elimination target in all three pillars and is a very good example of the importance of collaboration with the government and stakeholders in the elimination initiative. The country could attain its elimination target through the successful collaboration of the Ministry of Health in including HPV vaccination in their national immunization schedule, the costs of the vaccine and HPV kits were included in the national budget, and a screen-and-treat approach was implemented in all the screening facilities, thereby reducing the lost to follow-up population. International organizations provide partnerships in technical expertise, funding, and support in resource-limited settings. For example, Gavi, the Vaccine Alliance, is providing support for LMICs to introduce and scale up HPV vaccines, while the Bill & Melinda Gates Foundation supported critical HPV vaccine research. International Atomic Energy Agency (IAEA), IARC, and WHO together assist through joint reviews and strengthening the clinical skills of surgeons/oncologists across LMICs.

Collectively, these efforts represent a meaningful starting point to advance this ambitious agenda. Pharmaceutical companies contribute by making vaccines and treatments accessible and affordable.

Data collection and analysis

A robust monitoring and evaluation system is required for tracking progress and identifying areas needing improvement. Data on vaccination coverage, screening rates, treatment outcomes, and disease incidence should be collected regularly and analyzed. This enables evidence-based decision-making, early intervention in underperforming areas, and the identification of trends and challenges. Transparent reporting mechanisms build trust and accountability among stakeholders.

Challenges and mitigation

Implementing the Cervical Cancer Elimination Initiative is not without challenges. These may include financial constraints, limited health care infrastructure, cultural barriers, vaccine hesitancy, and reaching marginalized populations. To mitigate these challenges, a combination of strategies is necessary, including securing sustainable funding through domestic and international sources, strengthening health care systems, conducting culturally sensitive awareness campaigns, investing in research to address vaccine hesitancy, and utilizing mobile technology to reach remote communities.

Screen-and-treat approach for hard-to-reach populations

The uptake of community screening for cervical cancer with existing programs, such as VIA, has several drawbacks. Though a simple procedure, training and, more importantly retaining the trained personnel is a huge challenge. To reach the masses, health care workers in India, such as the ASHAs or community health workers have been successfully trained in the past to tackle health issues at the community level. With one ASHA for approximately 1,000 people, there are now nearly one million ASHAs in the country; they can be a valuable workforce for mobilizing eligible women from the community, counseling them, delivering screening test reports, and recalling screen-positive women for triage and treatment. They have been found to be productive as a result of their proximity to the community, knowledge of the local population, and acceptance by families as providers of different health interventions.⁷⁴ Using this approach, the screening services can be packaged into the already existing health care system and offer testing at the doorstep, thereby overcoming the hurdles of accessibility, cost of travel, time away from home, vocation, and privacy.

With the introduction of testing for HPV as a primary screening test, self-sampling has gained broad attention due to its potential to increase screening coverage. In camp and outreach settings too, self-collection for HPV testing with a POC test is a good option.

Various other methods to include the hard-to-reach populations have been tried such as indigenous field worker sampling, where the field worker has special training pertinent to the objectives of the study, including interview skills and fieldwork protocols and have privileged access to the target population.⁷⁵ Another method would be facility-based sampling, which refers to recruiting members of the target population from a variety of facilities, including correctional and drug treatment centers, sexually transmitted disease clinics, or general health centers and hospitals in certain suburban areas. Some members of hidden populations, e.g., migrant workers, tend to gather at certain locations within the community, and therefore time–location sampling is used to recruit these groups of hard-to-reach populations at locations where they may be found at a given time.

In the screen-and-treat approach, the decision to treat is based on a positive primary screening test only without triage (i.e. no second screening test and no histopathological diagnosis). The emphasis is on reducing the burden of an additional visit, thus enhancing the impact of the screening. Depending on the findings of the screening test, if the patient is eligible for ablative treatment, this should ideally be done immediately (the single-visit approach). At some facilities, this is not feasible and a second visit may be needed (the multiple-visit approach). Women who are not eligible for ablation can have excisional treatment on the same day if the clinic has the capacity for large-loop excision of the transformation zone (LLETZ). If LLETZ is not available on-site, women need to be referred for excisional treatment or for further evaluation.

Although the current recommendation is for HPV testing as screening for the screen-and-treat approach, it is also suggested that existing programs with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational with respect to cost and quality assurance. Existing programs using VIA as the primary screening test need to be transitioned rapidly to HPV screening, given the inherent challenges with quality assurance and sustenance.

In the screen-and-treat strategy using primary HPV testing, women who are HPV-negative are not treated nor evaluated further. Women who are HPV-positive should all be treated based on the eligibility for ablative treatment with the application of acetic acid and visual evaluation using the naked eye or with a colposcope. Those who are ineligible for

ablative treatment should be referred for excisional treatment or further evaluation.

The treatment aims to destroy or remove the entire transformation zone of the cervix, including areas of the cervix that have been identified as abnormal by screening. In the HPV screen-positive women, it has been suggested that they undergo ablation even when there are no acetowhite lesions on acetic acid application. The rationale behind this is that these women are at a high risk of developing a high-grade lesion in the foreseeable future.

Introducing screening in ART centers for WLHIV

WLHIV are up to seven times more likely to develop cervical cancer than uninfected women, the reasons being a higher risk of coinfection with high-risk HPV types, HPV reactivation, and persistence and low regression of HPV infection. Cervical cancer is the most prevalent acquired immune deficiency syndrome (AIDS) defining malignancy.⁷⁶

Primary HPV screening is considered the standard for cervical cancer screening currently. In the study by Boddu et al.⁷⁷ (2021), HPV testing had the highest sensitivity (90.9% vs 75%) amongst various screening methods for the detection of high-grade preinvasive lesions with low specificity (68% vs. 83.9%) and diagnostic accuracy (69.4% vs. 83.3%) compared to Pap smear. This can be explained by the high prevalence of HPV infection in HIV-infected women, along with poor clearance, increasing the risk of malignancy.

The effect of antiretroviral therapy (ART) on the incidence of cervical cytological abnormalities remains unclear. Early ART initiation may reduce the risk of coinfection with hrHPV but does not prevent the persistence of the infection. With an increase in overall life expectancy, the risk of development of cervical cancer increases with significantly high morbidity and mortality.

According to WHO 2018 data, there are 18.2 million WLHIV, including 0.9 million women from India. The major challenges that affect the process of cervical screening in India in ART clinics are:

- 1) Fatalistic attitude toward the diagnosis of HIV/AIDS.
- 2) Difficulty in going to a separate clinic for screening.
- 3) Lack of knowledge and social support.⁷⁶

The prevalence of high-grade neoplasia among HIV-positive women is higher, which is 6.4% as compared to 0.5% in HIV-negative women.⁷⁷ Prevalence of high-grade neoplasia has been seen to be significantly associated with low CD4 counts in various studies.

The prevalence of HPV infection is high in WLHIV, reported as 37.6%–41%, which is much higher than the general population, i.e., 5.9–6.6%. The data of abnormal Pap smear have been variable ranging from 8.1% to 38.3%, whereas VIA positivity has been noted as 32.2% across various studies^{78,79}.

The evidence assessing the test accuracy of the various screening modalities (Pap smear, hrHPV testing, and VIA) is sparse. A study by Pimple et al. from a tertiary center in India in 2022 provided useful comparable measures of evaluation of three cervical screening tools. It is vital to choose the most feasible and effective screening strategies among WLHIV for implementation in public health programs. The screening tests provided to WLHIV showed high test-positive rates of 35.7%, 34.4%, and 9.6% for VIA, hrHPV, and cytology, respectively, in this study.⁷⁹

Pimple et al. demonstrated the use of diagnostic colposcopy with or without biopsy in investigating the true prevalence of CIN in HIV-infected women. Pap cytology and diagnostic colposcopy to detect high-grade lesions showed low sensitivity but high specificities with very high positive predictive value.⁷⁹

WHO recommends screening sexually active WLHIV for HPV or cervical abnormalities as soon as they are diagnosed with HIV, and then rescreening them within 3 years.¹⁸ Adding cervical screening to HIV services is cost-effective and scalable, yet these integrations are low. The feasible process of integrating cervical cancer screening tools in the STD/HIV/AIDS testing centers, technically known as integrated counseling and testing centers (ICTC), located in government facilities needs to be promoted. However, in most STD clinics, cervical cancer screening is not part of the routine testing offered to women attending the ICTC. Women are encouraged to visit the gynecology OPD after ART clinic appointment. There are several barriers to the process of cervical cancer screening in WLHIV. The stigma related to the increased risk of cancer diagnosis, lack of knowledge, and lack of financial and social support are amongst the many hurdles in the integration on both services.

Changing concepts in surgery

Surgical management of cervical cancer has always been ambivalent with concepts differing in terms of geographical region, histology, surgical expertise, and other factors. The most significant of these is perhaps a change back to the conventional open radical hysterectomy, along with various newer anatomical classifications and concepts of nerve sparing, as per Querleu Morrow. The LACC trial⁴⁴ showed a poor DFS and OS with a minimally invasive approach, and subsequently, this was incorporated in the International Guidelines wherein the standard and recommended approach for radical hysterectomy is an open abdominal approach.

However, there are ongoing studies in cases with tumor size less than 2 cm, which will give us a concrete answer in the future regarding surgical approach (open vs minimally invasive). Similarly, upcoming data (CONCERV, SHAPE, LESSER trial) suggest a possible role of simple hysterectomy providing similar oncologic outcomes as a radical hysterectomy in selected low-risk tumors [maximum diameter <2 cm, depth of invasion <10 mm, no lymphovascular space invasion (LVSI)].⁸⁰

Lymph node assessment can be achieved through complete lymphadenectomy or in select institutions with a sentinel lymph node (SLN) algorithm with an intent to decrease the postoperative morbidity of a systematic lymphadenectomy. Trials assessing the safety and oncologic outcomes of SLN algorithm (SENTICOL1 and 2) have established the safety of this technique.⁸¹

Since cervical cancer patients who report early enough to fulfil the criteria for being surgical candidates are relatively small in number considering the overall disease burden, it will still take some time to authenticate the surgical guidelines to achieve the optimum DFS and OS.

Newer radiation techniques to mitigate shortages and improve outcomes

RT protocol for cancer cervix

In early stages (IA, 1B1, and 1B2), both RT and surgery have equivalent oncologic outcomes. Decision regarding RT versus surgery is based on several factors, e.g., age, comorbidities, concomitant adnexal pathology, as well as patient preference. Stage 1B3 and beyond are treated by chemoradiation.

The standard treatment protocol is 45–50.4 Gray (Gy) in 25–28 fractions by external beam radiation therapy (EBRT) with weekly cisplatin in eligible patients. EBRT is followed by brachytherapy. Brachytherapy is delivered by intracavitary, interstitial, intravaginal, or hybrid methods. Brachytherapy doses in HDR era is 5–6 Gy in 5 fractions or 7 Gy in 3–4 fractions. At the All India Institute of Medical Sciences, New Delhi, 50.4 Gy in 28 fractions by EBRT followed by 7 Gy in 3 fractions to HR-CTV (high-risk clinical target volume) is the standard treatment regimen (with concurrent chemotherapy).

In a country like India, where there are budgetary constraints, optimal and judicious use of radiation techniques utilizing modern technology is very important to mitigate the lack of resources. Brachytherapy is an essential part of the treatment of carcinoma cervix and uterus. Due to the lack of brachytherapy facilities, there is often a waiting list in most RT centers. On average, waiting time for machine availability is 2–6 weeks. This is even

higher (up to 3 months) in high-volume centers where the number of cancer cases requiring radiation treatment is increasing disproportionately in comparison to the availability of radiation equipment. Undue prolongation of overall treatment time compromises the survival outcome of cervical cancer patients treated by RT.⁸²

Advances in RT technique to decrease toxicities

1. *Image guided intensity-modulated RT*: In a phase III randomized trial conducted in India, late toxicity after image-guided intensity-modulated radiotherapy (IG-IMRT) was compared with three-dimensional conformal radiation therapy (3D-CRT) in women with cervical cancer. IG-IMRT resulted in reduced toxicity with no difference in disease outcomes (grade > 2 late toxicity, 28.1% versus 48.9% (HR 0.50; 95% CI, 0.33 to 0.76; $P < .001$).⁸³

2. *Image-guided brachytherapy*: Emerging evidence from prospective studies shows a high rate of local control throughout all stages, superior to two-dimensional brachytherapy, with limited toxicity for each organ site. The EMBRACE – I study utilized magnetic resonance imaging (MRI) and the ongoing EMBRACE – II will also be utilizing functional MRI.⁸⁴

There is a need to innovate newer techniques/regimes of RT in order to mitigate the lack of resources. Some of the following strategies are suggested to overcome this demand versus supply gap.

- i) *Expansion of infrastructure*: As per the AERB data, India has about 0.30 RT machines per million population. This is grossly inadequate as WHO has recommended one machine per million population. The health care policy in the future must include galvanizing more RT resources in order to meet the required infrastructure.
- ii) *Adoption of newer technology in practice*: The modern RT facilities like advanced linear accelerator need to be strengthened. With modern advanced linear accelerators, the radiation treatment delivery is faster and thus, more patients can be accommodated during a given period. This will reduce the overall treatment course and the burden on existing infrastructure.
- iii) *Optimization of the RT resources*: Certain patients can be treated on brachytherapy alone rather than external beam RT. Optimal use of the existing brachytherapy machine will offload the EBRT machines which already are sparse in number.
- iv) *Short Hypofractionated RT*: (delivering higher dose per fraction) Hypofractionated course of RT is much shorter in duration and can potentially permit us to treat more patients. This kind of regime has already been in

use in certain cancer sites like lung, liver, etc., and may be researched in cervical cancer. This will facilitate the speedy completion of treatment and allow treating of more number of patients at a given time. A recent phase II clinical trial from India involving 41 patients explored this hypothesis. Toxicity was within acceptable limits (one patient with grade 2, and two patients with grade 3 rectal toxicity) and overall outcomes (2-year disease-free survival was 85%, and 2-year OS was 94.5%) were also not compromised.⁸⁵ Thus, the regularization of such a strategy can benefit a huge number of patients without increasing the burden on doctors and the existing infrastructure.

In summary, effective approaches need to be designed and experimented on existing and upcoming infrastructure. In addition, modern technology needs to be used with prudence so that it benefits a large patient population without increasing the cost.

New vistas in chemo- and immunotherapy in cervical cancer

Treatment of locally advanced disease

The benefit of adding a radio-sensitizing agent, cisplatin, to radiotherapy has been proven in five phase 3 trials. A meta-analysis of 19 randomized controlled trials between 1981 and 2000, including 4580 patients, established an improved OS (HR 0.71, $p < 0.0001$) and PFS (0.61, $p < 0.0001$), with chemoradiation.⁸⁶

The OUTBACK trial assessed the addition of adjuvant chemotherapy following chemoradiotherapy to LACC.⁸⁷ In this phase III multicentric trial, 926 patients with stage IB2-IVA disease were randomized to receive standard cisplatin-based chemoradiotherapy alone or chemoradiotherapy followed by adjuvant chemotherapy with four 3-weekly cycles of carboplatin and paclitaxel every 21 days. There were no differences in OS and PFS between the two arms, although the adjuvant chemotherapy arm experienced more grade 3 or worse adverse effects (81% versus 62%, $p < 0.0001$). However, 22% of the experimental arm declined adjuvant chemotherapy, likely due to residual adverse effects of the primary chemoradiation. Whether a more tolerable short course of chemotherapy prior to chemoradiation might improve patient outcomes will be answered by the ongoing INTERLACE trial (NCT01566240).

Treatment of metastatic/recurrent disease

1. Doublet chemotherapy: Metastatic or recurrent lesions, which cannot be excised or irradiated, are treated with palliative chemotherapy. Dual agent therapy with a platinum

agent and paclitaxel has a higher response rate (36% vs. 19%) and improved PFS (4.8 vs. 2.8 months; $P > .001$) compared to single-agent cisplatin, although the median OS remained 6–7 months.⁸⁸

2. Targeted therapy: Bevacizumab, a humanized VEGF-neutralizing monoclonal antibody, targets tumor angiogenesis. GOG 240, a phase III randomized clinical trial, examined the addition of bevacizumab to doublet chemotherapy regimens (cisplatin/paclitaxel or topotecan/paclitaxel) in patients with metastatic, persistent, or recurrent cervical cancer. The final analysis revealed that adding bevacizumab improved mean PFS (8.2 vs. 5.9 months, HR 0.68; 95% CI 0.56–0.84; $P=0.0002$) and mean OS (16.8 vs. 13.3 months, HR 0.77; 95% CI 0.62–0.95; $P=0.0068$) compared to chemotherapy alone.⁵⁵

The FDA approved bevacizumab for treating recurrent, metastatic, or persistent cervical cancer in August 2014, and its combination with paclitaxel and a platinum agent or topotecan forms the current first-line standard of care.

Immunotherapy

In the KEYNOTE-158 trial, a phase II study of pembrolizumab monotherapy in recurrent/metastatic cervical cancer regardless of tumor PD-L1 expression, objective response rates were 12.2% in the entire cohort and 14.6% in PD-L1-positive tumors. Accelerated approval of pembrolizumab was granted by the FDA for the treatment of PD-L1 positive advanced cervical cancer with disease progression after first-line chemotherapy.

KEYNOTE-826 trial, a multicenter randomized trial, analyzed the benefit of adding pembrolizumab to paclitaxel and cisplatin/carboplatin (with or without bevacizumab) as first-line therapy. ORR were 68% and 50% with a median duration of response of 18.0 and 10.4 months, respectively. Based on these results, the FDA granted regular approval to pembrolizumab for the first-line treatment of PD-L1-positive cervical cancer on October 13, 2021.⁵⁶

Conjugated monoclonal antibodies: Tisotumab vedotin is an antibody–drug conjugate directed against tissue factor (TF), a protein prevalent in solid tumors. This ADC binds to TF on target cells and is internalized to release monomethyl auristatin E (MMAE), a microtubule-disrupting agent, arresting the cell cycle arrest and prompting apoptosis. The mechanism of anti-tumor action is multifold, including bystander cytotoxicity and immunogenic cell death. In the GOG-3023/ENGOT-cx6/innovaTV 204 study in patients with recurrent/metastatic cervical cancer who received tisotumab vedotin every 3 weeks, ORR was 24% with 7 complete and 17 partial responses, with a median response duration of 8.3 months

(95% CI: 4.2, NR).⁸⁹ FDA granted accelerated approval to tisotumab vedotin-tftv to treat recurrent or metastatic cervical cancer with disease progression after chemotherapy on September 20, 2021. A combination of tisotumab vedotin with carboplatin, bevacizumab, and pembrolizumab is currently under investigation (NCT03786081).

Recurrent and metastatic cervical cancer was once treated with palliative intent. However, recent introductions of targeted and immunotherapy have produced increasing response rates and duration of treatment responses. Treatment goals should include symptom relief, minimal toxicity, and participation in clinical trials.

OPERATIONAL DEFINITIONS OF THE TERMS USED IN THE REPORT

Age-standardized rate – Summary rate that would have been observed, given the schedule of age-specific rates, in a population with the age composition of some reference population, often called the standard population.

Crude Rate – Number of new cases (or deaths) occurring in a specified population per year, usually expressed as the number of cases per 100,000 population at risk.

Cumulative risk – Combination of risks posed by aggregate exposure to multiple agents or stressors in which aggregate exposure is exposure by all routes and pathways and from all sources of each given agent or stressor.

Screen Positive – Women with a positive result on any screening test (HPV test, cytology, VIA).

High-Risk HPV – HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

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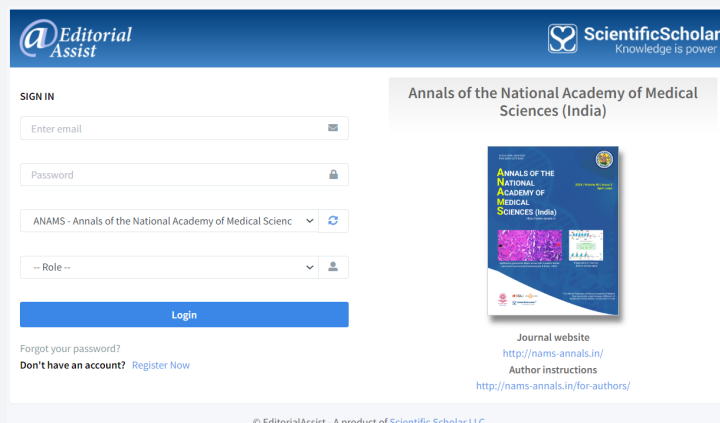
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