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Highlights of the Issue

- Effect of Modifiable Lifestyle Risk Factors on the Incidence and Prevention of Cancer in Modern Society: A Review Article
- NAMS Task Force Reports on
  - Venous thromboembolism
  - Organ donation and transplantation
  - Alcohol, substance use disorders, and behavioral addictions in India

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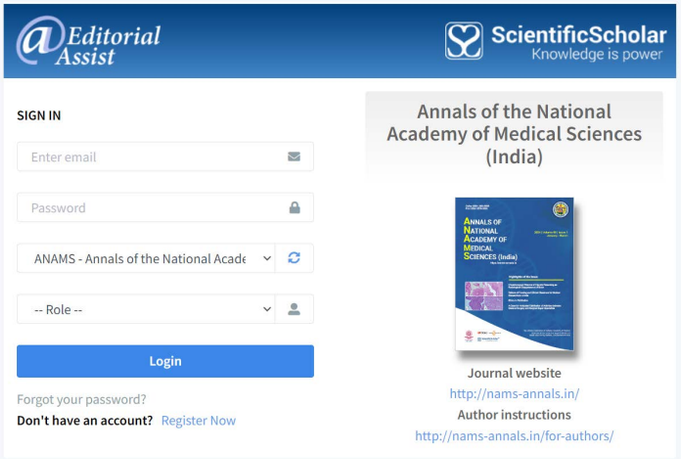

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Annals of the National Academy of Medical Sciences (India)

Editorial

Journey of Annals of the National Academy of Medical Sciences (India) (ANAMS)

Anil K. Jain[1,2,3]

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A New Beginning

Annals of the National Academy of Medical Sciences (India) (ANAMS), the official journal of NAMS (National Academy of Medical Sciences, India) under the aegis of the Ministry of Health and Family Welfare, Govt. of India, has been serving the biomedical research fraternity of India since its inception 59 years ago. The journal was launched in 1965 with Dr. Viswanathan as the first Chief Editor with a modest beginning of two issues per year with print pages 156. Later, the frequency was increased to four issues per year. Back in 2016, NAMS decided to go for digital transition and ANAMS got its online presence. Since then, the journal has been growing progressively and has published high-quality articles in a multi-disciplinary format. The year 2024 marks the 60th volume of the journal and it will come with a new face and appeal starting the Jan–Feb 2024 issue.

The new website of the journal is https://nams-annals.in, whereas the new submission site of the journal is https://editorialassist.com/#/login/ANAMS. Potential authors are encouraged to submit their engaging original research investigations, narrative reviews, systematic reviews, meta-analysis, unique case reports, engaging case series, appealing letters, and short communications. Medical students and researchers are also encouraged to submit conference posters and research abstracts as well. The aim of the journal has always been to promote medical research happening in the nooks and corners of our country and we will stay committed to the same. By bringing in a new, user-friendly submission portal for our authors and reviewers, where authors will experience a seamless submission process and reviewers will instantly receive a reviewer certificate upon successful completion of an article's review, we are enthusiastically looking forward to bring to our reader base vigorously engaging journal issues and even strongly contributing to the dissemination of competitive research content.

The successful journey of ANAMS wouldn't have been possible without the selfless contribution of our reviewers and editors, who have been tirelessly contributing toward the journal for the past 6 decades. However, we are deeply thankful to our authors above all, who have enriched the journal with such diverse clinical content. In 2023, we published a variety of content in the form of original articles, reviews, case reports, short communications, etc.

The journal has always advocated for publishing current trends in clinical practices. In this regard, we published an original investigation addressing trends on awareness and knowledge about glaucoma.[1] The journal published interesting molecular investigations on topics like Schiff Base monomers and their anticancer activity[2] and Cystatin A down-regulation associated with attenuation of cancer hallmark signatures in squamous cell carcinoma cell lines.[3] The journal published regional investigations from around the country on topics like home-based prophylaxis versus institutionalized prophylaxis,[4] as well as articles addressing populations from overseas countries on topics such as clinical, demographic, and biochemical profiles of Trinidadian patients.[5]

Apart from such engaging original investigations on various topics and nature, the journal regularly published educative and informative reviews on diverse topics as well such as applicability and bioactivity of Sesamum indicum L-Oil,[6] sleep restriction during pregnancy on fetal brain programming and neurocognitive development of offspring,[7] the role and significance of hepatokines and adipokines in metabolic syndrome,[8] the underutilization of forensic microbiology,[9] etc.

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We also brought to our readers some insights that should positively reflect the current state and future prospects of ethical medical research and funding in our country,[10] and aspects of appointment of medical faculty and subsequent promotions.[11]

Continuing our practice to bring in new features for our readers and ways of expression for our authors, the journal will be bringing an altogether new section from 2024 onwards. This will be called "Task Force Reports" and will be addressing the emerging trends and best practices guidelines in several areas of clinical practice and healthcare services and are prepared by the best subject experts. In this issue, we are publishing task force report on "Venous thromboembolism", "Organ donation and transplantation," and "Alcohol, substance use disorders, and behavioral addictions in India." It is the need of the hour that students, professors, and clinical practitioners are well-versed with emerging trends and innovative approaches in their field of interest. National Academy of Medical Sciences (India), being the torchbearer of establishing the best practices information in India, thus takes the responsibility to enlighten and educate the biomedical fraternity by starting this new section in our journal.

In totality, ANAMS has been publishing clinical content on diverse topics, which are not only bringing to the reader the latest developments in various practicing fields and day-to-day bench to bedside challenges but at the same time the published content is educative and vastly informative for students and budding researchers who aim to establish a career in their domain. We aim to continue our endeavors with even more enthusiasm as we come with a new look and feel and sincerely believe that the content published in our beloved journal will continue contributing significantly to the overall development of scientific and medicinal practices.

Prof. Anil Kumar Jain MS, FIOA, FRCS (Eng.), FAMS

Editor-in-Chief

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REFERENCES

1. Jain AK, Singh N, Singh NK, Singh PK, Rajpoot S. Glaucoma the silent thief of vision! A study to assess current trends on awareness and knowledge about glaucoma. Ann Natl Acad Med Sci 2023;59:202–8.
2. Ibrahim AM, Shabeer TK. Molecular docking insights of newly synthesized Schiff base monomers and evaluating the anticancer activity of their polymers. Ann Natl Acad Med Sci 2023;59:219–24.
3. Boora GS, Chauhan A, Bal A, Verma RK, Pal A. Cystatin A down-regulation in head and neck squamous cell carcinoma cell lines decreases cancer hallmark signatures. Ann Natl Acad Med Sci 2023;59:152–7.
4. Dutta A, Boruah D, Boruah A, Das A. Adherence and cost effectivity of home-based prophylaxis over institutionalized prophylaxis in patients with hemophilia. Ann Natl Acad Med Sci 2023;59:21–6.
5. Nayak B S, Monplaisir TK, Bhaktha G, Ali R, Mohan SK, Priya V. Evaluation of clinical, demographic, and biochemical profiles of Trinidadian patients undergoing coronary angiography. Ann Natl Acad Med Sci 2023;59:90–6.
6. Naseem S, Khan AA, Uddin Q, Jabeen A, Ahmad K, Asad M. A comprehensive review on applicability and bioactivity of Rogan-I-kunjad (Sesamum indicum L-oil): Unani prospective. Ann Natl Acad Med Sci 2023;59:175–85.
7. Gulia KK. Effect of sleep restriction during pregnancy on fetal brain programming and neurocognitive development of offspring: A review. Ann Natl Acad Med Sci 2023;59:129–38.
8. Mukhuty A, Mondal SA, Mukhopadhyay S. Hepatokines and adipokines in metabolic syndrome. Ann Natl Acad Med Sci 2023;59:4–12.
9. Saha R, Kaushik S, Kumar A, Choudhary S. The underutilization of forensic microbiology: A narrative review. Ann Natl Acad Med Sci 2023;59:139–46.
10. Das S, Chandra A, Nongkynrih B. Options of funding and ethical clearance for medical researchers in India. Ann Natl Acad Med Sci 2023;59:68–76.
11. Teixeira da Silva JA. Reforming the culture of medical faculty promotion and appointment. Ann Natl Acad Med Sci 2023;59:62–4.

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Annals of the National Academy of Medical Sciences (India)

Review Article

Effect of modifiable lifestyle risk factors on the incidence and prevention of cancer in modern society: A review

Nandini Bhattacharjee[1], Tania Sarkar[1]

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ABSTRACT

Human society has been influenced by modernization, which has altered our pattern of living. It is believed that several environmental and lifestyle factors, including urbanization, employment linked to socioeconomic transition, increased affluence, and altered social and family structures, are partially to be blamed for cancer. Lifestyle changes associated with urbanization such as smoking, alcohol consumption, excessive body weight, and being physically inactive are well-known risk factors for cancer. Anxiety due to stressful events can increase the production of free radicals, which in turn causes oxidative damage and the emergence of cancer. Economic liberty provides more leisure time and inclination toward ready-to-eat food, more screen time, and sedentary habits to some extent. All these factors have a positive impact on cancer initiation and development. Hence, a healthy lifestyle, together with nutritious food and regular exercise should be prioritized for cancer prevention. A healthy lifestyle has been associated with a decreased risk of different types of cancer, involving the lungs, liver, colon, breast, endometrium, and kidney. To outline this review, searches were performed with PubMed and Scopus databases up to August 2022. The lifestyle risk factors for cancer have been described in this review, along with recommendations for improving lifestyle choices for human welfare.

Keywords: Cancer, Lifestyle, Physical Activity, Stress

INTRODUCTION

Over the past few decades, a trend has been observed wherein there is an increase in the incidence of noncommunicable diseases than infectious diseases and the prevalence of noncommunicable diseases such as cardiovascular diseases and cancer has been on the rise mostly in developing countries[1–3] In modern world, our way of living has changed as a result of globalization, increased wealth, altered social and family structures, a lack of physical activity, and anxiety brought on by stressful events.[4] The incidence of cancer has increased greatly due to these lifestyle factors, but it can be prevented by major lifestyle changes.[5] It has been reported that these lifestyle risk factors are related to various types of cancer involving breast, lung, prostate, colon, and stomach.[6]

When the world's population reaches 8.3 billion in 2030, there are likely to be 21.4 million cases and 13.2 million deaths due to cancer.[7] The increased incidence of cancer has been documented in various studies.[8] Lung cancer is a prominent cause of mortality in males,[9] and breast cancer is prevalent among females.[8] Other common causes of death in males are colorectal cancer (CRC) and prostate cancer.[8] Hepatocellular carcinoma (HCC), affecting all age groups in both males and females is in the sixth position after breast, lung, prostate, colon, and stomach cancer.[8,10] Smoking, alcohol consumption, unhealthy eating habits, and excess body weight are lifestyle risk factors and are responsible for 35% of cancer deaths worldwide.[11] In 2021, Friedenreich *et al.* documented that obesity and sedentary behavior are associated with cancer.[12] While these aspects of lifestyle are not inherently unique to contemporary culture, they have become more prevalent in many societies due to the effect of globalization. Healthy lifestyles may reduce the incidence of cancer morbidity and mortality to a great extent and for cancer prevention, priority should be given to these factors.[13] Among many modifiable risk factors, the most notable are alcohol consumption, smoking, obesity (high BMI, measured in kg/m^2), and insufficient physical activity (sufficient physical activity ≥ 30 min/five times/week or minimum 1,600–2,400 calories/day burnt for adult women and 2,000–3,000 calories/day burnt for adult men)[14,15] and 30–40% of cancers are preventable by the transformation of modifiable lifestyle risk factors.[16] A healthy

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lifestyle combined with proper diet and exercise should be prioritized for cancer prevention as it negatively impacts lymphoma, myeloma, lung, colon, breast, endometrial, and kidney cancer incidence.

However, it is important to understand that cancer is a complicated illness, and a number of circumstances might lead to its occurrence. Lifestyle factors are just one piece of the puzzle, and it is often difficult to isolate their effects from other factors such as genetics, environmental exposures, and medical history.

REVIEW METHODOLOGY

For this review, searches were conducted in databases such as PubMed, Scopus, and Web of Sciences for all full-text articles up to August 2022 using combinations of various key terms such as "cancer", "lifestyle", "modifiable risk factors", "lung cancer", "liver cancer" or "hepatocellular carcinoma", "melatonin", "sleep deprivation", and "tobacco smoking/adverse effects". The lifestyle factors mainly included tobacco smoking, alcohol consumption, sedentary behavior, overweight/obesity, and diet, while some studies also included green tea consumption, fruit and vegetable consumption, the damaging effect of blue light, sleep deprivation, exposure to indoor air pollution, practicing yoga and physical activity. Besides the reference lists of original studies, reviews and meta-analyses were also scrutinized to identify relevant studies.

Included studies fulfilled the following criteria: (i) prospective cohort studies; (ii) review article; (ii) incident total and site-specific cancer or cancer mortality; (iii) focusing on a single lifestyle factor; (iv) a combination of only two lifestyle factors; and (v) using the combination of lifestyle factors as an exposure variable. Studies were excluded if they were: (i) other publication types (such as protocols, case-control studies) or not peer-reviewed publications (such as editorials and commentaries); (ii) formulation or validation of prediction models; (iii) duplicate reporting from the same cohort studies or duplicate publications; and (iv) studies without necessary or sufficient data.[17]

THE INCIDENCE OF CANCER AND LIFESTYLE FACTORS

Obesity and cancer

Obesity (BMI ≥ 30 kg/m^2)[18] is linked to an enhanced risk of cancer of the endometrium, esophagus, colon, kidney, liver, pancreatic tissues, and breast in postmenopausal women, and also poses a threat of malignant melanoma.[19,20]

It has been reported that intentional weight loss among obese women can reduce the risk of endometrial cancer by 54%.[21] Excessive body fat at a young age is linked to the development of eight kinds of cancer in later stages of life.[22] Postmenopausal breast cancer risk is greater in adult women who have a body mass index > 23.4 kg/m^2 at 20 years of age.[23] Chronic inflammations, inhibition of apoptosis, and oxidative stress have been observed in carcinogenesis, which is stimulated by obesity.[24]

Sedentary behavior and cancer

Inflammatory factors like tumor-necrosis factor-α, interleukin-6, and leptin might lead to the progression of cancer in the lung and these factors might aggravate due to sedentary behaviors.[25] It has been reported by a meta-analysis that sedentary behavior and television watching are linked to lung cancer, colon cancer, and endometrial cancer.[26]

More than a quarter of the global population is not properly active.[27] An inverse relationship has been found between physical activity and many types of cancer.[28] Obesity-induced carcinogenesis has been linked to oxidative stress, apoptotic suppression, and chronic inflammation.[24] It has been observed that moderate-to-vigorous physical activity (sufficient physical activity ≥ 30 min/five times/week or minimum 1,600–2,400 calories/day burnt for adult women and 2,000–3,000 calories/day burnt for adult men) during leisure time and reduction of television watching has been related to an increase of cancer-free (colorectal, lung, prostate, and postmenopausal breast cancer) life span.[29] It is also reported that television watching is associated with the risk of lung cancer and less television watching especially in smokers might avert lung cancer.[30] Hence, moderate physical activity of 150 minutes or vigorous physical activity of not less than 75 minutes per week has been recommended (sufficient physical activity ≥ 30 min/five times/week or minimum 1,600–2,400 calories/day burnt for adult women and 2,000–3,000 calories/day burnt for adult men).[14,15,28,31] Global action plan of WHO on physical activity 2018–2030 may be implemented by some countries[32] to combat the situation.

Smoking and cancer

The smoke of tobacco contains carcinogens that induce somatic mutation as a result of the generation of DNA adducts.[33] Passive smoke is also considered carcinogenic by the International Agency for Research on Cancer (IARC).[34] It has been reported that cigarette smoking caused 48% of all cancer deaths in the United States.[35] The incidence of cancer and cancer death associated with tobacco smoking has been extensively documented in a population-based Australian cohort study.[36] Tobacco smoke causes the development of cancer in different organs throughout the body like the mouth, pharynx, trachea, voice box, lungs, liver, and esophagus [Figure 1]. Carcinogens produced during tobacco smoking are associated with pancreatic, colon, uterine and bladder

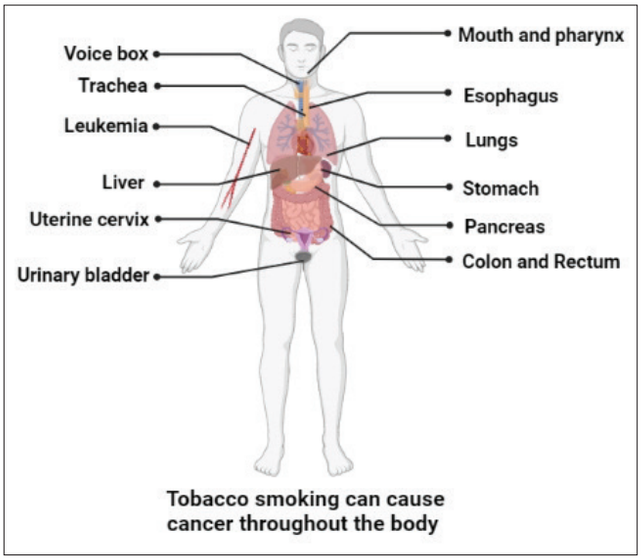

Figure 1: Tobacco smoking can cause cancer throughout the body. Tobacco smoke contains various types of carcinogens which promote the progression of cancer in multiple sites throughout the body, for example, in mouth, pharynx, voice box, trachea, lungs, liver, esophagus, stomach, pancreas, bladder and colon. (Created in Biorender.com)

cancer.[37] Tobacco use is a major factor in the development of cancer; however, obesity and lack of physical activity pose a greater threat to carcinogenesis, which we have described in the previous segment.[38]

Alcohol consumption and cancer

Researchers showed that alcohol consumption is associated with pancreatic cancer.[39] Consumption of alcohol escalates cancers such as of the liver, stomach, colorectal area, mouth, larynx, and pharynx.[19] As alcohol plays a major role in the development of cancer, population awareness regarding the risk of cancer due to alcohol consumption should be increased and alcohol restriction policy measures need to be implemented.[40]

Indoor and outdoor ambient air pollution and cancer

Indoor air pollution due to the use of coal has been associated with lung cancer.[41] Globally, it has been observed that outdoor ambient air pollution is linked to an increased incidence of lung cancer and many lung cancer–related deaths.[42] The carcinogenic potential of outdoor air pollution might be associated with black carbon exposure.[43] Polluted air contains particles as well as gases.[44] Particulate matter ($PM_{2.5}$) has been recognized as a risk factor for lung cancer by IARC.[45]

Air pollution might cause a risk of brain cancer through oxidative stress mediated by neuroinflammatory signaling pathways.[46] The IARC Working Group has reckoned outdoor air pollution and particulate matter as carcinogenic to humans.[47] Long-term exposure to low-level ambient air pollution is also related to cancer incidence in the lung.[48]

Unhealthy diet and cancer

It has been well documented that some dietary and lifestyle factors such as the consumption of red meat has been associated with the incidence of colon cancer.[49] In the Chinese population, processed meat could cause nearly 1% of CRC deaths.[50] According to a study done in the United States of America, a daily increase in the consumption of processed and unprocessed red meat was associated with a 13% rise in cancer mortality.[51] It has been presumed that taking large amounts (determined by the United Nations to be 200 g or more on a daily basis) of red meat is linked to enhanced cancer risk.[52]

Heterocyclic aromatic hydrocarbons, which are hazardous chemicals, might originate during the processing, curing, and preservation of food and red meat.[53] Healthy eating patterns have been recommended by the American Cancer Society for all ages.[54] A healthy lifestyle should be followed to prevent cancer incidence.[55]

Effective role of fish oil in cancer prevention

Omega-3 fatty acids present in fish oil show anti-inflammatory, anti-proliferative, and anti-metastatic potential.[56]

Protective potential of green tea against cancer

Polyphenol present in green tea is epigallocatechin-3-gallate (EGCG), which is a phytochemical and it plays a significant role in various cancers mediated by epigenetic mechanisms.[57] Consumption of green tea along with green leafy vegetables might hinder ovarian cancer.[58] Green tea has been studied for its cancer-fighting properties, and the results are encouraging. EGCG has been linked to cancer prevention.[59] The recent information regarding the anti-cancer effects of green tea extracts in the prevention and treatment of prostate cancer has been reviewed.[60] EGCG has been reported to sensitize cancerous cells to apoptosis caused by antineoplastic drugs, and it can guard noncancerous cells against the dangerous outcome of ultraviolet radiation exposure.[61]

Endocrine-disrupting chemicals and cancer

It has been observed that endocrine-disrupting chemicals (EDCs) has carcinogenic potential.[62] It has been reported that EDCs such as Bisphenol A,[63] Phthalate,[64] Parabens,[65] various personal care products,[66] and other EDCs[67] can act as the triggering factor of cancer.

Mental and physical stress and generation of free radicals

Stress is the altered physiological condition in the body which occurs due to intrinsic or extrinsic stressors, and these affect the homeostasis of the body.[68] The production of free radicals, such as reactive oxygen species and reactive nitrogen species (ROS/RNS) is elevated during stress. Continuous stressful conditions can induce anxiety and depression, thereby producing these free radicals and oxidative damage.[69] Mental and physical stress result in the formation of free radicals and oxidative stress in the human body, which in turn destroy the antioxidant properties of our body, leading to cancer growth. The abundance of free radicals reduces the effectiveness of antioxidant enzymes which eventually increases cancer risk. It has been observed in cancerous and precancerous tissues that elevated ROS level is linked to changes in nucleobases.[70]

The development of HCC has been induced by oxidative stress.[71] The levels of glutathione peroxidase, catalase, and superoxide dismutase, which are potential antioxidant enzymes reduced during stress, are associated with cancer.[72] Increased generation of HO• (hydroxyl radical or hydroxide ion) and other free radicals makes the cells susceptible to DNA mutation and activates oncogenes, which cause initiation and progression of cancer.[73] Several lifestyle factors such as consumption of alcohol, smoking, improper diet, and lack of sufficient exercise play important roles in the development of oxidative stress.[74]

Changes in the sleep cycle and sleep deprivation

People need adequate sleep to function properly. Melatonin, which is required for sleep, is secreted at maximum levels till midnight from the pineal gland and gradually decreases in the morning.[75] People today are becoming more and more addicted to social media and use their electronic devices excessively. It is now established that blue light emitted from electronic gadgets is one of the most important reasons for sleep deprivation.[76] Sleep deprivation influences the generation of free radicals, which induces the development of many types of cancer in the body.[77] The sleep cycle is altered as a result of people sleeping less at night and more in the morning. Melatonin also acts as an antioxidant.[78] Hence, decreased melatonin levels due to sleep deprivation can be considered a cause of cancer.[79]

The damaging effect of blue light on the eye

The human eye may be badly affected by blue light. It is noted that a portion of blue light overlaps with UV which causes skin cancer.[80] Several physiological problems arise due to smartphone light fluxes (SPLF), such as reduction of melatonin secretion, changes in circadian rhythm, and faulty eyesight as (SPLF) spectrum overlaps in UVA (320–410 nm) portion.[81] It is reported that blue light at night produced by electronic devices such as smartphones causes a detrimental effect on the body's physiological activity.[82]

It is reported that intensive blue light (400 nm to 440 nm) induces damage to the retina and is associated with the process of photo-bleaching[83,] causing absorption of photons by rhodopsin and increasing the generation of reactive oxygen species which causes oxidative damage due to the accumulation of lipofuscin pigment (the yellow-brown pigment which consists of lipids and proteins and has fluorescent properties) in the retinal pigment epithelium.[75,84] Artificial blue light at night exposure results in a disruption of circadian rhythm, which might enhance breast and prostate cancer risk.[85] Exposure to outdoor blue light that has become enhanced in recent times might pose a threat to producing CRC.[86]

Harmful effects of blue light on circadian rhythm and sleep deprivation can cause oxidative stress

The suprachiasmatic nucleus in the hypothalamus regulates the circadian rhythm and sleep. Blue light emitted by electronic gadgets affects the phase delay of the circadian rhythm as well as causes suppression of melatonin release. Human physiology and mood are largely influenced by exposure to light.[75] Excessive involvement with digital devices at bedtime results in an alteration in the quality and amount of sleep.[87] Sleep deprivation causes oxidative stress.[88] Some chronic and degenerative diseases such as cancer, arthritis, cardiovascular and neurodegenerative diseases, etc., are associated with oxidative stress.[89] Reduced melatonin level is associated with major oxidative damage to DNA.[90]

The beneficial effect of melatonin

It has been reported that melatonin has anti-carcinogenic potentiality as well as antioxidant and immunomodulatory characteristics.[91] Melatonin protects the body from oxidative stress caused by free radicals produced at the time of metabolism.[92] Free radical scavenging activity of melatonin has been documented by many researchers.[93] There are several noteworthy functions of melatonin such as ameliorating sleep quality, decreasing free radicals formation, and restitution of antioxidant enzymes.[94]

Different reviews described anti-carcinogenic potential,[95] therapeutic efficacy,[96] and protective effect of melatonin against oxidative harm to DNA.[92] Melatonin has the potential to reduce breast cancer.[97] Melatonin can alleviate oxidative stress directly through a detoxification mechanism or indirectly by preventing prooxidative enzymes and inducing the body's antioxidant enzymes.[98] Initiation, progression, and metastasis of cancer can be prevented by melatonin.[99] By

combating oxidative damage, melatonin renders protection to proteins, lipids, and DNA.[100]

Detrimental effect of melatonin suppression at night

It has been documented that disruption of the normal secretion of melatonin at night due to exposure to light is associated with cancer risk.[101] Working at night for a long time with exposure to blue light disrupts the circadian rhythm and decreases melatonin secretion and results in sleep deprivation.[102] It is reported that shifting working hours increases the risk of breast cancer in females by 40%.[103] Disruption of circadian rhythm by exposure to light at night during shifting duty and night work may act as triggers of Group 2A carcinogen according to IARC.[104]

DISCUSSION

This review focuses on spreading public awareness about modifiable lifestyle risk factors with the help of scientific literature and evidence of experimental works and aims to overview the impact of changes in these factors to prevent the incidence of cancer. Obesity, smoking, alcohol use, physical inactivity, poor eating habits, disturbed sleep, and oxidative stress are few risk factors that can raise the risk of developing cancer. People who eat diets rich in trans fat, saturated fat, and high calories are generally obese. People who do not exercise regularly may be at increased risk of cancer. Inadequate sleep is reckoned as a vital risk factor for stress, which results in the initiation of cancer. Consumption of green tea along with green leafy vegetables might hinder ovarian cancer. Catecholamines' level increases on account of the inadequacy of sleep; as a result, blood pressure and blood glucose levels increase, causing oxidative stress and injury in the wall of blood vessels. Restoration of good health requires proper sleep at night. Unhealthy lifestyle choices might influence the risk of cancer [Figure 2].

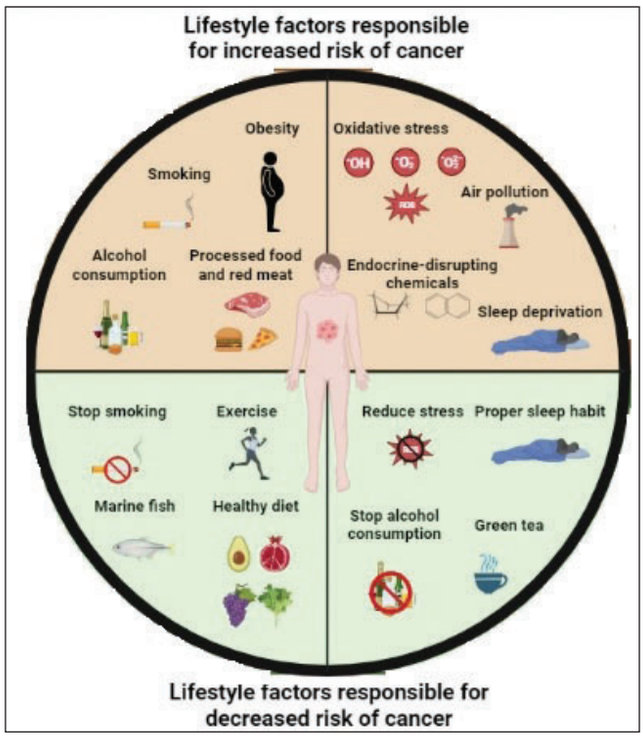

Figure 2: Cancer incidence and prevention are significantly impacted by changes in lifestyle risk factors. Among many risk factors, the most important are alcohol, processed food and red meat consumption, smoking, obesity, changes in circadian rhythm, excessive stress, air pollution and endocrine-disrupting chemicals and are responsible for different human malignancies. However, 30–40% of these cancers can be prevented by avoiding these lifestyle risk factors and maintaining a healthy lifestyle. (Created in Biorender.com)

RECOMMENDATIONS TO REDUCE THE RISK OF CANCER

Stop smoking

Consuming tobacco in any form (smoking or chewing) is linked to cancer of the mouth, larynx, throat, lung, pancreas, kidney, bladder, and cervix.[105–108] Passive smoking also triggers the risk of lung cancer.[34]

Avoid alcohol consumption

According to a report by World Cancer Research Fund International (WCRF), alcohol intake raises the risk of many forms of cancers, including those of esophagus, breast, colorectum, stomach, liver, mouth, pharynx, and larynx.[19] Drinking alcohol is a significant lifestyle risk factor for cancer.[40]

Avoid red meat consumption

Avoid eating red meat to prevent colon and liver cancer development. Replacement of red meat with foods such as legumes, soy, nuts, poultry, and fish would decrease the threat of cancer and reduce levels of cholesterol.[109]

Take a healthy diet

Fruits and vegetables have a possible anti-carcinogenic effect. Eating an abundance of fruits and vegetables with dietary fiber reduces the risk of CRC and liver cancer in males.[110] Bacteria reside in the colon and produce products through the fermentation of dietary fibers, having anti-proliferative potentiality.[111] Less quantity of vegetable and fruit consumption is ascribable to the burden of diseases worldwide, and available recommendations for the intake of fruit and vegetables should be followed.[112] Follow the WCRF/American Institute for Cancer

Research (AICR) recommendation to take a diet that consists of plenty of whole grains, beans, vegetables, and fruits to prevent cancer as well as various chronic diseases.[113] The Mediterranean diet, which contains fruits, vegetables, legumes, nuts, and grains, is considered to be an effective anti-cancer diet.[114]

Consume plenty of fish

Oily fish such as herring, salmon, and mackerel contain omega-3 fatty acid, and the effective role played by omega-3 fatty acids found in various types of cancer has been extensively reviewed.[115]

Drink green tea

It contains catechins, a large group of flavonoids which are polyphenolic compounds with antioxidant characteristics. The principal type of catechin is EGCG, which has strong chemopreventive, anti-obesity, anti-cancer, and immune modulatory effects.[116] Intake of green tea might be propitious for oral, esophageal, lung, ovarian, and endometrial cancer and cardiovascular disease.[117] EGCG could control the activity and restrain the cell cycle by inducing kinase-mediating apoptosis pathways and impeding cell division, which result in cell death.[118]

Maintain a healthy body weight and avoid obesity

Eat lighter and stick to a low-fat diet because it has been discovered that proper weight management is linked to a decrease in the risk of cancer. High-calorie foods such as fat from animal sources and processed meat intake should be restricted. Sugar intake should also be restricted.[113] When the consumption of non fried food increases, it reduces the risk of cancer of the pancreas.

Engage in physical activity

It will reduce the risk of cancer of the lung, prostate, kidney, colon, and breast. One must have physical activity of at least 30 minutes in the daily schedule. Higher levels of physical activity reduce the risk of several types of cancer.[28] Leisure-time physical activity reduces the risk of bladder cancer by 13%. Physically active women had a reduction of breast cancer by 12–21% compared to those of the least active. Both in premenopausal and postmenopausal women, physical activity has been linked to similar reductions in the risk of breast cancer.[119] In postmenopausal women, weight reduction due to physical exercise led to plummeting levels of C-reactive protein and estradiol, resulting in decreased risk of endometrial and breast cancer. According to the report of World Cancer Research Fund International, physical activity could reduce the risk of endometrial, breast, and colon cancer. World Health Organization provided guidelines that described the importance of physical activity.[120] It has been established that cancers that are related to obesity could be decreased by physical activity.[121] Exercise has also been beneficial for cancer survivors and the strength of cancer patients.[122] Recommended amounts of activity, i.e., 7.5–15 metabolic equivalent task [MET] hours/week in leisure time is correlated with reduced risk of seven different types of cancers including colon, breast, endometrium, kidney, myeloma, liver, non-Hodgkin lymphoma.[123]

Avoid exposure to outdoor and indoor air pollution

Lung cancer due to short-term and long-term exposure to indoor and outdoor air pollutants has been described earlier.[124,125] So try to avoid exposure to outdoor and indoor air pollution.

Avoid endocrine-disrupting chemicals

EDCs should be avoided as these can induce cancer.[126-128]

Consider maintaining a healthy lifestyle

Perform adequate physical exercise and practice yoga for a relaxed and healthy life. Smoking, drinking a large amount of alcohol, physical inactivity, and an unhealthy diet which are regarded by researchers as lifestyle and environmental factors are associated with pancreatic cancer.[129] Approximately 12% of pancreatic cancer is estimated to be caused by obesity and 29% are linked to smoking.[130] Yoga shows promising effects in decreasing the level of pro-inflammatory cytokines and upgrading the quality of human lives.[131] Yoga is good for people because it reduces the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, a transcription factor that increases the production of inflammatory genes in response to chronic stress.[132] A proper, healthy lifestyle regimen must be followed in order to reduce the cancer burden.[121]

Keep living a stress-free life

The effect of stress on the progression of cancer has been extensively reviewed. Mravec *et al*. described the importance of treatment with β-blocker and psychotherapy on the survival of cancer patients.[133] Animal studies showed the mechanisms through which cancer progression has been expedited by stressful conditions. Hence, stress management interventions could decrease repetitiveness and death in cancer.[134]

Sleep well and sufficiently

Since circadian rhythm, quantity, and quality of sleep are affected by blue light,[87] it is recommended to restrict oneself from using electronic gadgets before bedtime.[135]

Individuals should exercise daily and have a healthy lifestyle to prevent cancer

The American Cancer Society recommends physical activity of 150–300 minutes with moderate intensity or physical activity of 75–150 minutes with vigorous intensity per week in adults to reduce cancer risk.[54] Recommendations regarding lifestyle for cancer prevention have been advised.[55]

CONCLUSION

The comprehensive analysis of this review gives prominence to the effect that modifiable lifestyle risk factors exert on the incidence and prevention of cancer. As this review discusses, dietary habits, physical activity levels, tobacco use, and alcohol use are important factors in cancer prevention and mitigation. Incorporating a healthy diet while minimizing processed foods and red meat intake, coupled with regular exercise, substantially reduces the risk of cancer development. Furthermore, strategies aimed at smoking cessation and limiting alcohol consumption are imperative in mitigating cancer risk, prioritizing the critical role of behavioral modifications in preventive efforts. Equally significant is the maintenance of a healthy body weight, as obesity not only escalates cancer risk but also worsens prognosis.

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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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.

REFERENCES

1. Boutayeb A, Boutayeb S. The burden of non communicable diseases in developing countries. Int J Equity Health 2005;4:2.
2. Terzic A, Waldman S. Chronic Diseases: The emerging pandemic. Clin Transl Sci 2011;4:225–6.
3. Islam S, Purnat T, Phuong N, Mwingira U, Schacht K, Fröschl G. Non-communicable diseases (NCDs) in developing countries: A symposium report. Glob Health 2014;10:81.
4. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P, *et al*. Priority actions for the non-communicable disease crisis. Lancet 2011;377:1438–47.
5. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, *et al*. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008;25:2097–3116. [Erratum in: Pharm Res 2008;25:2200. Kunnumakara, Ajaikumar B [corrected to Kunnumakkara, Ajaikumar B].
6. Gonzalez CA, Riboli E. Diet and cancer prevention: Contributions from the European prospective investigation into cancer and nutrition (EPIC) study. Eur J Cancer 2010;46:2555–62.
7. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.
8. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, *et al*. Cancer statistics for the year 2020: An overview. Int J Cancer 2021;149:778–89.
9. Thakur SK, Singh DP, Choudhary J. Lung cancer identification: A review on detection and classification. Cancer Metastasis Rev 2020;39:989–98.
10. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
11. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Comparative risk assessment collaborating group (Cancers). Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risk factors. Lancet 2005;366:1784–93.
12. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical Activity, obesity and sedentary behavior in cancer etiology: Epidemiologic evidence and biologic mechanisms. Mol Oncol 2021;15:790–800.
13. Zhang YB, Pan XF, Chen J, Cao A, Zhang YG, Xia L, *et al*. Combined lifestyle factors, incident cancer, and cancer mortality: A systematic review and meta-analysis of prospective cohort studies. Br J Cancer 2020;122:1085–93.
14. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011;105:S77–S81.
15. Poirier AE, Ruan Y, Volesky KD, King WD, O'Sullivan DE, Gogna P, *et al*. The current and future burden of cancer attributable to modifiable risk factors in Canada: Summary of results. Prev Med 2019;122:140–7.
16. Kulhánová I, Znaor A, Shield KD, Arnold M, Vignat J, Charafeddine M, *et al*. Proportion of cancers attributable to major lifestyle and environmental risk factors in the Eastern Mediterranean region. Int J Cancer 2020;146:646–56.
17. Cook DA, Reed DA. Appraising the quality of medical education research methods: The medical education research study quality instrument and the newcastle-ottawa scale-education. Acad Med 2015;90:1067–76.
18. Cortellini A, Bersanelli M, Santini D, Buti S, Tiseo M, Cannita K, *et al*. Another side of the association between body mass index (BMI) and clinical outcomes of cancer patients receiving

programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) checkpoint inhibitors: A multicentre analysis of immune-related adverse events. Eur J Cancer 2020;128:17–26.
19. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective (the third expert report). https://www.wcrf.org/diet-and-cancer/ World Cancer Research Fund International. Continuous Update Project Expert Report 2018. http://dietandcancerreport.org. (World Cancer Research Fund International. Diet, nutrition, physical activity and cancer: A global perspective (the third expert report): 2018) (Accessed December 12, 2021).
20. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism 2019;92:121–35.
21. Luo J, Chlebowski RT, Hendryx M, Rohan T, Wactawski-Wende J, Thomson CA, *et al*. Intentional weight loss and endometrial cancer risk. J Clin Oncol 2017;35:1189–93.
22. Hidayat K, Du X, Shi BM. Body fatness at a young age and risks of eight types of cancer: Systematic review and meta-analysis of observational studies. Obes Rev 2018;19:1385–94.
23. Renehan AG, Pegington M, Harvie MN, Sperrin M, Astley SM, Brentnall AR, *et al*. Young adulthood body mass index, adult weight gain and breast cancer risk: The PROCAS study (United Kingdom). Br J Cancer 2020;122:1552–61.
24. Pérez-Hernández AI, Catalán V, Gómez-Ambrosi J, Rodríguez A, Frühbeck G. Mechanisms linking excess adiposity and carcinogenesis promotion. Front Endocrinol (Lausanne). 2014;5:65.
25. Zhan P, Wang J, Lv XJ, Wang Q, Qiu LX, Lin XQ, *et al*. Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: A systematic review with meta-analysis. J Thorac Oncol 2009;4:1094–103.
26. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: A meta-analysis. J Natl Cancer Inst 2014;106:dju098.
27. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: A pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob Health 2018;6:e1077–e1086. Erratum in: Lancet Glob Health 2019;7:e36.
28. McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, *et al*. Physical activity in cancer prevention and survival: A systematic review. Med Sci Sports Exerc 2019;51:1252–61.
29. Cuthbertson CC, Nichols HB, Tan X, Kucharska-Newton A, Heiss G, *et al*. Associations of leisure-time physical activity and television viewing with life expectancy cancer-free at age 50: The ARIC study. Cancer Epidemiol Biomarkers Prev 2020;29:2617–25.
30. Gao Y, Mi J, Liu Z, Song Q. Leisure Sedentary Behavior And Risk Of Lung Cancer: A two-sample mendelian randomization study and mediation analysis. Front Genet 2021;12:763626.
31. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: A prospective cohort study. Am J Clin Nutr 2015;101:558–69.
32. World Health Organization. Global action plan on physical activity 2018–2030: More active people for a healthier world. Geneva: World Health Organization; 2018. (Accessed January 18, 2022).
33. Centers for Disease Control and Prevention. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Publications and reports of the surgeon general. (Accessed March 10, 2022).
34. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83:1–1438.
35. U.S. Department of Health and Human Services. The health consequences of smoking: A report of the surgeon general. Atlanta, GA: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, Office on Smoking and Health; 2014. (Accessed March 18, 2022).
36. Weber MF, Sarich PEA, Vaneckova P, Wade S, Egger S, Ngo P, *et al*. Cancer incidence and cancer death in relation to tobacco smoking in a population-based Australian cohort study. Int J Cancer 2021;149:1076–88.
37. Lugo A, Peveri G, Bosetti C, Bagnardi V, Crippa A, Orsini N, *et al*. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. Eur J Cancer 2018;104:117–26.
38. WHO. Obesity estimates. Geneva: World Health Organization, 2020. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (WHO, Geneva, 2020). (Accessed April 5, 2022).
39. Vanella G, Archibugi L, Stigliano S, Capurso G. Alcohol and gastrointestinal cancers. Curr Opin Gastroenterol 2019;35:107–13.
40. Rehm J, Shield KD. Alcohol use and cancer in the European union. Eur Addict Res 2021;27:1–8.
41. Reid BC, Ghazarian AA, DeMarini DM, Sapkota A, Jack D, Lan Q, *et al*. Research opportunities for cancer associated with indoor air pollution from solid-fuel combustion. Environ Health Perspect 2012;120:1495–98.
42. Turner MC, Andersen ZJ, Baccarelli A, Diver WR, Gapstur SM, Pope CA 3rd, *et al*. Outdoor air pollution and cancer: An overview of the current evidence and public health recommendations. CA Cancer J Clin 2020;70:460–79.
43. Lequy E, Siemiatycki J, de Hoogh K, Vienneau D, Dupuy JF, Garès V, *et al*. Contribution of long-term exposure to outdoor black carbon to the carcinogenicity of air pollution: Evidence regarding risk of cancer in the Gazel cohort. Environ Health Perspect 2021;129:37005.
44. Coker E, Liverani S, Su JG, Molitor J. Multi-pollutant modeling through examination of susceptible subpopulations using profile regression. Curr Environ Health Rep 2018;5:59–69.
45. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC Monographs Volume 109: Outdoor Air Pollution. IARC Monogr Eval Carcinog Risks Hum, 109. International Agency for Research on Cancer, Lyon 9–444. https://monographs.iarc.fr/iarc-monographs-on-the-evaluationof-carcinogenic-risks-to-humans-7/. (2016). (Accessed April 8, 2022).
46. Wu AH, Wu J, Tseng C, Yang J, Shariff-Marco S, Fruin S, *et al*. Association between outdoor air pollution and risk of

malignant and benign brain tumors: The multiethnic cohort study. JNCI Cancer Spectrum 2020;4:pkz107.
47. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, *et al*. International agency for research on cancer monograph working group IARC. The carcinogenicity of outdoor air pollution. Lancet Oncol 2013;14:1262–3.
48. Hvidtfeldt UA, Severi G, Andersen ZJ, Atkinson R, Bauwelinck M, Bellander T, *et al*. Long-term low-level ambient air pollution exposure and risk of lung cancer – A pooled analysis of 7 European cohorts. Environ International 2021;146:106249.
49. Turner ND, Lloyd SK. Association between red meat consumption and colon cancer: A systematic review of experimental results. Exp Biol Med (Maywood) 2017;242: 813–39.
50. Chen W, Xia C, Zheng R, Zhou M, Lin C, Zeng H, *et al*. Disparities by province, age, and sex in site-specific cancer burden attributable to 23 potentially modifiable risk factors in China: A comparative risk assessment. Lancet Glob Health 2019;7:e257–e269.
51. Zheng Y, Li Y, Satija A, Pan A, Sotos-Prieto M, Rimm E, *et al*. Association of changes in red meat consumption with total and cause specific mortality among US women and men: Two prospective cohort studies. BMJ 2019;365:l2110.
52. Bamia C. Dietary patterns in association to cancer incidence and survival: Concept, current evidence, and suggestions for future research. Eur J Clin Nutr 2018;72:818–25.
53. Alomirah HF, Al-Zenki S, Al Hooti S, *et al*. Concentrations and dietary exposure to polycyclic aromatic hydrocarbons (PAHs) from grilled and smoked foods. Food Control 2011;22:2028–35
54. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, *et al*. American cancer society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 2020;70:245–71.
55. World cancer research fund, WCRF Cancer Prevention Recommendations, Word Cancer Research Fund, 2016. Available from: Cancer Prevention Recommendations | WCRF International (Accessed April 12, 2022).
56. D'Angelo S, Motti ML, Meccariello R. ω-3 and ω-6 polyunsaturated fatty acids, obesity and cancer. Nutrients 2020;12:2751.
57. Li F, Qasim S, Li D, Dou QP. Updated review on green tea polyphenol epigallocatechin-3-gallate as a cancer epigenetic regulator. Semin Cancer Biol 2022;83:335–52.
58. Khodavandi A, Alizadeh F, Razis AFA. Association between dietary intake and risk of ovarian cancer: A systematic review and meta-analysis. Eur J Nutr 2021;60:1707–36.
59. Chikara S, Nagaprashantha LD, Singhal J, Horne D, Awasthi S, Singhal SS. Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment. Cancer Lett 2018;413:122–34.
60. Miyata Y, Shida Y, Hakariya T, Sakai H. Anti-cancer effects of green tea polyphenols against prostate cancer. Molecules 2019;24:193.
61. Ng CY, Yen H, Hsiao HY, Su SC. Phytochemicals in skin cancer prevention and treatment: An updated review. Int J Mol Sci 2018;19:941.
62. Soto AM, Sonnenschein C. Environmental causes of cancer: endocrine disruptors as carcinogens. Nat Rev Endocrinol 2010;6:363–70.
63. Pellerin E, Caneparo C, Chabaud S, Bolduc S, Pelletier M. Endocrine-disrupting effects of bisphenols on urological cancers. Environ Res 2021;195:110485.
64. Alsen M, Sinclair C, Cooke P, Ziadkhanpour K, Genden E, van Gerwen M. Endocrine disrupting chemicals and thyroid cancer: An overview. Toxics 2021;9:14.
65. Amin MM, Tabatabaeian M, Chavoshani A, Amjadi E, Hashemi M, Ebrahimpour K, *et al*. Paraben content in adjacent normal-malignant breast tissues from women with breast cancer. Biomed Environ Sci 2019;32:893–904.
66. Lee HR, Hwang KA, Nam KH, Kim HC, Choi KC. Progression of breast cancer cells was enhanced by endocrine-disrupting chemicals, triclosan and octylphenol, via an estrogen receptor-dependent signaling pathway in cellular and mouse xenograft models. Chem Res Toxicol 2014;27:834–42.
67. Houston TJ, Ghosh R. Untangling the association between environmental endocrine disruptive chemicals and the etiology of male genitourinary cancers. Biochem Pharmacol 2020;172:113743.
68. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009;5:374–81.
69. Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro) inflammatory and oxidative and nitrosative stress pathways. Neuroendocrinol Lett 2011;32:7–24.
70. Olinski R, Jaruga P, Zastawny TH. Oxidative DNA base modifications as factors in carcinogenesis. Acta Biochim Pol 1998;45:561–72.
71. Ichiba M, Maeta Y, Mukoyama T, Saeki T, Yasui S, Kanbe T, *et al*. Expression of 8-hydroxy-2′-deoxyguanosine in chronic liver disease and hepatocellular carcinoma. Liver Int 2003;23: 338–45.
72. Zaidi SMKR, Banu N. Antioxidant potential of vitamins A, E and C in modulating oxidative stress in rat brain. Clin Chimica Acta 2004;340:229–33.
73. Halliwell B, Gutteridge JMC. Free radicals in biology and medicine 5th Edition. United Kingdom: Oxford University Press; 2015.
74. Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L, Panzarini E, *et al*. Lifestyle, oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. Front Physiol 2020;11:694.
75. Wahl S, Engelhardt M, Schaupp P, Lappe C, Ivanov IV. The inner clock-blue light sets the human rhythm. J Biophotonics 2019;12:e201900102.
76. Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. Proc Natl Acad Sci USA 2015;112:1232–7.
77. Poole EM, Schernhammer ES, Tworoger SS. Rotating night shift work and risk of ovarian cancer. Cancer Epidemiol Biomarkers Prev 2011;20:934–8.
78. Reiter RJ, Tan DX, Galano A. Melatonin: Exceeding expectations. Physiology 2014:29:325–33.
79. Hill SM, Blask DE, Xiang S, Yuan L, Mao L, Dauchy RT, *et al*. Melatonin and associated signaling pathways that control normal breast epithelium and breast cancer. J Mammary Gland Biol Neoplasia 2011;16:235–45.

80. de Gruijl FR, van Kranen HJ, Mullenders LHF. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B 2001;63:19–27.
81. Gomes CC, Preto S. Blue light: A blessing or a curse? Procedia Manufucturing 2015;3:4472–79.
82. Oh JH, Yoo H, Park HK, Do YR. Analysis of circadian properties and healthy levels of blue light from smartphones at night. Sci Rep 2015;5:11325.
83. Tosini G, Ferguson I, Tsubota K. Effects of blue light on the circadian system and eye physiology. Mol Vis 2016;22:61–72.
84. Călin EF, Patoni Popescu SI, Coman Cernat CC, Patoni C, Popescu MN, Mușat O. Lipofuscin: A key compound in ophthalmic practice. Rom J Ophthalmol 2021;65:109–13.
85. Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, *et al*. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain study). Environ Health Perspec 2018;126:047011.
86. Garcia-Saenz A, de Miguel AS, Espinosa A, Costas L, Aragonés N, Tonne C, *et al*. Association between outdoor light-at-night exposure and colorectal cancer in Spain. Epidemiology 2020;31:718–27.
87. Chinoy ED, Duffy JF, Czeisler CA. Unrestricted evening use of light-emitting tablet computers delays self-selected bedtime and disrupts circadian timing and alertness. Physiol Rep 2018;6:e13692.
88. Gopalakrishnan A, Ji LL, Cirelli C. Sleep deprivation and cellular responses to oxidative stress. Sleep 2004;27:27–35.
89. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci 2008;4:89–96.
90. Davanipour Z, Poulsen HE, Weimann A, Sobel E. Endogenous melatonin and oxidatively damaged guanine in DNA. BMC Endocr Disord 2009:9:22.
91. Di Bella G, Mascia F, Gualano L, Di Bella L. Melatonin anticancer effects: Review. Int J Mol Sci 2013;14:2410–30.
92. Galano A, Tan DX, Reiter RJ. Melatonin: A versatile protector against oxidative DNA damage. Molecules 2018;23:530.
93. Galano A, Tan DX, Reiter RJ. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. J Pineal Res 2013;54:245–57.
94. Barón V, Muriel P. Role of glutathione, lipid peroxidation and antioxidants on acute bile-duct obstruction in the rat. Biochim Biophys Acta 1999;1472:173–80.
95. Talib WH, Alsayed AR, Abuawad A, Daoud S, Mahmod AI. Melatonin in cancer treatment: Current knowledge and future opportunities. Molecules 2021;26:2506.
96. Gurunathan S, Qasim M, Kang MH, Kim JH. Role and therapeutic potential of melatonin in various type of cancers. Onco Targets Ther 2021;14:2019–52.
97. Mao L, Yuan L, Xiang S, Zeringue SB, Dauchy RT, Blask DE, *et al*. Molecular deficiency(ies) in MT1 melatonin signaling pathway underlies the melatonin-unresponsive phenotype in MDA-MB-231 human breast cancer cells. J Pineal Res 2014;56:246–53.
98. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: Under promises but over delivers. J Pineal Res 2016;61:253–78.
99. Reiter RJ, Rosales-Corral SA, Tan DX, Acuna-Castroviejo D, Qin L, Yang SF, *et al*. Melatonin, a full service anti-cancer agent: Inhibition of initiation, progression and metastasis. Int J Mol Sci 2017;18:843.
100. García JJ, López-Pingarrón L, Almeida-Souza P, *et al*. Protective effects of melatonin in reducing oxidative stress and in preserving the fluidity of biological membranes: A review. J Pineal Res 2014;56:225–37.
101. Woo SM, Min KJ, Kwon TK. Melatonin-mediated Bim up-regulation and cyclooxygenase-2 (COX-2) down-regulation enhances tunicamycin-induced apoptosis in MDA-MB-231 cells. J Pineal Res 2015;58:310–20.
102. Costa G, Haus E, Stevens R. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. Scand J Work Environ Health 2010;36:163–79.
103. Viswanathan AN, Schernhammer ES. Circulating melatonin and the risk of breast and endometrial cancer in women. Cancer Lett 2009;281:1–7.
104. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, firefighting, and shiftwork. IARC Monogr Eval Carcinog Risks Hum 2010;98:9-764.
105. Thun M, Henley S, Calle E. Tobacco use and cancer: An epidemiologic perspective for geneticists. Oncogene 2002;21:7307–25.
106. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risks Hum 2012;100:1–538.
107. Ray S, Saha D, Alam N, Mitra Mustafi S, Mandal S, Sarkar A, *et al*. Exposure to chewing tobacco promotes primary oral squamous cell carcinoma and regional lymph node metastasis by alterations of SDF1α/CXCR4 axis. Int J Exp Pathol 2021;102:80–92.
108. Weber MF, Sarich PEA, Vaneckova P, Wade S, Egger S, Ngo P, *et al*. Cancer incidence and cancer death in relation to tobacco smoking in a population-based Australian cohort study. Int J Cancer 2021;149:1076–88.
109. Huang Y, Cao D, Chen Z, Chen B, Li J, Guo J, Dong Q, Liu L, Wei Q. Red and processed meat consumption and cancer outcomes: Umbrella review. Food Chem 2021;356:129697.
110. Guo XF, Shao XF, Li JM, Li S, Li KL, Li D. Fruit and vegetable intake and liver cancer risk: A meta-analysis of prospective cohort studies. Food Funct 2019;10:4478–85.
111. Encarnação JC, Abrantes AM, Pires AS, Botelho MF. Revisit dietary fiber on colorectal cancer: Butyrate and its role on prevention and treatment. Cancer Metastasis Rev 2015;34: 465–78.
112. Yip CSC, Chan W, Fielding R. The associations of fruit and vegetable intakes with burden of diseases: A systematic review of meta-analyses. J Acad Nutr Diet 2019;119:464–81.
113. Clinton SK, Giovannucci EL, Hursting SD. The world cancer research fund/american institute for cancer research third expert report on diet, nutrition, physical activity, and cancer: Impact and future directions. J Nutr 2020;150: 663–71.
114. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. Br J Pharmacol 2019;177:1241–57.
115. Nabavi SF, Bilotto S, Russo GL, Orhan IE, Habtemariam S, Daglia M, *et al*. Omega-3 polyunsaturated fatty acids and cancer: Lessons learned from clinical trials. Cancer Metastasis Rev 2015;34:359–80.

116. Yiannakopoulou EC. Interaction of green tea catechins with breast cancer endocrine treatment: A systematic review. Pharmacology 2014;94:245–8.
117. Abe SK, Inoue M. Green tea and cancer and cardiometabolic diseases: A review of the current epidemiological evidence. Eur J Clin Nutr 2021;75:865–76.
118. Ganguly R, Kumar R, Pandey A, Pandey AK. Therapeutic role of green tea in obesity and cancer. In: Kumar S, Gupta S, editors. Obesity and cancer. Singapore: Springer; 2021. p. 143–64.
119. Hardefeldt PJ, Penninkilampi R, Edirimanne S, Eslick GD. Physical activity and weight loss reduce the risk of breast cancer: A meta-analysis of 139 prospective and retrospective studies. Clin Breast Cancer 2018;18:e601–12.
120. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, *et al*. World health organization 2020 guidelines on physical activity and sedentary behavior. Br J Sports Med 2020;54:1451–62.
121. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: An update and emerging new evidence. Lancet Oncol 2017;18:e457–e471.
122. Ngo-Huang A, Fricke BC, Schadler KL, Parker NH. Preliminary evidence on the effects of exercise on tumor biology: A potential guide for prescribing exercise. Curr Physical Med Rehabilitation Rep 2021;9:136–41.
123. Matthews CE, Moore SC, Arem H, Cook MB, Trabert B, Håkansson N, *et al*. Amount and intensity of leisure-time physical activity and lower cancer risk. J Clin Oncol 2020;38:686–97.
124. Yuan Y, Luo Z, Liu J, Wang Y, Lin Y. Health and economic benefits of building ventilation interventions for reducing indoor PM2.5 exposure from both indoor and outdoor origins in urban Beijing, China. Sci Total Environ 2018;626:546–54.
125. Xing DF, Xu CD, Liao XY, Xing TY, Cheng SP, Hu MG, *et al*. Spatial association between outdoor air pollution and lung cancer incidence in China. BMC Public Health 2019;19:1377.
126. Shafei A, Ramzy MM, Hegazy AI, Husseny AK, El-Hadary UG, Taha MM, *et al*. The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer. Gene 2018;647:235–43.
127. Ahern TP, Broe A, Lash TL, Cronin-Fenton DP, Ulrichsen SP, Christiansen PM, *et al*. Phthalate exposure and breast cancer incidence: A danish nationwide cohort study. J Clin Oncol 2019;37:1800–09.
128. Eve L, Fervers B, Le Romancer M, Etienne-Selloum N. Exposure to endocrine disrupting chemicals and risk of breast cancer. Int J Mol Sci 2020;21:9139.
129. Weisbeck A, Jansen RJ. Nutrients and the pancreas: An epigenetic perspective. Nutrients 2017;9:283.
130. Pai M, Spalding D. Pancreatic cancer. Medicine 2015;43: 329–33.
131. Venkatesh HN, Ravish H, Wilma Delphine Silvia CR, Srinivas H. Molecular signature of the immune response to yoga therapy in stress-related chronic disease conditions: An insight. International journal of yoga, 2020;13:9–17.
132. Buric I, Farias M, Jong J, Mee C, Brazil IA. What is the molecular signature of mind-body interventions? A systematic review of gene expression changes induced by meditation and related practices. Front Immunol 2017;8:670.
133. Mravec B, Tibensky M, Horvathova L. Stress and cancer. Part II: Therapeutic implications for oncology. J Neuroimmunol 2020;346:577312.
134. Eckerling A, Ricon-Becker I, Sorski L, Sandbank E, Ben-Eliyahu S. Stress and cancer: Mechanisms, significance and future directions. Nat Rev Cancer 2021;21:767–85.
135. Touitou Y, Touitou D, Reinberg A. Disruption of adolescents' circadian clock: The vicious circle of media use, exposure to light at night, sleep loss and risk behaviors. J Physiol Paris 2016;110:467–79.

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Original Article

Comparison of seven commercial RT-PCR kits with the NIV kit for the diagnosis of Covid-19

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ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread across the globe in an unprecedented manner and was declared a pandemic on March 11, 2020 by the World Health Organization (WHO). This study was carried out with the aim to compare the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and agreement of the eight different RT-PCR kits for the diagnosis of COVID-19.

Material and Methods: This observational cross-sectional study was carried out in the Department of Microbiology of a tertiary care hospital in Central Delhi from July to October 2021. A total of 45 nasopharyngeal and/or oropharyngeal swabs in Viral Transport Medium (VTM) from suspected COVID-19 patients were received in the laboratory for RT-PCR. These samples were tested by eight different Indian Council of Medical Research (ICMR)-approved RT-PCR kits with different gene targets. The comparison was made with the National Institute of Virology (NIV), the Pune COVID-19 RT-PCR kit. Statistical analysis: sensitivity, specificity, PPV, and NPV were calculated for each kit and compared using the McNemar test. Agreement of different kits was evaluated using Kappa analysis.

Results: The results of the 45 samples of suspected COVID-19 cases were recorded as per the cycle threshold (Ct) provided in the kit insert. Of these, 15 samples detected both E and RdRp genes and 30 were negative for both the genes of SARS CoV-2 by NIV, the Pune COVID-19 RT-PCR kit. All kits showed 100% sensitivity and had 100% NPV when compared with the NIV kit. However, specificity, PPV, and agreement were variable as compared to the NIV kit.

Conclusion: The reporting should be carried out as per the manufacturer's instructions. However, positive results with Ct values ≥ 36 showed variable results with different RT PCR kits and hence should be interpreted with caution.

Keywords: Agreement, COVID-19, RT-PCR Kits, SARS CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread across the globe in an unprecedented manner and was declared a pandemic on March 11, 2020 by the World Health Organization (WHO).[1] The disease presents with nonspecific clinical symptoms, and a definitive diagnosis can only be established in the laboratory. Laboratory testing is essential not only for diagnosis and management but also for containment and mitigation strategies to prevent further transmission.[2]

Over the course of time, numerous diagnostic technologies like nucleic acid amplification tests (NAAT) by real-time reverse transcription polymerase chain reaction (RT-PCR) and rapid antigen detection tests were approved for the laboratory diagnosis of COVID-19. However, RT-PCR remains the gold standard diagnostic test.[1,2]

Multiple RT-PCR protocols for the detection of COVID-19 were published by WHO based on different target structural and nonstructural genes like envelope (*E*), nucleocapsid (*N*), RNA-dependent RNA polymerase (*RdRp*), open reading frame segments1 a/b (*Orf1a/b*), and the gene-encoding

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spike (S) protein. The E gene codes for nonstructural protein were specific to Sarbecovirus (β-CoV) while other structural and nonstructural genes target was specific to SARS-CoV-2.[3] As performance characteristics of molecular tests may vary with reagents, PCR, and instrumentation, an understanding of the analytical performance of different RT-PCR kits is essential for the proper interpretation of the results.[4] Also, COVID-19 diagnostic tests have less accuracy in asymptomatic or Low-risk population and those person who may be have less viral load.[5,6] Multiple Indian Council of Medical Research (ICMR)-approved RT-PCR kits are currently available and are being used for the diagnosis of COVID-19.[2] This study was carried out with the aim to compare the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and agreement of the seven different RT-PCR kits for the diagnosis of COVID-19 with the ICMR-NIV kit.

MATERIAL AND METHODS

This study was performed at the molecular virology laboratory in the Department of Microbiology after obtaining ethical approval from the Institutional Ethics Committee (No: 439(88/2020) IEC). **This was an observational, cross-sectional study in which 45 nasopharyngeal and oropharyngeal swab samples were incorporated fourbetween July 2021 and October 2021.**

Collection of Samples: Forty-five nasopharyngeal and oropharyngeal swabs were collected in a Viral Transport Medium (VTM) tube from suspected COVID-19 patients. A repeat sample, after a gap of 2–3 days, was requested from the patients who had Ct values of ≥36. **During the first wave of the COVID-19 pandemic, samples received for testing in the microbiology laboratory were for clinical symptomatic suspected COVID-19 diseases from the outpatients, inpatients, and patients of various intensive care units of the hospital.**

Nucleic acid extraction: All the specimens were initially processed in Class II, Type A2 biosafety cabinet. Specimens were added into the lysis buffer, and RNA extraction was performed as per the manufacturer's instructions using **Easy Mag BioMerieux system (United States origin-based company).**

RT-PCR kits: Eight different ICMR-approved kits (ICMR-NIV, LabGun™ COVID-19 Assay, TIB MOLBIOL Roche, ARGENE SARS-CoV-2 R-GENE, BGI SARS-CoV-2, Perkin Elmer SARS-CoV-2, MyLab Patho Detect,™ and COROSURE SARS-CoV-2) were used for testing these samples.[2] All the kits were based on TaqMan Fluorogenic probe-based chemistry except COROSURE SARS-CoV-2, which used SYBER Green dye and quantitative kit [Table 1].

ICMR-NIV RT-PCR kit has been indigenously developed by the National Institute of Virology (NIV), Pune, using internationally approved primer and probes.[7] In this kit, coronaviruses under the subgenus Serbecovirus that includes 2019-nCoV, SARS-CoV, and bat SARS-like coronaviruses were used to generate a nonredundant alignment for screening of samples. Confirmatory assays using *RdRp* and *ORF* were designed based on their matching to the Wuhan virus as per inspection of the sequence alignment. **Suspected**

Table 1: Overview of RT-PCR kits used in this study for the detection of SARSCoV-2.

Kit name	Kit chemistry	Reaction time (min)	Cycle threshold (Ct value)	Gene target	
				Screening gene (Serbecovirus)	Confirmatory gene
ICMR-NIV (Pune)	TaqMan Fluorogenic probe	134 min	≤35	*E*	*RdRp ORF-1a/b*
ARGENE SARS-CoV-2-R-Gene (France)	TaqMan Fluorogenic probe	110 min	≤34	-	*N RdRp*
BGI SARS-CoV-2 (China)	TaqMan Fluorogenic probe	102 min	≤38	-	*ORF-1a/b (+)* Sigmoid (S)-shaped curve
COROSURE SARS-CoV-2 (Faridabad)	SYBER Green dye	72 min	≤37	-	***S1 gene*** (+) ***S 2gen***e (+) (124 bp)
LabGun™ COVID-19 Assay (Korea)	TaqMan Fluorogenic probe *(Limit of detection-100 copies/mL)	135 min	≤40	*E*	*RdRp*
MylabPathoDetect™ (China)	TaqMan Fluorogenic probe	105 min	≤38	*E*	*RdRp*
Perkin Elmer SARS-CoV-2 (United States)	TaqMan Fluorogenic probe	150 min	≤40	-	*N ORF-1a/b gene*
TIB MOLBIOL Roche (Germany)	TaqMan Fluorogenic probe	104 min	≤38	*E*	*RdRp*

human samples were first tested by (screening) *E* gene assay and then by confirmatory assay for the detection of *RdRp* and *ORF* gene in duplicates and other structural and nonstructural genes according to various SARS-Cov-2 detection kits. All samples were tested along with internal quality control, positive control, and negative control from various SARS-CoV-2 kits.

Amplification and detection: The RT-PCR tests were performed as per the manufacturer's instructions described in each kit insert. Every run included a positive and negative control provided in the kit. For internal quality control, one known positive and negative sample was included in each run. All the RT-PCR assays were performed using **BIORAD CFX-96 Real time system (Singapore origin-based company)** according to the manufacturer's instructions. The run was considered valid for any kit when the Ct value of controls was in the defined range, and the results for individual samples were recorded as per the Ct provided in the kit insert.

Statistical analysis: ICMR NIV, the Pune COVID-19 RT-PCR kit was used as the standard kit for the calculation of sensitivity, specificity, PPV, negative predictive value (NPV), and agreement of the different RT-PCR kits. The sensitivity and specificity of test kits were compared using the McNemar test. An inbuilt command in STATA 12E Statistical Software was used to obtain the kappa measure of integrated agreement between two COVID-19 RT-PCR Kits. None of the manufacturers were involved in the assessment and interpretation of the results.

RESULTS

Out of the 45 samples of suspected COVID-19 cases, both *E* and *RdRp* genes of SARS-CoV-2 were detected in 15 samples by ICMR-NIVCOVID-19 RT-PCR kit, and the remaining 30 samples were negative for SARS-CoV-2 genes. All the 15 samples that tested positive by the ICMR-NIV kit were also positive by other kits. However, out of the 30 samples that tested negative by the ICMR-NIV kit, 15 samples tested negative by all the kits, whereas 15 samples gave variable results with different kits [Table 2].

The sensitivity = number of true positives/number of true positives + number of false negatives; specificity: number of true negatives/number of true negatives + number of false positives; PPV = 100 × true positives/true positives + false positives; and NPV = 100×true negatives/false negatives+true negatives formulae were used to calculate the sensitivity, specificity, PPV, and NPV. All the kits showed 100% sensitivity and had 100% NPV when compared with the ICMR-NIV kit. However, specificity and PPV varied in comparison to the ICMR-NIV kit [Table 3].

The results of ARGENE-R, COROSURE, and MyLab PathoDetect™ kits showed 100% concordance with the ICMR-NIV kit. Sensitivity, specificity, PPPV, NPV, and agreement of these kits were 100% (Kappa analysis 1.0000) [Tables 3 and 4].

With the BGI SARS-COV-2 RT-PCR kit (Cutoff Ct value ≤ 38), 26 samples tested positive and 19 tested negative. However, 11 samples that tested positive with Ct values ranging from

Table 2: Variable cycle threshold (Ct) of the patient samples from different COVID-19 RT PCR kits.

S.No.	Cycle threshold (Ct)							
	ICMR-NIV (Ct ≤ 35)	BGI SARS-CoV-2 (Ct ≤ 38)	COROSURE SARS-CoV-2 (Ct ≤ 37)	ARGENE SARS-CoV-2-R-Gene (Ct ≤ 34)	LabGun™ COVID-19 Assay (Ct ≤ 40)	Mylab Patho Detect™ (Ct ≤ 38)	Perkin Elmer SARS-CoV-2 (Ct ≤ 40)	TIB MOLBIOL Roche (Ct ≤ 38)
1	26	22	30	30	19	25	28	27
2	29	32	31	28	29	29	26	32
3	30	32	28	28	30	30	30	33
4	28	30	32	30	29	28	29	32
5	26	26	30	32	23	26	28	31
6	24	28	30	30	26	26	31	28
7	28	30	33	28	29	28	30	33
8	28	32	34	30	28	28	29	31
9	34	30	30	34	32	31	31	34
10	31	28	34	32	30	31	32	32
11	29	30	30	30	28	29	28	32
12	21	24	25	24	20	22	21	24
13	24	20	24	28	23	23	21	28
14	30	30	30	30	29	31	28	33
15	20	22	24	24	20	21	20	22

Table 3: Sensitivity, Specificity, PPV, and NPV of various kits as compared to the NIV kit.

RT-PCR Kits	Sensitivity % (95% Confidence interval)	Specificity % (95% Confidence interval)	PPV % (95% Confidence interval)	NPV % (95% Confidence interval)
ARGENE SARS-COV-2-R-Gene	100	100	100	100
BGI SARS-COV-2	100	73	57	100
COROSURE SARS-COV-2	100	100	100	100
LabGun™ COVID-19 Assay	100	66	50	100
MylabPathoDetect™	100	100	100	100
Perkin Elmer SARS-COV-2	100	81	68	100
TIB MOLBIOL Roche	100	88	78	100

Note: Sensitivity = number of true positives/number of true positives + number of false negatives
Specificity: number of true negative/number of true negative + number of false positive
Positive Predictive Value (PPV) = 100 × True positive/True positive + False positive)
Negative Predictive Value (NPV) = 100 × True negative/False negative + True Negative

Table 4: Kappa analysis for the measurement of agreement with the National Institute of Virology Kit.

COVID-19 RT-PCR kits	Agreement with NIV RT-PCR kits (%)	Expected Agreement (%)	Kappa value	Standard error	z	Prob > z
ARGENE SARS-COV-2-R-Gene	100.0	55.56	1.0000	0.1491	6.71	0.0000
BGI SARS-COV-2	75.56	47.41	0.5352	0.1320	4.05	0.0000
COROSURE SARS-COV-2	100.0	55.56	1.0000	0.1491	6.71	0.0000
LabGun™ COVID-19 Assay	66.67	44.44	0.4000	0.1193	3.35	0.0004
Mylab Patho Detect™	100.0	55.56	1.0000	0.1491	6.71	0.0000
Perkin Elmer SARS-COV-2	84.44	50.37	0.6866	0.1416	4.85	0.0000
TIB MOLBIOL Roche	91.11	52.59	0.8125	0.1464	5.55	0.0000

Note: The kappa-statistic measure of agreement is scaled to be 0 when the amount of agreement is what would be expected to be observed by chance and 1 when there is perfect agreement.

36 to 38 by the BGI kit were negative by the ICMR-NIV kit. Results of the BGI kit showed 73% specificity, 57% PPV, and moderate agreement (Kappa value 0.5352) when compared with the ICMR-NIV kit [Tables 3 and 4].

With the LabGun ™ COVID-19 RT PCR kit (Cutoff Ct value ≤ 40), 30 samples tested positive and 15 tested negative. However, 15 samples that tested positive with Ct values ranging from 36 to 40 by LabGun™ were negative by the ICMR-NIV kit. Results of the LabGun ™ kit showed 66% specificity, 50% PPV, and only fair agreement (Kappa value 0.4000) when compared with the ICMR-NIV kit [Tables 3 and 4].

With the Perkin Elmer SARS-CoV-2 RT PCR kit (Cutoff Ct value ≤ 40), 24 samples tested positive and 21 tested negative. However, 9 samples that tested positive with Ct values of 36–40 by Perkin Elmer were negative by the ICMR-NIV kit. Results of the Perkin Elmer kit showed 81% Specificity, 68% PPV, and substantial agreement (Kappa value 0.6866) when compared with the ICMR-NIV kit [Tables 3 and 4].

With the TIB MOLBIOL Roche SARS-CoV-2 RT PCR kit (Cutoff Ct value ≤ 38), 19 samples tested positive and 26 tested negative. However, 4 samples that tested positive with Ct values of 36–38 by the TIB MOLBIOL Roche kit were negative by the ICMR-NIV kit. Results of the TIB MOLBIOL Roche kit showed 88% Specificity, 78% PPV, and almost perfect agreement (Kappa value 0.8125) when compared with the ICMR-NIV kit [Tables 3 and 4].

Repeat samples were requested from 15 patients who had Ct ≥ 36, after a gap of 2–3 days. Only 14 patients submitted the repeat sample. Of these, 13 (92.8%) tested negative and 01 (7.2%) sample tested positive for SARS-CoV-2 by the respective kit and the ICMR-NIV kit.

DISCUSSION

Here we provide the comparison of seven commercially available RT-PCR kits with the ICMR-NIV kit for the diagnosis of COVID-19. These kits have been standardized to have different cutoff CTs ranging between 36 and 40 by the manufacturers. All the kits had 100% sensitivity and NPV,

suggesting that these can correctly identify positive cases, and a negative report rules out infection. However, only three kits, namely, ARGENE-R, COROSURE, and Mylab PathoDetect™ had 100% specificity, 100% PPV, and perfect agreement with the ICMR-NIV kit, suggesting that these can correctly identify negative cases, and a positive report indicates infection in the individual.

Four kits, namely, TIB MOLBIOL Roche, Perkin Elmer, BGI, and LabGun™ had 88%, 81%, 73%, and 66% specificity, respectively. Manufacturer's instructions should be followed for reporting of the results; however, our study revealed that Ct value ≥ 36 gave variable results with different kits. We found that 66.6% (30/45) of results were 100% concordant with NIV and COVID-19 RT PCR kit results hile 33.3% (15/45) showed variable results with 4 kits as compared to NIV, COVID-19 RT PCR kit results. On repeat testing of these (n = 14; one person did not submit the sample) samples, after 2–3 days, 13 (92.8%) tested negative, and 1 (7.2%) was positive for SARS-CoV-2 genes with the respective kit and NIV, COVID-19 RT PCR kit. Thirteen samples may either be "true negative" or in the late course of illness and hence became negative after 2–3 days. One that tested positive may have been in the early course of illness and hence tested positive after two days with respective kit and NIV, COVID-19 RT PCR kit. **Overall, it can be stated from our obtained result that kits depending on a higher number of target genes show less false positive results. Our finding was comparable with the other study conducted in Bangladesh in 2023 published by Dip SD *et al.*[8]**

Variability of results in samples with Ct values > 36 suggests that these should be interpreted with caution. A false positive result in such cases may unnecessarily lead to quarantine/isolation of the individuals. In such cases, it is suggested that the test results should be reported as "Inconclusive" or "Indeterminate" and a repeat sample should be tested after a gap of 2–3 days to give the benefit of the doubt to the patient for appropriate management and public health authorities for the implementation of preventive measures. In addition, these may show inconsistent results in inter-laboratory comparison as different labs may be using different RT PCR kits.

All the kits were based on TaqMan Fluorogenic probe–based chemistry except COROSURE SARS-CoV-2, which uses SYBER Green dye. This kit showed 100% agreement with the NIV kit. The result was obtained faster (~75 min) as compared to other kits (~105 to 135 min). The SYBR green-based assay has been found to be equally sensitive to TaqMan assay for the diagnosis of West Nile Virus (WNV). Importantly, it also detected 100% of possible WNV target region variants.[7] Probe-based assays are usually expensive, and the availability of SYBER Green dye–based assay may be an economical alternative for large-scale routine testing.

The main limitation of the study is its small sample size; however, considering the findings, this study suggests that all the seven COVID-19 RT-PCR kits can be used for routine diagnosis of COVID-19 patients. However, positive results having Ct values ≥36 should be interpreted with caution and a repeat sample should be asked to ascertain the presence of infection.

CONCLUSION

We also found that detection kits targeting more genes showed better accuracy, which yields less false positive results (<20%).

Ethical approval

The authors declare that they have taken the Institutional Ethics Committee approval and the approval number is 439(88/2020) IEC.

Declaration of patient consent

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

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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.

REFERENCES

1. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report 154. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200622-covid-19.
2. ICMR performance evaluation of commercial kits for real time pcrfor covid by icmridentified validation centres. Available from: https://www.finddx.org/covid-19/pipeline/.
3. Molecular assays to diagnose COVID-19: Summary table of available protocols. Available from: https://www.who.int/publications/m/item/molecular-assays-to-diagnose-covid-19-summary-table-of-available-protocols.

4. Hatchette TF, Drews SJ, Bastien N, Li Y, German G, Antonishyn N, *et al*. Detection of influenza H7N9 virus: All molecular tests are not equal. J Clin Microbiol 2013;51:3835–38.
5. Shuren J, Stenzel T. Covid-19 molecular diagnostic testing - lessons learned. N Engl J Med 2020;383:e97.
6. Gupta N, Potdar V, Praharaj I, Giri S, Sapkal G, Yadav P, *et al*. Laboratory preparedness for SARS-CoV-2 testing in India: Harnessing a network of virus research & diagnostic laboratories. Indian J Med Res 2020;151:216–25.
7. Papin JF, Vahrson W, Dittmer DP. SYBR green-based real-time quantitative PCR assay for detection of west nile virus circumvents false-negative results due to strain variability. J Clin Microbiol 2004;42:1511–8.
8. Dip SD, Sarkar SL, Setu MAA. Das PK, Pramanik MHA, Alam ASMRU, *et al*. Evaluation of RT-PCR assays for detection of SARS-CoV-2 variants of concern. Sci Rep 2023;13:2342.

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Original Article

A comparative study of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in bipolar mania and schizophrenia

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ABSTRACT

Objectives: The role of immunological disturbance in bipolar disorder (BD) and schizophrenia has been highlighted by some studies. There are few studies available that compared the inflammatory markers between schizophrenia and BD, but only one study demonstrated the difference in terms of neutrophil/lymphocyte ratio (NLR) and Platelet/lymphocyte ratio (PLR) between them. So this study was conducted to compare the NLR and PLR values among schizophrenia, bipolar mania, and healthy controls in order to find out a potential biomarker for these disorders.

Material and Methods: Eighty consecutive patients suffering from bipolar mania, 80 suffering from schizophrenia, and 80 healthy controls were recruited in the psychiatric center situated at a tertiary care hospital. Blood samples of all groups were transferred to the laboratory for complete blood count analysis. Thereafter, all the groups were compared by applying proper statistics.

Results: Significant higher level of neutrophil count and NLR value was seen in both bipolar mania and schizophrenia groups compared to healthy controls. There was no difference observed between schizophrenia and the bipolar mania group regarding NLR, PLR, neutrophils, lymphocytes, and platelets values.

Conclusion: NLR has appeared as a potential marker in our study, and it reflects a state of low-grade inflammation in both schizophrenia and bipolar mania. BD and schizophrenia have been considered as part of one continuum, which is also supported by the findings of our study. These markers can help in the prognosis and treatment of at least a subsection of patients and also are inexpensive and easy to assess.

Keywords: Neutrophil/lymphocyte ratio; Platelet/lymphocyte ratio; Bipolar mania; Schizophrenia.

INTRODUCTION

Bipolar disorder (BD) and schizophrenia were considered in the psychotic spectrum by the psychiatric classification system until the 19th century.[1] Later, Kraepelin differentiated dementia praecox and manic-depressive disorder, setting it as a milestone in psychiatric diagnostic classification.[2] Nowadays, a continuity model has been established linking mania and psychosis and thereafter between BD and schizophrenia, which was in contrast to the conventional approach.[3] Besides this, few studies suggested that BD and schizophrenia were extensions of each other on a neurodevelopmental basis.[4]

The role of immunological disturbance in schizophrenia and bipolar illness has also been highlighted by some etiological studies.[5–7] Some studies reported alteration of peripheral inflammatory markers like cytokines, acute phase proteins, and lymphocyte cell activation in BD patients. [5,8–12] Jilma found increased neutrophils and decreased lymphocytes in general immune response to endotoxemia.[13] Thereafter, Zahorec developed the neutrophil/lymphocyte ratio (NLR) as a parameter that reflects the systemic inflammation and stress intensity in critically ill patients,[14] thus suggesting that these markers also contribute to the development of psychiatric disorders, particularly BD, and schizophrenia.

Various studies proposed the role of NLR value as a poor prognostic sign in some medical illnesses like pancreatitis, malignancy, and coronary heart disease.[15–17] Later on, scholars tried to find out its role in psychiatric illness as well. Many studies that have been done on patients with BD and schizophrenia tried to find out levels of NLR and PLR.[18–31] Better treatment response has been suggested in

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patients suffering from schizophrenia who had normal initial neutrophil and lymphocyte numbers and poor response in those who had lower lymphocyte and higher neutrophil count.[32]

Based on our current understanding and available information, we found that only a single study tried to ascertain the difference between schizophrenia and BD with respect to NLR and PLR. This study demonstrated a significantly higher NLR level in schizophrenia than BD (mania) patients.[20] In India, no study has been done on this subject so far. Therefore, we planned to conduct this study in a tertiary care center in India.

The main objective of this study was to assess and compare the levels of NLR and PLR among bipolar mania patients, schizophrenia patients, and healthy controls in order to find out a potential biomarker for these disorders. Our a priori hypothesis for this study was that the NLR and PLR values are higher among the subjects with mania and schizophrenia in comparison to healthy controls.

MATERIAL AND METHODS

The study was conducted as a cross-sectional and observational research in the Department of Psychiatry at a tertiary care hospital in North India. Ethical permission was taken from the ethics committee of the institute. The enrolment criteria were male or female participants aged greater than 18 years, who expressed a willingness to participate in the research and gave their written consent. The exclusion criteria for bipolar mania and schizophrenia groups included having any pre-existing chronic medical conditions and treatments, substance use including heavy smoking (>15 cigarettes per day),[21] clinical evidence related to active infections, as well as active or chronic inflammatory or autoimmune diseases among the participants, obesity (body mass index (BMI) >30 kg/m^2), taking immunosuppressive or anti-inflammatory medications, and the presence of clinically significant abnormalities during the baseline assessment (such as tachycardia, tachypnea, or fever) or abnormality in a laboratory test (e.g. anemia, leukocytosis, leukopenia, and thrombocytosis).[21] The exclusion criteria for healthy controls included any pre-existing psychiatric illness and treatment and parameters that were applicable to the bipolar and schizophrenia groups. The sample size for the study was determined based on a desired study power of 80% and a significance level (α-error) of 0.05, assuming a standard deviation of 1.0 as per the results of the reference article.[20] For a minimum detectable difference in means of 0.5 (NLR), 80 subjects were required as the sample size in each group. The patients who met both the inclusion as well as exclusion criteria were included in the study until the intended sample size was reached.

A total of 80 consecutive patients diagnosed with bipolar mania and 80 consecutive patients diagnosed with schizophrenia, according to the ICD-10 "(International Classification of Disease 10th Revision)", were recruited. The diagnosis of each patient was confirmed by two senior psychiatrists who were not part of the study. In addition, 80 healthy controls, preferably individuals accompanying the patients, were also included in the study. Psychiatric illnesses were ruled out in the healthy control group using the "ICD-10 symptom checklist for mental disorders."[33] Individuals who willingly participated in the study, provided written consent and met the inclusion criteria. Blood samples were collected from the antecubital vein of all subjects using vacutainer tubes containing ethylenediamine tetraacetic acid (EDTA) as an anticoagulant. The samples were collected in the morning hours (9 am–11 am) after overnight fasting and were sent to the laboratory for complete blood count (CBC) by a three-part blood cell counter manufactured by Sysmex (XP-100). Among CBC parameters, we included neutrophil, lymphocyte, and platelet counts for our study as they are involved in the inflammatory process. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, the PLR (platelet to lymphocyte ratio) was determined by dividing the absolute platelet count by the absolute lymphocyte count.

Statistical Analysis

The data collected in this study were entered into a Microsoft Excel 2007 worksheet and organized into a master chart. The data were then classified and analyzed according to the study's aims and objectives. The Pearson's chi-square test was used to analyze categorical variables. The normality of the data distribution was assessed using the "Shapiro–Wilk test." For normally distributed data, one-way Analysis of Variance (ANOVA) test was utilized, while for data that did not follow a normal distribution, the "Kruskal–Wallis post hoc Dunn's test" was applied. Statistical significance was considered at a p-value of less than 0.05 ($p < 0.05$).

RESULTS

Characteristics of participants

Bipolar mania, schizophrenia, and the healthy control groups were found to be comparable in terms of age, BMI, and distribution of gender.

The mean age of bipolar mania patients, schizophrenia patients, and healthy controls was 28.5 ± 5.5 years, 27.8 ± 6.2 years, and 28.11 ± 5.3 years ($p = 0.746$), respectively, and mean BMI was 24.6 ± 1.8 Kg/M^2, 24.5 ± 1.9 Kg/M^2, and 24.01 ± 1.9 Kg/M^2 ($p = 0.103$), respectively. In all the groups, there was an equal distribution of males and females (1:1) [Table 1].

Laboratory findings of various groups

There was a significant increase in the mean value of neutrophil count and NLR in bipolar mania than control subjects (5.32 ± 1.30 v/s 4.58 ± 1.18; p = 0.001 and 2.55 ± 1.13 v/s 1.93 ± 0.59; p < 0.001, respectively). Similarly, higher neutrophil and NLR mean values were observed in the schizophrenia group than the healthy control (5.26 ± 1.28 v/s 4.58 ± 1.18; p = 0.001 and 2.52 ± 1.07 v/s 1.93 ± 0.59; p < 0.001, respectively) [Table 2].

When a comparison was made between schizophrenia and bipolar groups, no significant difference of mean neutrophil count and NLR was observed between them (p = 1.00 for both neutrophil count and NLR) [Table 2].

According to the study findings, there were no significant differences observed in the mean values of lymphocyte count, platelet count, and PLR among all the groups (p = 0.058, p = 0.870, and p = 0.094, respectively) [Table 2].

DISCUSSION

The study findings reveal a significant increase in the value of neutrophils and NLR in both bipolar mania and schizophrenia groups compared to the control group. These results show an association of BD and schizophrenia with inflammatory parameters. Most of the studies that have been done so far are consistent on a higher NLR level in schizophrenia and BD while inconclusive over the neutrophil levels.[18–31]

BD and schizophrenia groups do not differ significantly when considering lymphocytes, neutrophil count, and NLR as a parameter of inflammation in the study. As per our knowledge, there is only a single study available till now that compared these markers in BD and schizophrenia. It showed a contradictory result of significantly higher NLR level in schizophrenia than BD (mania) patients.[20]

The NLR serves as an indicator of the balance between the innate immune response (neutrophils) and the adaptive immune response (lymphocytes).[34] Neutrophils, as the first line of defense, play a role in phagocytosis and apoptosis, releasing various inflammatory mediators like cytokines, which can lead to cellular DNA damage.[35] Lymphocytes play a crucial role in the immune system as they have protective and regulatory functions. Lymphopenia, which refers to a decrease in lymphocyte count, can be an indicator suggesting compromised overall health and physiological stress.[36,37] Considering that NLR represents an integrated parameter of these two immune pathways, it has the potential to be more predictive as a biomarker for BD during manic states and schizophrenia than using either parameter alone.[34] Therefore, NLR could serve as a valuable indicator and biomarker for these psychiatric conditions.

Indeed, the relationship between mental disorders and platelet parameters has been acknowledged for a considerable time. The PLR has shown promise in predicting the inflammatory response in affective disorders. Platelets serve

Table 1: Characteristics of participants.

Variables		Bipolar mania (n = 80)	Schizophrenia (n = 80)	Healthy control (n = 80)	P-value
Age	(Mean ± SD)	28.45 ± 5.53	27.76 ± 6.21	28.11 ± 5.25	0.746*
	Median	29 Yrs	27 Yrs	28 Yrs	
BMI (Kg/M^2)	(Mean ± SD)	24.59 ± 1.76	24.50 ± 1.86	24.01 ± 1.87	0.103*
Sex	Male	40 (50%)	40 (50%)	40 (50%)	1.00†
N (%)	Female	40 (50%)	40 (50%)	40 (50%)	

*One way ANOVA; †chi square test; SD – Standard deviation; BMI – Body mass index; N – Number

Table 2: Laboratory findings of various groups.

Variables	Bipolar mania (n = 80) Mean ± SD	Schizophrenia (n = 80) Mean ± SD	Healthy control (n = 80) Mean ± SD	H(2)	P1	P2	P3
Neutrophil (µl)	5.32 ± 1.30	5.26 ± 1.28	4.58 ± 1.18	17.7	**0.001**	**0.001**	1.00
Lymphocyte (µl)	2.28 ± 0.65	2.26 ± 0.60	2.47 ± 0.57	5.7		0.058	
Platelet (µl)	225.18 ± 81.82	224.14 ± 71.90	219.55 ± 73.65	0.28		0.870	
NLR	2.55 ± 1.13	2.52 ± 1.07	1.93 ± 0.59	20.8	**<0.001**	**<0.001**	1.00
PLR	105.80 ± 43.50	106.40 ± 41.77	93.96 ± 37.61	4.7		0.094	

Kruskal–Wallis H test post-hoc Dunn's test; SD – Standard deviation; P1 – Bipolar mania v/s Healthy Control; P2 – Schizophrenia v/s Healthy Control; P3 – Bipolar mania v/s Schizophrenia; NLR – neutrophil/lymphocyte ratio; PLR – Platelet/lymphocyte ratio; H(2) – Test statistics; Bold value signifies the significant difference among the groups (P < 0.05).

as specific first-line inflammatory markers and play a role in regulating various parameters, including neutrophil and macrophage recruitment as well as endothelial permeability.[26] A meta-analysis has reported that patients with BD exhibit higher PLR values compared to controls.[26] Indeed, platelets are known to contain significant amounts of glutamate and serotonin within their dense granules. Serotonin and glutamate are neurotransmitters that play crucial roles in various physiological processes, including mood regulation.[38] In this study, no significant differences were observed in PLR values and platelet count among the groups being compared. Similarly, a study done by Ozdin *et al.* didn't find any significant difference in the PLR level between BD and schizophrenia groups.[20] The findings regarding platelet count and activation in psychiatric disorders have been contradictory and inconclusive in various studies.[18–19,24,29–31,39,40] Considering the inconsistent findings, it is important to acknowledge that PLR may not be a consistent and reliable marker for BD and schizophrenia.

In the study, the age distribution, BMI, and distribution of gender in all the groups (bipolar mania, schizophrenia, and control groups) were compared, and no significant differences were found among these variables. This suggests that the study groups were well-matched in terms of age, BMI, and gender distribution, which reduces the potential confounding effects of these factors on the study results.

Our study has the following limitations: Since this study is conducted in a cross-sectional manner, it is not possible to establish causal relationships. Other indicators of inflammation like cytokines, interferon-gamma, C-reactive proteins, acute phase proteins, and lymphocyte cell activation have not been studied. The patients were on different psychotropic drugs, which can influence blood cell count. Any lifestyle factors or levels of psychological distress were not assessed, which may affect NLR levels.

CONCLUSION

The NLR has emerged as a promising indicator, and it reflects a state of low-grade inflammation in both schizophrenia and bipolar mania. BD and schizophrenia have been considered as part of one continuum, proven by the fact that no significant differences were observed in the levels of neutrophils, lymphocytes, platelets, NLR, and PLR between these disorders. These markers can help in the prognosis and treatment of at least a subsection of patients and also are inexpensive and easy to assess.

More such studies are required in the future to definitively establish the role of inflammatory markers in psychiatric illnesses. The longitudinal study is required to ascertain whether the markers are state- or trait-specific markers. This will open the gate for new treatment strategies.

Ethical approval

The research/study is approved by the Ethics Committee at SMS Medical College and attached hospitals Jaipur, number 46/MC/EC/2020, dated 23 January 2020.

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.

REFERENCES

1. Noll R. Madness, psychosis, schizophrenia: A brief history. In: George L, editor. The encyclopedia of schizophrenia and other psychotic disorders, 3rd ed. New York: Infobase Publishing; 2009. p. ix–xx.
2. Kraepelin E. Psychiatry: A textbook for students and physicians. In: General psychiatry. Vol. 1, Canton, MA: Watson Publishing International; 1899/1990.
3. Tamminga CA, Pearlson G, Keshavan M, Sweeney J, Clementz B, Thanker G. Bipolar and schizophrenia network for intermediate phenotypes: Outcomes across the psychosis continuum. Schizophr Bull 2014;40:S131–7.
4. Akabaliev VH, Sivkov ST, Mantarkov MY. Minor physical anomalies in schizophrenia and bipolar I disorder and the neurodevelopmental continuum of psychosis. Bipolar Disord 2014;16:633–41.
5. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord 2007;104:91–5.
6. Ortiz Domínguez A, Hernández ME, Berlanga C, Gutiérrez Mora D, Moreno J, Heinze G, *et al*. Immune variations in bipolar disorder: Phasic differences. Bipolar Disord 2007;9:596–602.
7. Fillman SG, Sinclair D, Fung SJ, Webster MJ, Shannon Weickert C. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. Transl Psychiatry 2014;4:e365.

8. Barbosa IG, Huguet RB, Mendonça VA, Sousa LP, Neves FS, Bauer ME, *et al*. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. Eur Arch Psychiatry Clin Neurosci 2011;261:139–43.
9. Munkholm K, Braüner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. J Psychiatric Res 2013;47:1119–33.
10. Cunha AB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Gonçalves CA, *et al*. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur Arch Psychiatry Clin Neurosci 2008;258:300–4.
11. Barbosa IG, Rocha NP, Assis F, Vieira ÉL, Soares JC, Bauer ME, *et al*. Monocyte and lymphocyte activation in bipolar disorder: A new piece in the puzzle of immune dysfunction in mood disorders. Int J Neuropsychopharmacol 2014;18:pyu021.
12. Drexhage RC, Knijff EM, Padmos RC, Heul-Nieuwenhuijzen Lv, Beumer W, Versnel MA, *et al*. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev Neurother 2010;10:59–76.
13. Jilma B, Blann A, Pernerstorfer T, Stohlawetz P, Eichler HG, Vondrovec B *et al*. Regulation of adhesion molecules during human endotoxemia. No acute effects of aspirin. Am J Respir Crit Care Med 1999;159:857–63.
14. Zahorec R. Ratio of neutrophil to lymphocyte counts - rapid and simple parameter of systemic inflammation and stress in critically ill. Bratislavské lekárske listy 2001;102:5–14.
15. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B, *et al*. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology 2011;11:445–52.
16. Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, *et al*. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer 2013;108:1677–83.
17. Fowler AJ & Agha RA. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography – the growing versatility of NLR. Atherosclerosis 2013;228:44–5.
18. Kalelioglu T, Akkus M, Karamustafalioglu N, Genc A, Genc ES, Cansiz A, *et al*. Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. Psychiatry Res 2015;228:925–7.
19. Mert DG, Terzi H. Mean platelet volume in bipolar disorder: The search for an ideal biomarker. Neuropsychiatr Dis Treat 2016;12:2057–62.
20. Özdin S, Sarisoy G, Böke Ö. A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients – a retrospective file review. Nord J Psychiatry 2017;71:509–12.
21. Cakir U, Tuman TC, Yildirim O. Increased neutrophil/lymphocyte ratio in patients with bipolar disorder: A preliminary study. Psychiatria Danub 2015;27:180–4.
22. Mayda H, Ahsen A, Bagcioglu E, Öztürk A, Bahçeci B, Soyuçok E, *et al*. Effect of inc reased neutrophil-to-lymphocyte ratio (NLR) and decreased mean platelet volume (MPV) values on inflammation in acute mania. Noro Psikiyatr Ars 2016;53: 317–20.
23. Ayhan MG, Cicek IE, Inanli I, Caliskan AM, Ercan SK, Eren I. Neutrophil/lymphocyte and platelet/lymphocyte ratios in all mood states of bipolar disorder. Psychiat Clin Psychopharmacol 2017;27:278–82.
24. Yildiz M, Batmaz S, Songur E, Sahin S, Demir O. Simple markers for subclinical inflammation in the different phases of bipolar affective disorder. Arch Clin Psychiatry (Sao Paulo) 2016;43:143–6.
25. Inanli I, Aydin M, Metehan A, Caliskan AM, Eren I. Neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and mean platelet volume as systemic inflammatory markers in different states of bipolar disorder. Nord J Psychiatry 2019;73:372–9.
26. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A metaanalysis. Prog Neuropsychopharmacol Biol Psychiatry 2018;84:229–36.
27. Mazza MG, Tringali AGM, Rossetti A, Botti ER, Clerici M. Cross-sectional study of neutrophil-lymphocyte, plateletlymphocyte and monocyte-lymphocyte ratios in mood disorders. Gen Hosp Psychiatry 2019;58:7–12.
28. Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, *et al*. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub 2014;26:220–5.
29. Bustana Y, Drapisza A, Dora DHB, Avrahamia M, Lifshitza MS, Weizmana A, Barzilay R. Elevated neutrophil to lymphocyte ratio in non-affective psychotic adolescent inpatients: Evidence for early association between inflammation and psychosis. Psychiatry Res 2018;262:149–53.
30. Kulaksizoglu B, Kulaksizoglu S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. Neuropsychiatr Dis Treat 2016;12:1999–2005.
31. Özdin S, Böke O. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res 2019;271:131–5.
32. Zorrilla EP, Cannon TD, Kessler J, Gur RE. Leukocyte differentials predict short-term clinical outcome following antipsychotic treatment in schizophrenia. Biol Psychiatry 1998;43:887–96.
33. Janca A, Ustun TB, Van Drimmelen J, Dittmann V, Isaac M. The ICD-10 classification of mental and behavioural disorders. Symptom checklist. Version 1.1. Geneva: World Health Organization; 1994 (WHO/MNH/MND/94.12).
34. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, *et al*. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol 2010;106:470–6.
35. Mayadas TN, Cullere X, Lowell CA. The Multifaceted Functions of Neutrophils. Annu Rev Pathol 2014;9:181–218.
36. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, *et al*. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010;105:186–91.
37. Melo MCA, Garcia RF, de Araujo CFC, Abreu RLC, de Bruin PFC, de Bruin VMS. Clinical significance of neutrophil-lymphocyte and platelet-lymphocyte ratios in bipolar patients: An 18-month prospective study. Psychiatry Res 2019;271:8–14.

38. Dietrich-Muszalska A, Wachowicz B. Platelet haemostatic function in psychiatric disorders: Effects of antidepressants and antipsychotic drugs. World J Biol Psychiatry 2017;18: 564–74.
39. Aykut DS, Arslan FC, Karaguzel EO, Aral G, Karakullukçu S. The relationship between neutrophil-lymphocyte, platelet – lymphocyte ratio and cognitive functions in bipolar disorder. Nord J Psychiatry 2017;72:119–24.
40. Wysokinski A, Szczepocka E. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. Psychiatry Res 2016;237:238–45.

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Case Report

Rifampicin-induced thrombocytopenia in a patient with abdominal tuberculosis

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ABSTRACT

Most anti-tubercular drugs are relatively safe, but adverse reactions are not uncommon. Rifampicin is one of the most effective and widely used anti-tuberculosis drugs. Adverse effects due to rifampicin are not uncommon and the patients usually have skin rash, gastrointestinal disturbances, and hepatotoxicity. Rarely, the patients may also have allergic and autoimmune manifestations, which may include life-threatening thrombocytopenia. A high index of suspicion and careful evaluation for temporal association with the suspected drug are required to diagnose drug-induced immune thrombocytopenia. We present a case of rifampicin-induced thrombocytopenia; though relatively rare, it needs attention.

Keywords: ATT, Rifampicin, Thrombocytopenia, Tuberculosis

INTRODUCTION

Tuberculosis has a high prevalence rate in India, and its treatment has been a therapeutic challenge because of non-compliance and side effects of anti-tubercular therapy (ATT) drugs. Rifampicin is among the most effective and widely used anti-tuberculosis drugs. Adverse reactions (ADR) due to rifampicin are common, and the patients usually have skin rash and gastrointestinal disturbances, but rarely require stoppage of the drug.[1] Hepatotoxicity is another frequent ADR and may require the substitution of the drug with other second-line agents. Rarely, the patients may also develop allergic and autoimmune manifestations, like acute renal failure and thrombocytopenia.[2] Thrombocytopenia may be life-threatening and can be seen with several ATT drugs, including rifampicin.[3,4] It is typically reversible if diagnosed early and treated appropriately. We report a case of rifampicin-induced thrombocytopenia, presented with severe bleeding manifestations, and recovered after the drug was substituted from the treatment regimen.

CASE REPORT

A 12-year-old girl with no prior comorbidities, presented with complaints of low-grade fever, abdominal pain, and loss of appetite for two months. She also had a history of weight loss of 4–5 kg during this period. On examination, she had subcentimetric level-III cervical lymphadenopathy. Her vitals were stable, and detailed systemic evaluation performed was non-contributory. On evaluation, her hemoglobin (Hb) was 7.5 g/dL, white blood cells/total cell count (WBC/TLC) was 6,800/cmm, and platelet count was 2,82,000/cmm. Renal and liver function tests were normal. The contrast-enhanced computed tomography (CECT) images of the abdomen showed moderate ascites and thickening of the ileocaecal region with subcentimetric lymphadenopathy. Ascitic fluid analysis showed a WBC of 5,600/cmm with lymphocyte predominance (80%). Ascitic fluid for acid-fast bacilli was negative, but adenosine deaminase was elevated at 78.6 U/L(<40 U/L). Based on clinical and radiological findings, she was diagnosed with abdominal tuberculosis. She was started on ATT (thrice weekly isoniazid 300 mg, rifampicin 450 mg, ethambutol 800 mg, and pyrazinamide 1,000 mg) with pyridoxine 40 mg under directly observed treatment short-course (DOTS) category I. She tolerated the treatment well, became asymptomatic in the next two weeks, and was discharged on ATT.

Four weeks later, she presented with skin rashes over bilateral extremities and the lower lip [Figures 1a, 1b]. She also had

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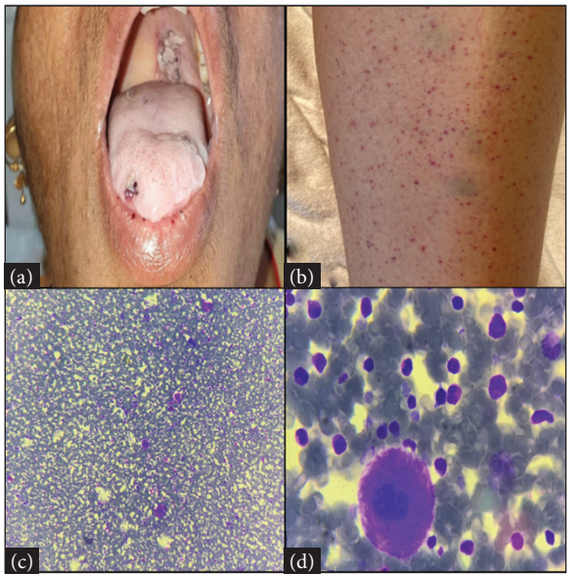

Figure 1: (a–b): Clinical photograph showing petechiae over (a) Lower lip; (b) Lower limb; (c–d): Bone marrow aspirate showing trilineage hematopoiesis with increased Megakaryocytes (c) 100x and (d) 1000x.

gum bleeding for the last three days. Her detailed clinical examination revealed multiple palpable, non-blanching purpura over bilateral lower limbs and trunk. Examination of the oral cavity revealed a wet purpura on the soft palate.

Her investigations showed low hemoglobin (Hb-6.9 g/dL), low platelet (platelet-4,000/cmm), and normal (WBC-6700/cmm). Peripheral blood smear (PBS) showed predominantly normocytic normochromic red blood cells and severe thrombocytopenia, with no evidence of schistocytes. Dengue profile, HIV, hepatitis viral serology, and antinuclear antibody (ANA) profile were negative. The reticulocyte count was 0.8%. Bone marrow aspirate revealed normocellular marrow with megakaryocytic hyperplasia. No evidence of any atypical cells or blasts in the marrow [Figures 1c–1d]. Before considering the diagnosis of immune thrombocytopenia (ITP), drug-induced thrombocytopenia (DITP) was thought of, as the patient was on ATT.

The ATT was stopped with a suspicion of DITP, as her platelet count was normal before the initiation of ATT. Because of wet purpura, she was immediately transfused with platelet-rich plasma followed by intravenous immunoglobulin (IVIG-1g/kg). Two days later, the platelet count showed an increasing trend. In the next two weeks, she had a platelet count of 160,000/cmm. After complete recovery of the platelet, ATT was restarted. Considering the assumed rifampicin toxicity, it was omitted from the regimen. Modified ATT was initiated, and one drug was introduced at one time, starting with isoniazid. Pyrazinamide was added seven days later, followed

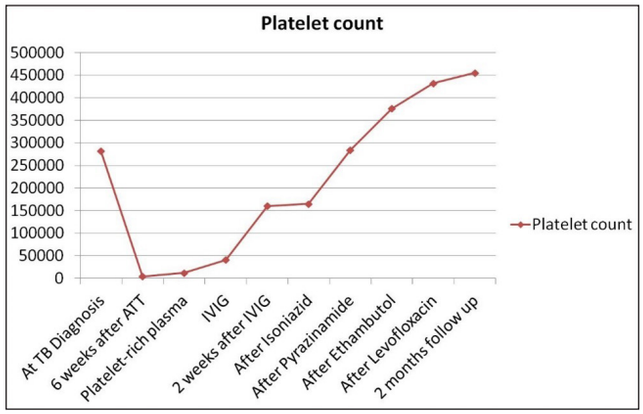

Figure 2: Trend of platelet count during the course of the treatment (ATT: Anti tubercular therapy; IVIG: Intravenous immunoglobulin).

by ethambutol and levofloxacin in that order. The patient is planned for nine months of modified ATT. The platelet count showed an increasing trend thereafter and subsequently became stable after achieving normal levels [Figure 2].

Rifampicin was subtracted from the regimen, and in two weeks the platelet count became normal and remained stable thereafter. The current platelet count on follow-up is 455,000/cmm. There were no other clinical, hematological, or biochemical abnormalities during the follow-up examinations.

DISCUSSION

Though anti-tubercular drugs are considered relatively safe, serious adverse events are also well known. All the first-line ATT drugs are known to cause thrombocytopenia. However, it is relatively common with rifampicin and is extremely rare with isoniazid, ethambutol, and pyrazinamide. Thrombocytopenia is among the rare yet life-threatening adverse effects seen with rifampicin.[5] Thrombocytopenia arising due to induced rifampicin was reported way back in 1970.[6] However, it is relatively rare, as reported by Tuberculosis Research Centre, Chennai, over 30 years among 8,000 patients treated; only a single case of rifampicin-induced thrombocytopenia was noted.[7] However, in a subsequently reported review, rifampicin was one of the most common drugs reported as the cause for thrombocytopenia.[8] Thrombocytopenia as an ADR is usually associated with intermittent or high-dose rifampicin regimen.[9] The postulated hypothesis is that continuous exposure to the drug results in the neutralization of antibodies, whereas in others (intermittent regimen) a sufficient quantity of antibodies are built up during the drug-free interval so that when the drug is re-administered, a strong reaction takes place.[10,11] Also noted is the occurrence of ADR significantly correlates with the presence of drug-dependent (rifampicin-dependent) antibodies.[12] However, the occurrence of thrombocytopenia with a daily regimen cannot

be completely ignored and has been previously reported.[13] Our patient also had thrombocytopenia on a continuous regimen (daily rifampicin) and it occurred 6 weeks after she was started on rifampicin.

Several drugs other than ATT are well-known causes of thrombocytopenia. They are heparin, quinine, sulfonamides, vancomycin, piperacillin, ampicillin, and some herbal medicines.[2] Concomitant use of these drugs should also be excluded during evaluation. These drugs cause thrombocytopenia either by suppression of platelet production or immunological destruction, the latter being the most common mechanism.[8] In the presence of offending antigen (drug), the immune complexes nonspecifically attach to the platelet membrane, and this results in platelet damage and their rapid clearance from the peripheral circulation.[5] In rifampicin-induced immune thrombocytopenia, the most important target is the binding site located in the glycoprotein GPIb/IX.[14] Confirmation of DITP at presentation is often difficult, as the tests for drug-dependent antiplatelet antibodies are not readily available. George *et al*., defined standard criteria for diagnosing DITP after a thorough evaluation of the literature.[15] The four criteria are: (1) The offender drug not only preceded the thrombocytopenia but also the drug withdrawal led to complete and sustained recovery of the platelet count. (2) The offender drug was the only drug used prior to the thrombocytopenia onset, or any other drugs used were continued (or reintroduced) after discontinuation of the offender drug with a persistent normal platelet count. (3) Any other cause of low platelet count was excluded. (4) Re-introduction of the offender drug resulted in the re-occurrence of thrombocytopenia. In the present case, three out of four criteria are met suggestive of probable DITP. The patient was not re-exposed to the offending drug, as even a miniscule quantity of the drug is sufficient to set up a severe immune reaction as reported in some of the published literature.[11,16]

DITP, though fatal, is a potentially reversible adverse effect. The index case had wet purpura, a sinister sign suggestive of impending intracranial hemorrhage.[3] There is an urgency to increase platelets in these cases. After stopping the offending drug, platelet transfusion, corticosteroids, and intravenous immunoglobulin are used alone or in combination.[8,17] The benefit of platelet transfusions remains unclear, as it has not been studied in any clinical trial. Further, the majority of the drugs are cleared from circulation within a few hours to a few days, and platelet counts often start to rise within days to weeks after discontinuing the offending drug. Rarely, low platelet count and bleeding manifestations persist for up to a month or longer. A high index of suspicion and early stoppage of suspected drugs are necessary to overcome this potentially fatal adverse effect.

CONCLUSION

The case highlights the need for suspicion, confirmation, and corrective measures to be taken in the case of drug-induced thrombocytopenia.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

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

Financial support and sponsorship

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.

REFERENCES

1. Arbex MA, Varella MD, Siqueira HR, Mello FA. Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations-part 1: First-line drugs. J Bras Pneumol 2010;36:626–40.
2. Sandal R, Mishra K, Jandial A, Sahu KK, Siddiqui AD. Update on diagnosis and treatment of immune thrombocytopenia. Expert Rev Clin Pharmacol 2021;14:553–68.
3. Mishra K, Jandial A, Malhotra P, Varma N. Wet purpura: A sinister sign in thrombocytopenia. BMJ Case Rep 2017;2017:bcr2017222008.
4. Mishra K, Sahu KK. Re: Risk factors and predictors of treatment responses and complications in immune thrombocytopenia. Ann Hematol 2022;101:447–8.
5. Garg R, Gupta N, Mehra S, Singh R, Prasad R. Rifampicin induced thrombocytopenia. Indian J Tuberc 2007;54:94.
6. Blajchman MA, Lowry RC, Pettit JE, Stradling P. Rifampicin-induced immune thrombocytopenia. Br Med J 1970;3:24–6.
7. Rekha VB, Adhilakshmi AR, Jawahar MS. Rifampicin-induced acute thrombocytopenia. Lung India 2005;22:122–4.
8. George JN, Aster RH. Drug-induced thrombocytopenia: Pathogenesis, evaluation, and management. Hematol Am Soc Hematol Educ Program 2009;2009:153–8.
9. Agrawal A, Gutch M, Jain N, Singh A. Do not miss rifampicin-induced thrombocytopenic purpura. Case Rep 2012;2012:bcr1220115282.

10. Bassi L, Di Berardino L, Perna G, Silvestri LG. Antibodies against rifampin in patients with tuberculosis after discontinuation of daily treatment. Am Rev Respir Dis 1976;114:1189–90.
11. Mishra K, Pramanik S, Sandal R, Jandial A, Sahu KK, Singh K, *et al*. Safety and efficacy of azathioprine in immune thrombocytopenia. Am J Blood Res 2021;11:217–26.
12. Poole G, Stradling P, Worlledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. Br Med J 1971;3:343–7.
13. Verma AK, Singh A, Chandra A, Kumar S, Gupta RK. Rifampicin-induced thrombocytopenia. Indian J Pharmacol 2010;42:240.
14. Pereira J, Hidalgo P, Ocqueteau M, Blacutt M, Marchesse M, Nien Y, *et al*. Glycoprotein Ib/IX complex is the target in rifampicin-induced immune thrombocytopenia. Br J Haematol 2000;110:907–10.
15. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, *et al*. Drug-induced thrombocytopenia: A systematic review of published case reports. Ann Intern Med 1998;129:886–90.
16. Dosi R, Chandelkar A, Jain A, Motiwale S, Joshi P, Jain P. Rifampicin-induced thrombocytopenia: A rare complication. J Assoc Chest Physicians 2019;7:38–40.
17. Mishra K, Kumar S, Jandial A, Sahu KK, Sandal R, Ahuja A, *et al*. Real-world experience of rituximab in immune thrombocytopenia. Indian J Hematol Blood Transfus 2021;37:404–13.

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Annals of the National Academy of Medical Sciences (India)

Brief Report

Diminished LC3 expression with unchanged Beclin 1 levels in right atrial appendage tissue of diabetic patients undergoing coronary artery bypass graft

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ABSTRACT

Type 2 diabetes potentiates the risk of heart failure. A vital physiologic process, autophagy, may be impaired in the diabetic heart. The purpose of the present work was to explore the autophagic status in the human diabetic heart. Techniques like immunohistochemistry and western blotting were employed to examine the expression of some of the important proteins involved in autophagic machinery. Our brief study reports, for the first time, evidence of decreased cardiac autophagic levels in diabetic patients.

Keywords: Autophagy, Heart, Type 2 Diabetes, CABG, LC3

INTRODUCTION

One of the important predisposing factors for cardiovascular diseases is type 2 diabetes mellitus (T2DM), it reduces life expectancy by several years and is a main cause of mortality and disability.[1,2] Long-standing hyperglycemia can impair cardiac function, blood vessels, nerves, eyes, kidneys, etc., leading to diabetic cardiomyopathy, myocardial infarction, diabetic retinopathy, neuropathy, and stroke.[3,4] The strong relationship existing between high blood glucose levels and cardiac metabolism can cause alterations in functions, energetics, and even the structure of the heart.[5–7] Several mechanisms have been proposed for the enhanced worsening of cardiac diseases in relation to T2DM.

Certain studies in animal models have shown increased autophagic activity in type 1 diabetes mellitus (T1DM) while it is decreased in T2DM.[8] The changes observed in autophagic levels during diabetes might have depended on the overall experimental design, type, and extent of diabetes and model organism used, etc.[9] Till now, there is only a single study on increased autophagy observed in the right atrial appendage of T2DM patients,[10] and no such studies have been reported in the Indian population. Hence, the study was conducted to determine cardiac autophagic status in T2DM Asian Indian subjects.

MATERIAL AND METHODS

Patient characteristics

Right atrial appendage tissues were collected from T2DM and non-T2DM patients ($n = 40$ each) admitted for coronary artery bypass graft surgery (CABG). Institutional ethics committee (IEC) approval was obtained for the conduct of the study, and informed consent was obtained from patients undergoing CABG. The study subjects were categorized as non-diabetic and diabetic based on glycated hemoglobin (HbA1c) values and random blood glucose. The exclusion criteria adopted were atrial fibrillation, T1DM, and left ventricular ejection fraction <40%. Average HbA1c and random blood glucose levels of the T2DM group were 7.87% and 169.67 mg/dL, respectively. None of the other factors showed statistically significant difference, including levels of triglyceride and cholesterol, left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) class.

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Collection and processing of human right atrial appendage

The right atrial appendage samples were excised from the site of cannulation during cardiopulmonary bypass. A small bit of biopsy was instantly immersed in buffered formalin for performing immunohistochemistry and the remaining portion was stored at –80°C for western blot experiments.

Western blot

Isolated proteins from the tissue lysate were heat denatured and resolved on SDS-PAGE and blotted onto the nitrocellulose membrane. It was then probed for LC3 B, p62/SQSTM1, Beclin 1, and β-Tubulin (Cell Signaling Technology, Massachusetts, USA) as loading control at 4°C overnight. HRP-conjugated anti-rabbit secondary antibodies were used for the study. A chemiluminescence reagent kit (Thermo Fisher Scientific, USA) was used for visualizing protein bands. The image was documented and quantified using the analysis software of Bio-Rad (Quantity one 1D, Hercules, USA).

Immunohistochemistry

Tissue expression of LC3 B, p62, and Beclin 1 was performed by immunohistochemistry (Abcam, Cambridge, UK). Briefly, 5 µm thick atrial sections were obtained from paraffin blocks of tissue samples using a microtome. After deparaffinization and rehydration of tissue sections with different grades of alcohol, sections were subjected to heat-mediated antigen retrieval method, following which endogenous peroxidases were blocked. Specific antibodies (1:100 dilution) were incubated at 4°C overnight. Diaminobenzidine (DAB) was used as a coloring agent, and the sections were counterstained with hematoxylin, followed by dehydration of sections, and mounted with Dibutylphthalate polystyrene xylene (DPX). Photomicrographs of tissues were taken, and using Image J software, the intensity of specific protein expression was quantified.

Statistical analysis

Representation of the values was done as mean ± standard deviation (SD). Significance was assigned when the *p*-value was <0.05. Comparison of means of diabetic and non-diabetic groups was done using Student's t-test when normality was observed in the data distribution otherwise, the Mann–Whitney U-test was performed. Statistical package for Social Sciences (SPSS) (IBM, NY, USA) and Graphpad (Graphpad software, CA, USA) were used to perform the statistical calculations and graphs, respectively.

RESULTS

Decreased autophagic markers in diabetic human heart

LC3 is the commonly used autophagic marker as its amount represents the number of autophagosomes present in cells. Steady-state level of autophagy was analyzed using immunohistochemistry and western blot [Figure 1]. LC3-II protein expression was found to be decreased in the diabetic cardiac tissue [Figures 1a, 1b, and 1c]. Since LC3 II is formed from LC3 I by lipidation in nascent autophagosomes, a ratio of LC3 II/I was also calculated [Figure 1d]. A statistically significant reduction of the LC3 II/I ratio too was observed in the diabetic cardiac tissues.

To document the level of autophagic process in diabetic human heart, expression of p62 and Beclin 1 were probed. Beclin 1, a 52 kDa protein interacting with the Vps34-Vps15 core complex, is known to promote autophagy. Western blot and immunohistochemistry analysis of Beclin1 revealed no statistically significant difference in expression in both groups [Figures 1e, 1g, and 1i]. p62, an adaptor molecule which

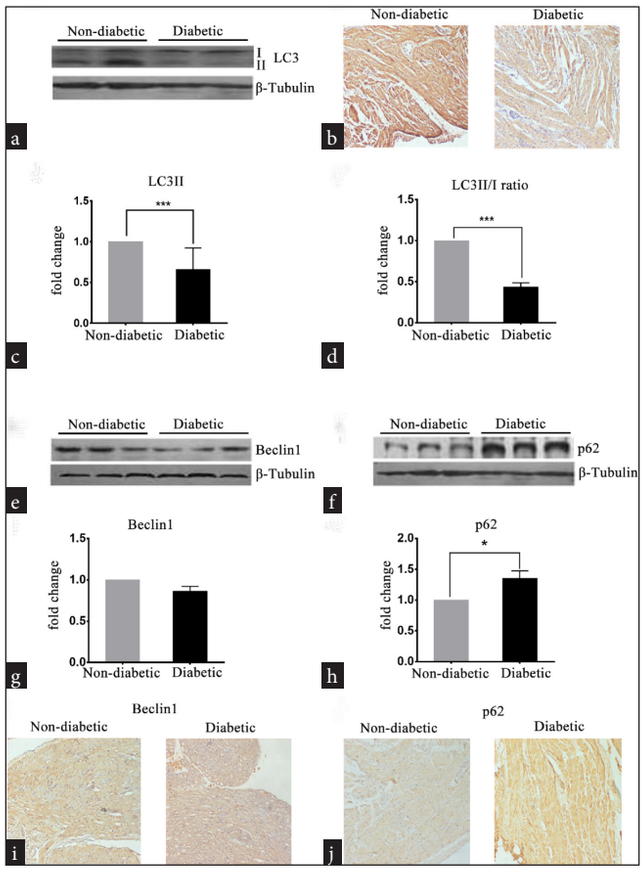

Figure 1: Expression of autophagic proteins: LC3, N = 18 p62, and Beclin 1, N = 8. Expression of LC3-II was represented by (a, c) western blotting and (b) immunohistochemistry (IHC) in diabetic human heart tissue. (d) LC3-II/LC3-I ratio was calculated from the western blot data and the bar graph depicts the fold change of the LC3-II/LC3-I ratio. Error bars denote standard deviation (SD; p-value <0.001; n = 18 in each group). (f, h) Expression of p62, western blotting and (j) IHC. Error bars represent SD (p-value < 0.05; n = 8 in each group). (e, g) Expression of Beclin 1, western blotting and (i) IHC in diabetic human heart tissue. Error bars represent SD (n = 8 in each group).

interacts with intracellular cargo tagging and transporting them to autophagosomes for degradation. During the induction of the autophagic process, p62 itself gets degraded. Degradation of p62 and the resultant diminished p62 protein indicates the typical presence of autophagy, while augmented p62 levels indicate autophagic inhibition. In the current analysis, a significant increase of p62 expression was observed in the diabetic cardiac biopsies [Figures 1f, 1h, and 1j].

DISCUSSION

The objective of the study was to assess whether basal cardiac autophagy differs in diabetic subjects undergoing Coronary Artery Bypass Graft (CABG) surgery than in non-T2DM patients. Our results indicate diminished cardiac autophagy in diabetic than in non-diabetic patients. Reduced LC3 II protein levels and a lower LC3 II/I ratio denoted the blockage of autophagosome formation in diabetic human heart. Meanwhile, increased p62 levels indicated a block of its degradation via a defective fusion between autophagosomes and lysosomes. However, a significant difference was not observed in the protein expression of Beclin 1. In summary, cardiac autophagy was found to be diminished in T2DM subjects. This, according to us, is the first report on cardiac autophagic status in T2DM Asian Indian patients.

So far, there is only a sole work published on cardiac autophagy in T2DM human subjects. Elevated levels of autophagy were reported in diabetic patients of the New Zealand population, which is in contrast to our observations.[10] In their study, higher levels of Beclin-1 and LC3 II proteins and a decline in adaptor molecule p62 were found, which indicated a robust formation of autophagosomes in T2DM cardiac tissue. The increased autophagy documented may be due to the increased presence of fatty acids in the heart during T2DM, as suggested by Wu *et al.*[11] Interestingly, our results were contrary to that reported by Munasinghe *et al.*[10] The contradictory observations may be due to the difference in ethnicity of subjects, duration of diabetes, and the number of samples included in the studies. The present study included patients belonging to NYHA class II only, and the differences observed could be due to the varied NYHA class of patients. A major difference between the present study and that by Munasinghe and colleagues is that the latter compared cardiac autophagic levels between T2DM and non-T2DM patient groups with comparable body mass index (BMI) while the BMI status of diabetic patients included in the present study differed significantly (non-T2DM 23.42 ± 0.75, T2DM 25.27 ± 0.49). Diabetes is closely linked with obesity and is directly correlated with high circulating Low-density lipoprotein (LDL), triglycerides, and amino acids in obese patients. These high nutrient status and elevated insulin levels can suppress autophagy in diabetic subjects. A recent exploratory study using peripheral blood mononuclear cells isolated from newly diagnosed and those with long-standing diabetes latter showed reduced expression of LC3 II, parkin, and PTEN-induced kinase 1 (PINK1) (markers of mitophagy).[12] Since there are a limited number of human studies, important studies done in animal models offer support to our findings, though it should be considered with caution. In a mice model of streptozotocin-induced diabetes, suppressed autophagy/mitophagy, along with increased mitochondrial injury and cardiac apoptosis was reported.[13] Few reports in a genetic mice model of type 2 diabetes indicated decreased autophagy with few lysosomes, degenerated mitochondria, and defective autolysosomes in cardiac tissue.[8,14,] These animal studies also support our data showing reduced autophagy in diabetic heart.

There are some inherent limitations associated with the conduct of human studies, which we acknowledge. The first one is the unavailability of healthy human atrial tissue, to serve as a normal control. The atrial biopsy collected from the non-T2DM subjects who underwent CABG are not the actual normal controls. The subjects of both groups had an underlying coronary artery disease and were taking several drugs, which might have altered the results obtained. The patients of both groups included in the study were having similar sex, age, lipid levels, and drugs (except for antidiabetics) while the hyperglycemic status was significantly different. With these normalizations done, our results suggest a reduced cardiac autophagic status in diabetic patients. Whether such diminished autophagy would affect cardiac function in the long term and the mechanisms of such complications, if any, is to be studied in future in a larger sample population.

CONCLUSION

The current study emphasizes the importance of autophagy, as a promising potential area for pharmaceutical intervention, highlighting its potential involvement in mitigating abnormalities existing in diabetic hearts.

Ethical approval

The research/study is approved by the Institutional Ethics Committee at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum SCT/IEC/418/MAY-2012 dated 09/05/2012.

Declaration of patient consent

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

Financial support and sponsorship

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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.

REFERENCES

1. Unnikrishnan AG, Sahay RK, Phadke U, Sharma SK, Shah P, Shukla R, *et al*. Cardiovascular risk in newly diagnosed type 2 diabetes patients in India. PLoS ONE 2022;17:e0263619.
2. Xu J, Sun Y, Gong D, Fan Y. Impact of preexisting diabetes mellitus on cardiovascular and all-cause mortality in patients with atrial fibrillation: A meta-analysis. Front Endocrinol 2022;13:921159.
3. Papatheodorou K, Papanas N, Banach M, Papazoglou D, Edmonds M. Complications of diabetes 2016. J Diabetes Res 2016;2016:6989453.
4. Rajbhandari J, Fernandez CJ, Agarwal M, Yeap BXY, Pappachan JM. Diabetic heart disease: A clinical update. World J Diabetes 2021;12:383–406.
5. Matheus AS de M, Tannus LRM, Cobas RA, Palma CCS, Negrato CA, Gomes M de B. Impact of diabetes on cardiovascular disease: An update. Int J Hypertens 2013;2013:653789.
6. El Hayek MS, Ernande L, Benitah JP, Gomez AM, Pereira L. The role of hyperglycaemia in the development of diabetic cardiomyopathy. Arch Cardiovasc Dis 2021;114:748–60.
7. Wu H, Norton V, Cui K, Zhu B, Bhattacharjee S, Lu YW, *et al*. Diabetes and its cardiovascular complications: Comprehensive network and systematic analyses. Front Cardiovasc Med 2022;9:1–19.
8. Kanamori H, Takemura G, Goto K, Tsujimoto A, Mikami A, Ogino A, *et al*. Autophagic adaptations in diabetic cardiomyopathy differ between type 1 and type 2 diabetes. Autophagy 2015;11:1146–60.
9. Dewanjee S, Vallamkondu J, Kalra RS, John A, Reddy PH, Kandimalla R. Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. Ageing Res Rev 2021;68:101338.
10. Munasinghe PE, Riu F, Dixit P, Edamatsu M, Saxena P, Hamer NS, *et al*. Type-2 diabetes increases autophagy in the human heart through promotion of beclin-1 mediated pathway. Int J Cardiol 2016;202:13–20.
11. Wu Y, Mou X, Sun X. Autophagy may be impelled by collected fatty acids in type 2 diabetic myocardial cells. Int J Cardiol 2017;229:3.
12. Bhansali S, Bhansali A, Walia R, Saikia UN, Dhawan V. Alterations in mitochondrial oxidative stress and mitophagy in subjects with prediabetes and type 2 diabetes mellitus. Front Endocrinol 2017;8:347.
13. Yu W, Gao B, Li N, Wang J, Qiu C, Zhang G, *et al*. Sirt3 deficiency exacerbates diabetic cardiac dysfunction: Role of foxo3a-parkin-mediated mitophagy. Biochim Biophys Acta Mol Basis Dis 2017;1863:1973–83.
14. Kanamori H, Naruse G, Yoshida A, Minatoguchi S, Watanabe T, Kawaguchi T, *et al*. Morphological characteristics in diabetic cardiomyopathy associated with autophagy. J Cardiol 2021;77:30–40.

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Annals of the National Academy of Medical Sciences (India)

Task Force Report

NAMS task force report on Venous thromboembolism

National Academy of Medical Sciences (India), New Delhi, India.*

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PREFACE

There is a perceived gap in the utilization of appropriate prophylaxis for the prevention of venous thromboembolism (VTE) and its guidelines-based management across different strata of the healthcare system. In view of the aging population of India and the increasing burden of non-communicable diseases along with infectious diseases affecting healthcare service delivery, there is a dire need to have an early impact on the incidence and burden of deep venous thrombosis (DVT) and pulmonary embolism (PE) in India.

The measures required to be taken, call for stakeholders to take effective action to create a future for India where:

(a) The population at large is knowledgeable about the risk factors, triggering events, and symptoms of VTE, and individuals feel empowered to talk with their healthcare providers about VTE whenever appropriate.
(b) Evidence-based practices for the screening, prevention, diagnosis, and treatment of DVT/PE are clearly understood and routinely applied by all medical professionals in all settings.
(c) New scientific evidence is constantly being uncovered to fill gaps in knowledge, and these findings are quickly and easily disseminated to the public and put into practice by healthcare professionals.

The overall results of the above action agenda will be to save many lives each year and to reduce the suffering of many more. Implementing the vision for a VTE-free healthcare system, as proposed in this document, will not be an easy task, and undoubtedly, progress will take time. Many barriers will emerge; however, solutions must be found and, more importantly, set into motion sooner than later.

We will need the energy and commitment of individuals, families, the healthcare system, private sector organizations, and government systems at all levels to work together to build solutions that will bring better health to Indians. With these dedicated efforts, we can make this vision a reality. This document has been prepared by a the National Academy of Medical Sciences (India) (NAMS) Task Force and is intended to be a synthesis of a cross-section of available professional society guidelines focused on the prevention and management of VTE for the Government of India to issue suitable guidelines for implementation across the primary healthcare system. This initiative was wholeheartedly supported and encouraged by Prof SK Sarin, President of NAMS, and Prof Umesh Kapil, Secretary of NAMS.

EXECUTIVE SUMMARY

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It can result in significant mortality, morbidity, and healthcare costs. Approximately 30% of patients with symptomatic VTE manifest with PE, and others with DVT. The incidence of DVT in India in the general population is about 1.79 per thousand. More than 50% of post-surgical procedure patients are at risk of developing VTE. The prevailing notion that the incidence of VTE in Asians is less than that in the Western population has been disproved by recent reports.

Increasing age, male gender, trauma, surgery, prolonged hospitalization, malignancy, neurologic disease, central venous catheter, prior superficial vein thrombosis, and varicose veins have been identified as some of the major risk factors for developing VTE. In women, oral contraceptive pill use, pregnancy, and hormone replacement therapy are established as independent risk factors. Some of the important risk factors for surgical patients developing VTE are age, type of surgery, length of procedure, and duration of immobilization.

An extensive review of up-to-date published literature and consensus statements/guidelines was undertaken by a Task Force (TF) of the NAMS, specifically focusing on the prevention and management of VTE. These guidelines have emerged therefrom.

The TF has recommended that consensus be achieved among the various stakeholders in the health of the people of India toward a national Vision, that is, a *VTE-free healthcare system and eventually a VTE-free population.*

The key issues identified by the TF on taking recourse to a systems approach to appropriate prevention and management of VTE include but are not limited to lack of *trained human resources* (healthcare professionals); inadequate *laboratory diagnostic support*; inadequate *availability of pharmaceutical supplies; lack of awareness in the community*; *need for suitable research along with equitable distribution of facilities for the management of VTE.*

Efficient use of healthcare resources is extremely crucial, and diagnostic testing without significant clinical utility is not recommended as per multiple specialty societies, including the current American College of Chest Physicians (ACCP) and American Society of Hematology (ASH) guidelines. Reduction of the risk of VTE can be done by screening patients pre- and postoperatively with accurate diagnostic testing. By diagnosing VTE early, treatment could be provided to halt progression and avoid morbidity and mortality associated with acute VTE. Screening "at-risk" patients is impractical and too expensive to be undertaken outside of clinical trials.

Recommendations have been made to bridge critical gaps/deficiencies as identified, including capacity building. Presently, there is no formal system for the upgradation and verification of skill sets of healthcare professionals in managing and prescribing prophylaxis for VTE. Recommendations have been made by the TF to address this suitably.

There needs to be concerted efforts by policymakers and medical professional bodies to focus attention on the policy gaps and also India-specific recommendations on awareness and training for the prevention of VTE. Consideration may also be given in due course to the identification of high-risk populations for screening and further management as per treatment guidelines.

Thus, there is a need for budgetary allocation of funds and policy initiatives, for assigning research priorities, and a need for convergence of medical specialties, to better serve the Indian population.

A community-based strategy is recommended to create awareness periodically. This is recommended to be steered by a special Committee or Cell that may be established by the Ministry of Health and Family Welfare, with the cooperation of the Indian Society of Hematology & Blood Transfusion, in coordination with the Indian Public Health Association.

After due deliberations on the need for current evidence about thromboprophylaxis practices, the NAMS TF has proposed the conduct of a rapid multicentric cross-sectional study on a pan India basis to ascertain a representative view of the VTE burden and real-world prophylaxis practices. This is intended to be undertaken to develop indigenous VTE risk assessment tools and prophylaxis strategies.

INTRODUCTION

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It can result in significant mortality, morbidity, and healthcare costs. Approximately 30% of patients with symptomatic VTE manifest with PE, and others with DVT. The annual incidence of PE ranges from 39 to 115 per 100,000 population, and for DVT, the incidence ranges from 53 to 162 per 100,000 population. VTE not only disables patients but also prolongs hospital stay, leading to an increase in the cost of treatment.

PE is one of the most common causes of sudden unexplained deaths in hospitalized patients. An early diagnosis and prompt, effective treatment is crucial, as the mortality rate of untreated PE is about 30%, and nearly 30% of untreated DVTs suffer severe swelling or ulceration of the lower limbs. With timely diagnosis and treatment, PE-related deaths are less than 1%. Venous thrombosis (VT) generally lacks specific signs and symptoms, which can lead to a delayed or inaccurate diagnosis and inferior patient outcomes. Hence, awareness creation amongst treating physicians is a key approach to combating VTE.

The most common presentations of VT are DVT of the lower extremity and PE. These can result in significant mortality, morbidity, and healthcare costs. The causes of VT can be divided into two groups: hereditary and acquired, and are often multiple in a given patient. A major theory delineating the pathogenesis of VTE, often called Virchow Triad, proposes that VTE occurs as a result of:

(a) Alterations in blood flow (i.e., stasis)
(b) Vascular endothelial injury
(c) Alterations in the constituents of the blood (i.e., inherited or acquired hypercoagulable state)

A risk factor for thrombosis can be identified in over 80% of patients with VT. Furthermore, there is often more than one factor at play in a given patient. Accordingly, many patients with VTE fulfill most or all of Virchow's triad of stasis, endothelial injury, and hypercoagulability. As examples:

(a) Fifty percent of thrombotic events in patients with inherited thrombophilia are associated with the additional presence of an acquired risk factor (e.g., surgery, prolonged bed rest, pregnancy, oral contraceptives). Some patients have more than one form of inherited thrombophilia or more than one form of acquired thrombophilia and appear to be at even greater risk for thrombosis.
(b) In a population-based study of the prevalence of VTE, 56% of the patients had three or more of the following six risk factors present at the time of VTE: > 48 hours of immobility in the preceding month; hospital admission,

surgery, malignancy, or infection in the past three months; or current hospitalization.

BACKGROUND

The incidence of DVT in India in the general population is about 1.79 per thousand. Approximately 30% of patients with symptomatic VTE have PE, and others have DVT. More than 50% of post-surgical procedure patients are at risk of developing VTE. The risk of VTE following total knee arthroplasty (TKA) is 72.2%, following abdominal or thoracic surgeries is 40%, and following total hip arthroplasty (THA) is 42.9%. Idiopathic DVT is noted in 43% of patients, with 52% of patients developing DVT after a precipitating event and 6% of patients showing recurrence of DVT. The incidence of DVT after major lower limb surgery in Indian patients is comparable to Western data.

Increasing age, male gender, trauma, surgery, prolonged hospitalization, malignancy, neurologic disease, central venous catheter, prior superficial vein thrombosis, and varicose veins have been identified as some of the major risk factors for developing VTE. In women, oral contraceptive pill use, pregnancy, and hormone replacement therapy have been established as independent risk factors. Some of the important risk factors for surgical patients developing VTE are age, type of surgery, length of procedure, and duration of immobilization.

VTE is a major cause of cardiovascular morbidity and mortality and has a known genetic contribution. Genetic risk factors predispose to thrombophilia and play the most important etio-pathogenic role in VTE in people younger than 50 years. At least one inherited risk factor could be found in about half of the cases with a first episode of idiopathic VTE. A revolutionary contribution to the genetic background of VTE was brought by the achievements of the genome-wide association studies which analyze the association of a huge number of polymorphisms in a large sample.

The detection of hereditary thrombophilia has an impact on the management of the anticoagulation in children with purpura fulminans, and pregnant women at risk of VTE and may be useful in the assessment of the risk for recurrent thrombosis in patients presenting an episode of VTE at a young age (<40 years) and in cases with positive family history regarding thrombosis. Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone. Patients with inherited thrombophilia can often be identified by coagulation experts on the basis of the patient's personal and family history of VTE, even without knowledge of test results. Factors associated with the presence of an inherited thrombophilia include VTE at a young age (often considered to be less than 40–50 years of age); a strong family history of VTE, VTE in conjunction with weak provoking factors at a young age; recurrent VTE events; and VTE in an unusual site such as the central nervous system or splanchnic veins.

While acute precipitants and clinical risk factors are often the focus of determining the cause of VTE, a small minority of patients have a mutation in a limited number of genes leading to an inherited thrombophilia. To that end, hypercoagulability and/or genetic testing can identify some uncommon genetic mutations such as factor V Leiden, antithrombin deficiency, protein C or S deficiency, or a prothrombin gene mutation. However, standard testing is usually unrevealing, with mutations present in only about 5% of the general population. Thus, for many patients with VTE, no clear precipitant or risk factor is ever identified.

When a patient experiences a VTE event without an acute precipitant such as recent surgery, immobilization, or trauma, one often considers clinical risk factors and contemplates testing for a handful of known monogenic thrombophilia disorders. However, the use of thrombophilia testing has fallen out of favor in part due to the low yield in terms of the number of patients identified. Given the genetic backdrop, the studies done in India have certain limitations, which include but are not limited to sample size being quite limited and the studies having been done in the context of VTE with some other co-morbidity. Further, mostly targeted polymorphisms have been analyzed, with no study involving a global approach at the genome-wide level. Indian data depict that the established thrombophilia genetic markers Factor V Leiden and Prothrombin G20210A have a limited role from the Indian perspective. Several studies have shown the role of Factor V Leiden in VTE risk but only with certain comorbidity in the Indian population. In recently published landmark studies regarding the genetics of VTE in the journals *Blood* and *Nature Genetics*, in contrast to uncommon thrombophilias, genome-wide association studies were used to identify 297 independent single nucleotide polymorphisms associated with VTE, from which a polygenic risk score was developed. These data demonstrate that consideration of broader polygenic risk can identify a much larger proportion of patients at risk for VTE and is a stronger predictor than many chronic clinical risk factors. We need to extend these kinds of studies in the Indian population to get a comprehensive genetic view on VTE.

Preventing fatal PE is the primary goal of anticoagulant prophylaxis for VTE. Prevention of VTE also avoids significant post-VTE morbidity. Conditions that can develop despite appropriate treatment of VTE are post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension

(CTEPH), and post-PE syndrome. The prevalence and potential severity of these conditions must be considered when determining the potential benefits of preventing VTE. Averting sudden death and reducing post-PE morbidity are not the only benefits of anticoagulant prophylaxis, and prevention of VTE is important to avoid patient discomfort, anticoagulant treatments and their associated risks, specialist visits, delays in procedures, and the potential for additional testing.

Terms of Reference for the Task Force

The Executive Council of the National Academy of Medical Sciences (India) had assigned the following terms of reference for the Task Force (TF) on VTE in April 2022. All recommendations of the TF were to be placed before the Executive Council of the NAMS by the end of July 2022, for approval and onward submission to the Government of India.

(a) The TF was required to make recommendations to the Government of India for the prevention and control of VT and embolism in India at the health policy and implementation levels.
(b) The TF would prepare a "White Paper" which may include the existing morbidity and mortality status, if available due to VT and thromboembolism.
(c) The TF would identify existing lacunae and deficiencies in the thematic area and make recommendations to address these.

METHODOLOGY

On receipt of the terms of reference from the NAMS Executive Council, the TF was convened under the Chairmanship of Lt Gen Velu Nair with membership from a cross-section of domain experts enlisted in the task force.

Through a process of discussions in the virtual mode, a consensus was reached among the members of the TF, on the methodology to be adopted for developing ibid guidelines. The task at hand was divided into sections, and members allocated the sections based on their specific domain expertise.

An extensive literature review was undertaken using the websites PubMed and Google Scholar using the search terms "Venous Thromboembolism" AND "Management" AND "Prophylaxis" AND "Prevention" for English language documents, with a preference for review articles, clinical trials, consensus statements and guidelines. Professional society websites were browsed for the latest guidelines and consensus statements. Contribution from the scientific committee was requested through personal communication from the Chairperson to all members of the Indian Society for Hematology. Thus, almost all published work from India was reviewed along with all similar international work on VTE. A synthesis of the obtained literature was prepared and deliberated upon by the TF.

A series of weekly meetings were conducted in virtual mode for reviewing the progress being made and to discuss the allocated sections of the White Paper. Minutes of the meetings were prepared and circulated within the TF for information and guidance.

While developing the document, the PICO framework was relied upon to define the various at-risk patient groups and recommend the interventions required. Iterations of the document developed with the contributions of the members were circulated and discussed sequentially over the term of the TF. This modification of the Delphi technique was essential for the process of eventual consensus, as the guidelines required reference to the latest evidence and conformity with professional society guidelines, keeping in view the requirements of the country and the best interests of the patient population.

SITUATIONAL ANALYSIS

Current situation in India

The prevailing notion that the incidence of VTE in Asians is less than that in the Western population has been disproved by recent reports. The incidence of postoperative DVT in Indian patients undergoing major lower limb surgery is as high as seen in the Western world (43.2% and 60% of patients in the groups with and without prophylaxis, respectively). In a study covering 549 patients, acute DVT without PE, acute DVT with PE, and PE alone were reported in 64%, 23%, and 13% of patients, respectively. The mean age was 47 (±16) years, and 70% of the patients were males. A history of DVT (34%), surgery including orthopedic surgery (28%), trauma (16%), and immobilization >3 days (14%) were the most common risk factors for VTE. Hypertension (25%), diabetes (19%), and neurological disease (other than stroke) (8%) were the most common comorbidities. Most (94%) were treated with heparin alone (82%) or fondaparinux (2%) for initial anticoagulation; low molecular weight heparin alone (5%) or warfarin/acenocoumarol (76%) for long-term anticoagulation.

In the MEGA study, patients who were tested for thrombophilia after a first episode of VTE were analyzed for the outcomes of testing and for reduction in the risk of recurrence. It was observed that despite thrombophilia testing at the time of first VTE, 35% of patients had recurrent VTE during follow-up compared with 30% of patients who did not have recurrent VTE. This indicated that testing at the time of the first VTE did not reduce the risk of recurrence of VTE. Testing for inherited thrombophilia does not reduce the recurrence of VT. The recurrence risk for VTE is determined by the clinical situation (e.g., provoked vs. unprovoked) along

with non-Mendelian risk factors (e.g., body mass index and age) rather than the inherited thrombophilia panel.

The proportion of Indian patients at risk for VTE (53.6%) was similar to that of the global patients at risk for VTE (51.8%). However, ENDORSE data showed that globally, 50.2% of at-risk patients received ACCP-recommended prophylaxis, whereas in India, only 17.4% of at-risk patients received such prophylaxis. Among at-risk patients, 18.5% of surgical and 22.4% of medical patients received any VTE prophylaxis. Similarly, 16.3% of surgical and 19.1% of medical patients received ACCP-recommended thromboprophylaxis. In a prospective registry on venous thromboembolic events (PROVE) conducted in 19 countries, 3,526 patients with symptomatic DVT were enrolled, out of which 667 were from India. Prior VTE prophylaxis had been given to only 5% of enrolled Indian patients compared to 12% in the overall PROVE population.

Thus, thromboprophylaxis in India may not be routine practice in most institutions other than tertiary care hospitals. This large population of patients at-risk for VTE identifies an unmet need. There is thus a need to understand the incidence and prevalence of VTE in various medical and surgical settings better.

The most common reasons for the underutilization of pharmacological thromboprophylaxis are varied and often include (but are not limited to) lack of knowledge, ignorance, fear of bleeding, and any contraindication to anticoagulants. This can be interpreted to imply poor awareness of the risks of VTE in patients. The current paradigm for diagnosis and management of thrombosis has provided a variety of tools. However, it has also left some unanswered questions, such as methods for risk stratification to predict the risk for recurrent VTE requires aggressive anticoagulation.

Current infrastructure, facilities, technologies, policies, programs, etc., in India in the context of the problem of VTE

The ICMR has recently launched a National Hospital-based Registry on Venous Thromboembolic Disorders (i-RegVeD) with the aim of establishing a nationwide surveillance network through selected hospitals for the collection of data for generating evidence on VTE prevalence. This will be of relevance for planning suitable, calibrated responses and strengthening healthcare facilities across different treatment settings. This registry is based on a standard reporting framework with data capture using electronic information technology for timely analytics of patterns of disease distribution, treatment, and outcomes of VTE patients. The data are intended to be used for relevant and appropriate research and innovation, including identifying risk factors for VTE disease. It is anticipated that the registry shall contribute to improving patient management for VTE and related manifestations, and also guide policy and health planning in the future.

Presently, there is no formal campaign or system for the upgradation and verification of skill sets of healthcare professionals in managing and prescribing prophylaxis for VTE. Online consensus statements and guidelines are available from international professional societies which can be accessed by any interested healthcare professional; however, there is no focused initiative to regulate or standardize the approach across the Indian healthcare system.

Across the healthcare hierarchy in India, in the governmental public healthcare system, the availability of laboratory diagnostic capabilities and pharmaceutical supplies for managing, monitoring, and providing prophylaxis for VTE is not uniform. This problem is especially acute at the peripheral levels of the healthcare system, from the district hospital downward, compounded by the problem of a relative lack of trained and specialist human resources. In the private healthcare system, which accounts for the majority of tertiary healthcare sought by the Indian population with considerable out-of-pocket expense being incurred, the management of VTE among other conditions is dependent mostly on perceived commercial considerations.

With the Indian Public Health Standards being formulated to address the human resource and equipment needs across a standard template and scale, in an ideal scenario, the requirements of trained human resources have been addressed. However, ground reality indicates otherwise, with scorecards from the Niti Aayog revealing the realities. So far, there has been no comprehensive assessment of the competence per se of such trained personnel across a spectrum of clinical domains, leave alone VTE as a focus area.

The National Essential Diagnostics List was promulgated in 2019, with states being empowered to augment the list and provide equipment to suit their specific inclinations or areas of focus in disease and health management. This guideline serves to provide a generic template for states to plan service delivery. The framework for VTE management thus can capture the parameters outlined in this document to provide support to states in planning their response.

Key issues/gaps identified in the context of VTE

These include but are not limited to the following:

(a) *Trained human resources* (healthcare professionals): Availability of an adequate number of personnel adequately oriented toward VTE and skilled suitably to manage VTE in different clinical settings and provide thromboprophylaxis as required.
(b) *Laboratory diagnostic support*: Facilities that are commensurate with the basic minimum requirements to

screen for, diagnose, and manage VTE at different levels of the healthcare system.

(c) *Availability of pharmaceutical supplies*: Appropriate drug stocking and replenishment systems, including required logistics, for the healthcare facilities to provide appropriate care and manage VTE at different levels of the healthcare system.

(d) *Awareness in the community*: Awareness about VTE and the risks posed to health. To inculcate required healthcare-seeking behavior with specific reference to prevention and early recognition.

(e) *Research and future direction*: To study the incidence and prevalence in the Indian population and undertake research to identify suitable protocols for screening, diagnosis, and management appropriate for the country.

(f) *Equitable distribution of facilities for management of VTE*: Availability of healthcare facilities that are adequate and accessible, affordable and sustainable, appropriate and acceptable in the geographical vicinity of at-risk population clusters.

RECOMMENDATIONS

Vision

It is recommended that consensus be achieved amongst the various stakeholders in the health of the people of India toward a national vision, that is, a *venous thromboembolism-free healthcare system and eventually a VTE-free population.*

The National Academy of Medical Sciences (India) envisions a healthcare system in India, both in the public sector and the private healthcare system, in which a collaborative, multidisciplinary approach will ensure a VTE-free population and a VTE-free healthcare system through standardized, evolving, evidence-based guidelines, to deliver sustainable, high-quality, affordable, and patient-focused care.

Further to National Health Policy 2017, the goal of a VTE-free healthcare system and VTE-free population, being proposed by the National Academy of Medical Sciences (India), is for the attainment of the highest possible level of health and well-being for all, at all ages, through a preventive and promotive healthcare orientation, and universal access to good-quality healthcare services without anyone having to face financial hardship as a consequence, by eliminating incidence of VTE amongst other initiatives of the Government of India.

Recommendations made to bridge critical gaps/ deficiencies

Presently, thromboprophylaxis as an approach in the management of patient populations at risk is underutilized in India; hence, measures to overcome this unmet need are warranted [Annexure 1]. There is also a need to have focused, simple guidelines with algorithms and charts for care providers for early diagnosis of VTE and prompt management in different VTE settings (including at the community level). In addition [Annexures 2–5], it is important to increase awareness among treating physicians regarding guidelines on testing for VTE, while avoiding unnecessary testing. These need to be undertaken in the backdrop of promoting health literacy on a broader palette for the larger population [Annexure 6].

The various recommendations of the NAMS TF include but are not limited to the following Table 1

Table 1: VTE : Key recommendations of NAMS TF

Key Focus areas/ Gaps	Action Recommended
Trained human resources	Periodically updated online training modules be made available for healthcare personnel nationally, with regional mentoring by medical institutions of eminence.
Laboratory diagnostic support	The National Essential Diagnostics List 2019 and the relevant facility-wise Indian Public Health Standards be utilized to standardize the laboratory requirements for basic minimum requirements to screen for, diagnose, and manage VTE at different levels of the healthcare system.
Availability of pharmaceutical supplies	States be advised to refine their Essential Drugs List to include/retain appropriate drugs and ensure stocking and replenishment systems, including required logistics, for their healthcare facilities to provide appropriate care and manage VTE at different levels of the healthcare system.
Awareness in the community	Periodic campaigns be launched regionally with standard content about VTE and the risks posed to individual health. Behavior change campaigns may also be promoted to inculcate required healthcare-seeking behavior with specific reference to prevention and early recognition of VTE.
Research and future direction	Funding be made available to study the incidence and prevalence in the Indian population and undertake research to identify suitable protocols for screening, diagnosis, and management appropriate for the country.
Equitable distribution of facilities for the management of VTE	State governments may be advised to plan for the availability of healthcare facilities that are adequate and accessible, affordable and sustainable, appropriate and acceptable in the geographical vicinity of at-risk population clusters.

NAMS: National Academy of Medical Sciences (India); TF: Task Force; VTE: venous thromboembolism.

WAY FORWARD

The NAMS TF, after due deliberations on the need for current evidence about thromboprophylaxis practices has proposed the conduct of a rapid multicentric cross-sectional study on a pan India basis to ascertain a representative view of the VTE burden and real-world prophylaxis practices. This is intended to be undertaken to develop indigenous VTE risk assessment tools and prophylaxis strategies.

Efficient use of healthcare resources is extremely crucial, and diagnostic testing without significant clinical utility is not recommended as per multiple specialty societies, including the current ACCP and ASH guidelines. There are two major ways to reduce the risk of VTE. The first is to screen patients pre- and postoperatively with accurate diagnostic testing. By diagnosing VTE early, treatment could be provided to halt progression and avoid morbidity and mortality associated with acute VTE. Unfortunately, contrast venography is expensive, painful, and impractical to perform outside of clinical studies. Less invasive studies, such as venous ultrasonography (US), are less sensitive in asymptomatic patients than in symptomatic patients. Screening "at-risk" patients is impractical and too expensive to be undertaken outside of clinical trials.

The second approach is to undertake measures to prevent VTE. General measures, such as encouraging early ambulation after surgery, can be adopted universally without harm. In addition, active prophylaxis with either mechanical or pharmacologic means has been proven to lower the risk of VTE. Mechanical prophylaxis refers to devices, such as graduated compression stockings and intermittent pneumatic compression devices, which decrease venous stasis in the lower extremities. Mechanical prophylaxis does not carry a risk of bleeding but can be uncomfortable, and prolonged use can lead to skin breakdown and other cutaneous complications.

Suggested policy activities and advocacy for policy makers

DVT and PE have been recognized to be major public health problems across the world today. Clinicians and hospitalists are assumed to know how to reduce the morbidity and mortality resulting from DVT/PE, yet it is perceived that this knowledge is mostly not being applied systematically at the population level or even uniformly across healthcare facilities [Annexure 7]. Without a concerted effort to stem the public health crisis that unrecognized VTE poses, the incidence and burden of these diseases will only grow larger as the population in India ages.

The key actions required to be taken by policymakers in various settings have been given in Annexures 8, 9.

The recently launched ICMR registry for VTE is recommended to be actively promoted for voluntary participation by healthcare facilities across the country.

Recommendations for healthcare professionals

It is proposed that a focused, continuing professional education campaign be conceptualized and launched, targeting healthcare professionals. An outline of such an educational module is given in Annexure 8. This is proposed to be done in tandem with a suitably structured patient and community-focused campaign.

Suggestions to create awareness among general public, NGOs, and community stakeholders

A community-based strategy is recommended to create awareness periodically [Annexure 6]. This is recommended to be steered by a special committee or cell that may be established by the Ministry of Health and Family Welfare, with the cooperation of the Indian Society of Hematology in coordination with the Indian Public Health Association.

The specific areas of focus of community-focused campaigns may include but not be limited to the following:

(a) All about healthcare-associated VTE, including risk factors
(b) All about blood clots and travel
(c) All about blood clots and pregnancy
(d) All about blood clots and cancers.

The intent would be to provide information as appropriate, with a regional flavor, and to promote healthcare-seeking behavior on a broader palette of behavior change communication aimed at health literacy.

Areas of future research

In the current scenario, establishing a thrombophilia testing setup in the Indian population is difficult as there is a relative lack of well-designed, population-based studies that could associate genetic risk factors with disease prevalence. A large-scale population-based genome-wide association study is thus essential to identify the genetic associations with VTE. Details are further outlined in Annexure 10.

DOCUMENTS REFERRED BY THE TF

Technical documents from various professional societies, such as the ASH, ACCP, etc., were perused. Apart from these, landmark peer-reviewed articles over the past two decades were also reviewed.

"Suggested further reading," includes some of the relevant articles/documents referred to by the TF.

ANNEXURE 1

Annexure 1 briefly outlines the task force VTE prophylaxis recommendations through Tables I–XV appended below

VTE PROPHYLAXIS: RECOMMENDATIONS

Table I: VTE prophylaxis recommendations in medical patients

Medical patients			
Risk stratification	**Score**	**Choice of VTE prophylaxis**	**Remarks**
IMPROVE VTE[1] **IMPROVE Bleeding Risk Score[2]**	IMPROVE VTE score < 3	Nil	
	IMPROVE VTE score ≥ 3 & IMPROVE Bleeding risk score < 7	LMWH UFH or Fondaparinaux	If • CrCl < 30 mL/min or • cost constraints then, UFH can be used as an alternative • LMWH is preferred over DOAC
	IMPROVE VTE score ≥ 3 & IMPROVE Bleeding risk score ≥ 7	Mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression	Switch to pharmacologic prophylaxis once the bleeding risks return to normal.

IMPROVE: International Medical Prevention Registry on Venous Thromboembolism; VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; CrCl: Creatinine clearance; DOAC: Direct oral anticoagulant.
Source: [1]Spyropoulos AC, *et al.* Chest 2011 Sep;140(3):706-714; [2]Decousus H, *et al.* Chest 2011 Jan;139(1):69-79.

Duration:

- For the period of hospitalization (UFH/LMWH) or
- Extended prophylaxis up to 40 days (Rivaroxaban)

Table II: VTE prophylaxis recommendations in general surgery patients

Surgical patients			
Risk stratification	**Score**	**Choice of VTE prophylaxis**	**Remarks**
Caprini score[1]	**<0** At **very low risk** for VTE	• Early ambulation is recommended. • No specific pharmacologic or mechanical prophylaxis	
	1–2 At **low risk** for VTE	• Mechanical prophylaxis, preferably with intermittent pneumatic compression	
	3–4 At **moderate risk** for VTE	• LMWH/UFH or • intermittent pneumatic compression	
	≥5 At **high risk** for VTE	• Combined prophylaxis	
Duration		• Extended antithrombotic prophylaxis (6 weeks) is preferred over short-term antithrombotic prophylaxis	LMWH or UFH preferred
		• Early or delayed antithrombotic prophylaxis (>12 hours) is acceptable.	
In case of high bleeding risk		• Mechanical prophylaxis • IVC filters are not to be used	

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; IVC: Inferior vena cava.
Source: Adapted from Caprini JA, *et al.* Semin Thromb Hemost 1991;17 Suppl 3:304-12. PMID: 1754886.

Table III: VTE prophylaxis recommendations in patients posted for orthopedic surgery

Orthopedic Surgical Cases			
Procedure	**Duration**	**Options**	**Remarks**
Total hip arthroplasty or TKA	Minimum of 10–14 days	Any one of LMWH Fondaparinux Apixaban Dabigatran Rivaroxaban, UFH Vit K antagonist Aspirin	Direct oral anticoagulants (DOACs) are preferred over low-molecular-weight heparin
Hip fracture repair	Minimum of 10–14 days	Any one of LMWH UFH Fondaparinaux Vit K antagonist Aspirin Intermittent pneumatic compression	
Arthroscopic knee surgery Foot or ankle surgery Upper limb surgery	6–12 hours after surgery for 14 days (Prophylaxis recommended only if any of the conditions mentioned under Remarks column apply)	LMWH	• if total anesthesia time is >90 minutes • person's risk of VTE outweighs their risk of bleeding • Immobilization is required postoperative period

TKA: Total Knee Arthroplasty; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

- Extended thromboprophylaxis is recommended in the outpatient period for up to 35 days from the day of surgery rather than for only 10–14 days.
- Dual prophylaxis may be preferred over mono-prophylaxis.
- For asymptomatic patients following major orthopedic surgery, Doppler ultrasound screening before hospital discharge is not needed.

Table IV: VTE prophylaxis recommendations in patients presenting with polytrauma

POLYTRAUMA	
Category	**Recommendation**
Major trauma and low to moderate risk for bleeding	LMWH or UFH
High bleeding risk	Do not use pharmacologic prophylaxis

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VTE: venous thromboembolism.

Table V: VTE prophylaxis recommendations in patients presenting with acute spinal cord injuries

ACUTE SPINAL CORD INJURIES	
Recommendation	**Remarks**
Mechanical prophylaxis And/Or pharmacological prophylaxis	Consider adding pharmacological VTE prophylaxis with LMWH 24 hours after initial admission if no surgery is planned in the next 24–48 hours, if the benefit of reducing the risk of VTE outweighs the risk of bleeding.
	Continue VTE prophylaxis in people with spinal injury for 30 days or until the person is mobile or discharged, whichever is sooner

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin.

Table VI: VTE prophylaxis recommendations in patients admitted for urological surgery

UROLOGIC SURGERY	
Category	**Recommendation**
Transurethral resection of the prostate	Do not use pharmacologic prophylaxis Instead, consider mechanical prophylaxis
Radical prostatectomy	
An extended node dissection and/or open radical prostatectomy	May consider LMWH/UFH
VTE risk factors	May consider LMWH/UFH

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VTE: venous thromboembolism.

Table VII: VTE prophylaxis recommendations in patients admitted for vascular surgery	
VASCULAR SURGERY	
Category	**Recommendation**
In routine surgeries	Do not use pharmacologic prophylaxis Instead, consider mechanical prophylaxis
Open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, when risk of VTE outweighs risk of bleeding	Consider pharmacological VTE prophylaxis with LMWH for a minimum of 7 days.
VTE: Venous thromboembolism; LMWH: Low molecular weight heparin.	

Table VIII: VTE prophylaxis recommendations in patients admitted for laparoscopic surgery	
LAPAROSCOPIC SURGERY	
Category	**Recommendation**
In routine surgeries	Do not use pharmacological prophylaxis Instead, consider mechanical prophylaxis
If risk factors for VTE are present	Consider pharmacological prophylaxis
VTE: Venous thromboembolism.	

Table IX: VTE prophylaxis recommendations in patients admitted for gynecological surgery	
GYNECOLOGICAL SURGERY	
Category	**Recommendations**
Major surgery	LMWH or UFH
LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.	

Table X: VTE prophylaxis recommendations in patients admitted for neurosurgery	
NEUROSURGERY	
Recommendation	**Remarks**
In routine, mechanical prophylaxis is indicated	Do not use pharmacological prophylaxis routinely.
If prolonged immobilization is anticipated, then plan for post-operative pharmacologic prophylaxis	

Table XI: VTE prophylaxis recommendations in patients admitted for bariatric surgery	
BARIATRIC SURGERY	
Recommendation	**Remarks**
LMWH or UFH or Intermittent pneumatic compression	Duration: for 10–15 days Dual prophylaxis if risk factors +, • age > 55 years • BMI > 55 • history of VTE • OSA • hypercoagulability • PAH
OSA: Obstructive sleep apnea; PAH: Pulmonary arterial hypertension; BMI: Body mass index; VTE: Venous thromboembolism; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin.	

Table XII: VTE prophylaxis recommendations in oncological patients

MALIGNANCY		
Category	**Prophylaxis**	**Remarks**
Hospitalized cancer patients	LMWH or UFH	Till discharge
Cancer patients undergoing surgery	LMWH or Fondaparinaux or Mechanical prophylaxis (only if the risk of bleed is high)	Should be prescribed pharmacological prophylaxis in the postoperative period
Ambulatory patients (Risk stratification by Khorana score)	If score < 2 No VTE prophylaxis	If receiving chemotherapy and at low risk for thrombosis
	If score ≥ 2 Rivaroxaban or Apixaban	Those who are receiving systemic anticancer therapy and are at intermediate-to-high risk of VTE
Multiple myeloma patients	Aspirin or low-dose Vit K Antagonists or LMWH	For those receiving lenalidomide, thalidomide, or pomalidomide-based regimens
Outpatients with cancer and indwelling central venous catheters	No role of routine prophylaxis with LMWH or UFH or Vit K Antagonists	

VTE: Venous thromboembolism; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin.
Source: Adapted from Dutia M *et al.* Cancer. 2012 Jul 15;118(14):3468-76.

Table XIII: VTE prophylaxis recommendations in long distance travellers (travel time > 4 hours)

LONG-DISTANCE TRAVELERS (travel time > 4 hours)	
No risk factors for VTE	**High VTE risk**
	Recent surgery, h/o VTE, postpartum, active malignancy, hormone replacement therapy, obesity, or pregnancy
No prophylaxis recommended	Graduated compression stockings or LMWH or Aspirin

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin.

Table XIV: VTE prophylaxis recommendations in pregnancy

PREGNANCY	
Category	**Recommendation**
Women undergoing assisted reproductive therapy	Routine prophylaxis **Not** recommended
If they develop severe ovarian hyperstimulation syndrome	Prophylactic antithrombotic therapy with aspirin/LMWH recommended
Women who have a history of VTE	Postpartum anticoagulant prophylaxis recommended
Women with a history of VTE that was unprovoked or associated with a hormonal risk factor	Antepartum anticoagulant prophylaxis recommended

(*continued*)

Table XIV: Continued

Pregnant women having	Family history of VTE		
	None	With family history	Regardless of family history
Antithrombin deficiency		Postpartum prophylaxis	
Antithrombin deficiency or are homozygous for prothrombin mutation	Antepartum prophylaxis to prevent a first VTE event **Not** recommended		
Heterozygous for Factor V Leiden or prothrombin mutation		Postpartum prophylaxis **Not** recommended	
Heterozygous for Factor V Leiden or prothrombin mutation/protein C or S deficiency			Antepartum prophylaxis to prevent a first VTE event **Not** recommended
Heterozygous for the factor V Leiden mutation or prothrombin mutation or who have antithrombin, protein C, or protein S deficiency	Postpartum prophylaxis **Not** recommended		
protein C, or protein S deficiency,		Postpartum prophylaxis with LMWH ×6 weeks	
Antithrombin deficiency, and for those who are homozygous for Factor V Leiden mutation or have combined thrombophilias		Antepartum prophylaxis	Antepartum prophylaxis
combined thrombophilias or are homozygous for Factor V Leiden mutation or prothrombin mutation			Postpartum prophylaxis with LMWH or Vit K antagonists targeted at an INR of 2.0–3.0 for 6 weeks

Note: Wherever not specifically mentioned, no anticoagulation is recommended.
VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; INR: International normalized ratio.

Table XV: VTE prophylaxis by health care workers are different levels of health care practice

Level of healthcare	Prophylaxis of VTE by HealthCare Workers					
	Patient/Family members	ASHA	ANM	Community Health Officer	Medical officer	Specialist
Community Level	Follow treatment as prescribed	Advise patients to follow treatment as prescribed				
Health & Wellness Centre				Advise patients to follow treatment as prescribed		
Primary Health Centre					Advise patients to follow treatment as prescribed Counsel on medication compliance	
Community Health Centre						Prescribe treatment as per guidelines
District Hospital						
Medical College Hospital						

VTE: venous thromboembolism; ASHA: Accredited Social Health Activist; ANM: Auxiliary Nurse Midwife.

ANNEXURE 2

VTE MANAGEMENT: RECOMMENDATIONS

Annexure 2 briefly outlines the task force VTE treatment recommendations through Tables I–XIV and Figure 1 appended below

Table I: Indications for outpatient management of VTE in settings

Outpatient Treatment (Home based)		
In DVT	Uncomplicated DVT and PE at low risk for complications	Uncomplicated DVT – No comorbid illness requiring admission – Low bleeding risk – No evidence of limb-threatening DVT – No Phlegmasia cerulea dolens, or limb ischemia
In PE	HESTIA[1] score 0	Low-risk PE + No RV dysfunction + Normal cardiac biomarker

DVT: Deep vein thrombosis; PE: Pulmonary embolism; RV: Right ventricle; VTE: venous thromboembolism.
Source: Adapted from [1]Zondag W, *et al.* J Thromb Haemost 2011 Aug;9(8):1500-7.

Table II: Preferred anticoagulant agent for VTE management

Choice of anticoagulant			
DOAC	**VKA preferred**	**UFH**	**LMWH**
Preferred agent in all settings other than those discussed under alternative agents	• Moderate to severe liver disease • eGFR < 30mL/min • APLA • Inhibitors or inducers of P-gp or • Strong inhibitors or inducers of CYP3A4 • Breast feeding mother • Financial constraints	• e GFR < 15 mL/min; • PE with hemodynamic instability	• Bridge for – VKA – Dabigatran – Edoxaban; Pregnancy; • APLA • Malignancy if DOAC cannot be used

eGFR: estimated glomerular filtration rate; APLA: Antiphospholipid syndrome; DOAC: Direct oral anticoagulants; VKA: Vitamin K antagonists; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; VTE: venous thromboembolism.

Table III: Recommended duration of anticoagulation in VTE

Duration of anticoagulation		
Category	**Primary phase**	**Secondary Phase**
VTE provoked by transient risk factors	3 months	
VTE provoked by chronic (persistent) risk factors	3 months	Indefinite anticoagulation with periodic assessment (annual) for risk factors of bleeding and risk factors for VTE
Unprovoked VTE	3 months	Indefinite anticoagulation with periodic assessment for risk factors of bleeding
HAS-BLED score ≥ 4		Avoid indefinite anticoagulation

VTE: Venous thromboembolism.

Remarks

- **Secondary treatment phase**
  Vit K Antagonist @ INR 2-3 (A)
  Low-dose DOAC (Apixaban/Rivaroxaban) is as good as standard dose DOAC
- Aspirin 75 mg or 150 mg daily in people who decline extended anticoagulation treatment or patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy.
- Routine use of prognostic scores HERDOO2, Vienna and DASH scores, D Dimer testing, or ultrasound to detect residual vein thrombosis is no longer recommended in unprovoked VTE.

APPROACH TO MANAGEMENT

Annexure 2

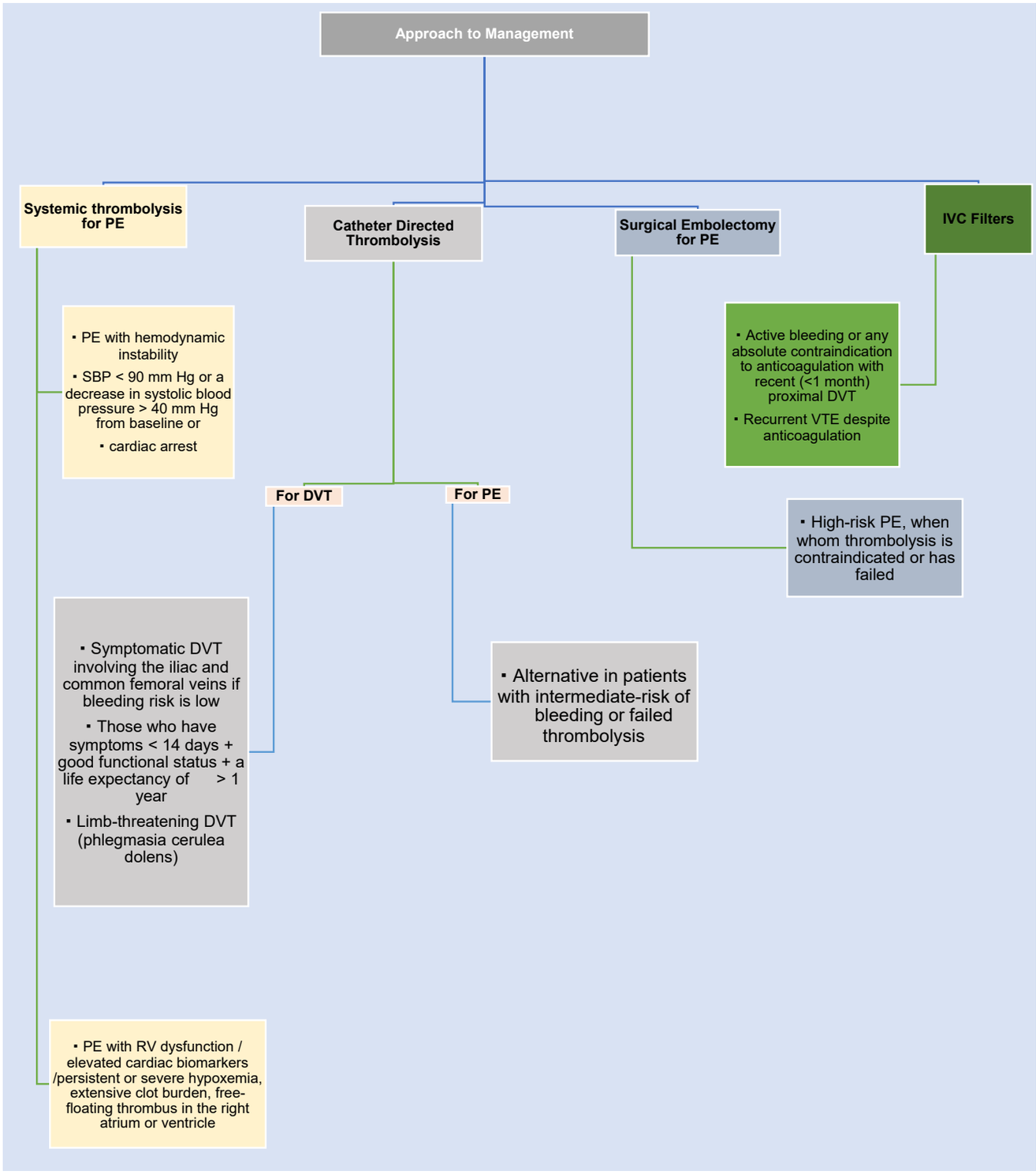

Figure 1: Approach to management of pulmonary embolism
DVT: Deep venous thrombosis; IVC: Inferior vena cava; PE: Pulmonary embolism; VTE: Venous thromboembolism; SBP: Systolic blood pressure.

Table IV: Recommendations for VTE treatment in pregnancy

PREGNANCY	
Drug of choice	**LMWH over UFH**
As soon as the patient is in labor, heparin should be stopped immediately	
⇩	
Spinal/epidural anesthesia or analgesia should be used 12 hours after prophylactic and 24 hours after therapeutic LMWH, while these techniques can be used 6 hours after stopping conventional heparin.	
⇩	
Heparins should be restarted at least 4–6 hours after removal of an epidural catheter.	
⇩	
At discharge, the patient may be transitioned to VKAs (safe during breastfeeding).	
⇩	
Total duration of anticoagulation for pregnancy associated DVT should be at least 3 months of anticoagulants or 6 weeks postpartum whichever is later.	

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VKAs: Vitamin K antagonist; VTE: venous thromboembolism; DVT: Deep venous thrombosis.

Table V: Recommendations for VTE treatment in malignancy

MALIGNANCY	
DOAC preferred	Apixaban Rivaroxaban Edoxaban
if DOAC cannot be used	LMWH
Alternative if patient does not accept injectable therapy	Vitamin K Antagonist
Duration	At least 6 months; Reassess the risk of recurrent VTE and bleeding before deciding on continued anticoagulation.

DOAC: direct oral anticoagulant; LMWH: Low molecular weight heparin; VTE: Venous thromboembolism.

Table VI: Recommendations for cerebral venous thrombosis treatment

CEREBRAL VENOUS THROMBOSIS		
Initial phase	**Primary & secondary phase**	**Duration**
LMWH or UFH	Warfarin or DOAC	3 months if transient risk factors
		At least 6 months if unprovoked
		Indefinite if persistent hypercoagulability identified

DOAC: direct oral anticoagulant; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

Table VII: Recommendations for splanchnic venous thrombosis (SVT) treatment

SPLANCHNIC VEIN THROMBOSIS	
Acute SVT	**Incidental chronic SVT**
• DOACs should be considered in noncirrhotic patients • DOACs are contraindicated in Child-Pugh class C liver disease and for rivaroxaban in class B and C liver disease. • LMWH or VKAs if contraindications to DOACs. • Indefinite anticoagulation: unprovoked or persistent risk factors • Prophylactic banding should be instituted in cirrhotic patients to decrease variceal bleeding	Anticoagulation if malignancy or extensive SVT

SVT: Splanchnic venous thrombosis; DOAC: direct oral anticoagulant; LMWH: Low molecular weight heparin; VKA: Vitamin K antagonists.

Table VIII: Recommendations for VTE in Anti Phospholipid Antibody syndrome (APLA) syndrome

APLA (Anti Phospholipid Antibody syndrome)	
Triple positive APLA or Arterial thrombosis or patients with small vessel thrombosis or aPL-related cardiac valvular disease	Vit K Antagonists preferred over DOAC Indefinite anticoagulation.

APLA: Anti Phospholipid Antibody syndrome; DOAC: direct oral anticoagulant.

Table IX: Recommendations for superficial venous thrombosis treatment (SfVT)

SUPERFICIAL VEIN THROMBOSIS	
Anticoagulation if	**Options:**
• SfVT > 5 cm • proximity to SFJ • other risk factors for VTE – male sex – >65 years – cancer – systemic inflammation – previous VTE – no contraindications to anticoagulation	Fondaparinux 2.5 mg SC OD × 45 days Rivaroxaban 10 mg OD or Enoxaparin 40 mg OD × 30 days

SfVT: Superficial venous thrombosis; SFJ: Saphenofemoral junction; VTE : Venous thromboembolism; SC: subcutaneously; OD: once daily.

Table X: Recommendations for isolated distal deep venous thrombosis treatment

ISOLATED DISTAL DVT	
Serial imaging of the deep veins for 2 weeks over anticoagulation	If severe symptoms or risk factors for extension are absent – Elevated D-dimer – Thrombosis is extensive (e.g., >5 cm in length, multiple veins, >7 mm in maximum diameter) – Thrombosis is close to the proximal veins – No reversible provoking factor for DVT – Active cancer – History of VTE – Inpatient status

DVT: deep venous thrombosis; VTE : Venous thromboembolism.

Table XI: Recommendations for isolated subsegmental pulmonary embolism

ISOLATED SUBSEGMENTAL PULMONARY EMBOLISM	
Clinical surveillance if low risk for recurrent VTE	Anticoagulation if high risk for recurrent VTE due to following risk factors: – Inpatient status – Reduced mobility – Active cancer – No reversible risk factor for VTE – Pregnancy

VTE: venous thromboembolism

Table XII: Recommendations for thrombosis associated with heparin induced thrombocytopenia (HIT)

Management of HIT	
4T score > 4	***4T score 4–5***
Pretest probability of HIT is intermediate/high	Pretest probability intermediate
⇩	⇩
Discontinue heparin	Anticoagulation for patients with suspected HIT + Prophylactic dose if bleeding risk is high
⇩	⇩
Switch to alternate anticoagulant • Argatroban/Bivaluridin/ Danaparoid • Fondaparinux • DOAC	No Vit K Antagonists No prophylactic platelet transfusion

Table XII: Continued

Choice of anticoagulant in HIT	
Critical illness, high bleeding risk or potential need for urgent procedure.	Argatroban/Bivalirudin
Clinically stable	Fondaparinux/DOAC
Life or limb threatening thrombosis.	Argatroban/Bivalirudin/ Danaparoid Fondaparinux
Child-Pugh Class B and C	Avoid DOAC or Argatroban
⇩	
Transition to DOAC when patient is clinically stable	
⇩	
Start DOAC • within 2 hours of stopping argatroban or bivalirudin infusion, • within 8–12 hours after stopping Danaparoid infusion, • 24 hours after last dose of fondaparinux VKAs if platelet count > 1.5L/ul: Overlap parenteral agent with warfarin for ≥ 5 days and until INR: 2–3	
Duration of anticoagulation	**3 months** **<u>or</u>** **till platelet recovery if no DVT**

HIT: heparin induced thrombocytopenia; DOAC: direct oral anticoagulants; VKAs: Vitamin K antagonist; INR: International normalized ratio.

Table XIII: Recommendations for management of post thrombotic syndrome (PTS)

POST THROMBOTIC SYNDROME (PTS)	
Prophylaxis	Optimal anticoagulation is key for PTS prevention.
	Use of compression stockings is not recommended
Catheter directed thrombolysis	▪ For DVT involving the iliac and common femoral veins if bleeding risk is low ▪ Those who have symptoms <14 days, ▪ good functional status, ▪ a life expectancy of >1 year
Management	<u>All cases</u> ▪ Elastic compression stockings, ▪ leg elevation, ▪ weight loss, ▪ exercise
	Pentoxifylline may be used for treating venous ulcers on its own or with compression stockings.
	<u>Moderate-to-severe PTS</u> Endovascular recanalization or surgical bypass or disobliteration may be considered in patients with chronic venous occlusion class CEAP 4–6
	<u>Severely symptomatic patients with PTS</u> Segmental vein valve transfer or venous transposition may be considered

PTS: post thrombotic syndrome; DVT: deep vein thrombosis; CEAP: Clinical Etiological Anatomical Pathophysiological.

Table XIV: VTE management recommendations at various levels of healthcare delivery

Level of healthcare	Management of VTE by healthcare worker					
	Patient/family members	ASHA	ANM	Community health officer	Medical officer	Specialist
Community Level	Follow treatment as prescribed	Advise patients to follow treatment as prescribed				
Health & Wellness Centre				Advise patients to follow treatment as prescribed		
Primary Health Centre					Advise patients to follow treatment as prescribed Counsel on medication compliance	
Community Health Centre						Advise patients to follow treatment as prescribed
District Hospital						
Medical College Hospital						

VTE: venous thromboembolism; ASHA: Accredited Social Health Activist; ANM: Auxiliary Nurse Midwife.

ANNEXURE 3

Annexure 3 describes the various scoring systems recommended by the task force for VTE treatment and prophylaxis through Tables I–IX.

SCORING SYSTEMS

Table 1: Scoring systems for VTE prophylaxis in medical and surgical patients

Scoring system	Population at risk	Outputs and risk categories	Lowest risk category	Highest risk category	Comments
Caprini[1]	Surgical patients	Risk of VTE at 3 months	Lowest risk <0.7% (0 points)	Highest risk 10.7% (≥9 points)	No formal validation with original study. External validation studies in surgical subpopulations.
Padua Prediction Score[2]	Medical inpatients	Risk of VTE at 3 months	Lowest risk 1.1% (<4 points)	Highest risk 3.5% (≥4 points)	Internal validation showing 32-fold variation in VTE risk across 11 studies An external validation in patients with sepsis did not find correlation with VTE risk.
IMPROVE Score[3]	Medical inpatients	Risk of VTE at 3 months	Lowest risk 0.4% (0 points)	Highest risk 5.7% (≥4 points)	Validation includes 1 retrospective, 1 case control, and 1 prospective multicenter study*
Khorana Score[4]	Ambulatory cancer patients	Risk of VTE at 2.5 months	Lowest risk 0.8% (0 points)	Highest risk 7.1% (≥3 points)	Internal development and validation cohort included in original study. Multiple prospective and retrospective validation studies

*AUC 0.69–8.77 for predicting VTE.
Negative predictive value 98.5%, Positive predictive value 6.7%, C-static = 0.7.
VTE: venous thromboembolism.
Source: [1]Caprini JA, *et al.* Semin Thromb Hemost 1991;17 Suppl 3:304-12. [2]Vardi M, *et al.* J Thromb Haemost 2013 Mar;11(3):467-73. [3]Spyropoulos AC *et al.* Chest 2011 Sep;140(3):706-14. [4]Dutia M *et al.* Cancer 2012 Jul 15;118(14):3468-76.

Table II: PADUA scoring systems for VTE prophylaxis in medical patients

PADUA score	
VTE risk factor	**Points**
Decreased mobility	3
Thrombophilia	3
Previous trauma or surgery within the last month	2
Age ≥ 70	1
Heart or respiratory failure	1
Ischemic stroke or acute myocardial Infarction	1
Acute rheumatologic disorder and/or acute infection	1
Obesity	1
Hormonal therapy	1

Score < 4	**Low risk**	Confers a <0.3% 90-day risk of symptomatic VTE in patients who do not receive anticoagulation during hospitalization
Score ≥ 4	**High risk**	Confers an 11% risk of symptomatic VTE

VTE: Venous thromboembolism.
Source: Vardi M, *et al.* J Thromb Haemost 2013 Mar;11(3):467-73.

Table III: IMPROVE VTE scoring systems for VTE prophylaxis in medical patients

IMPROVE VTE score	
VTE Risk Factor	**VTE risk score**
Previous VTE	3
Known thrombophilia	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CCU stay	1
Complete immobilization ≥1 day	1
Age ≥ 60 years	1

IMPROVE: International Medical Prevention Registry on Venous Thromboembolism (VTE); CCU/ICU: Cardiac/Intensive Care Unit.

Score < 3	**Low risk**	Confers a <1.5% VTE risk
Score ≥ 3	**High risk**	Confers an >4% risk of symptomatic VTE

Source: Spyropoulos AC *et al.* Chest 2011 Sep;140(3):706-14.

Table IV: 4T score for heparin induced thrombocytopenia risk stratification and portability

4T Score			
Category	**2 points**	**1 point**	**0 point**
Thrombo-cytopenia	>50% fall, or nadir ≥20 × 10^9/L	30–50% fall, or nadir 10–19 × 10^9/L	< 30% fall, or nadir <10 × 10^9/L
Timing of the decrease in platelet count	Days 5–10, or ≤ day 1 with recent heparin (past 30 days)	> Day 10 or timing unclear, or < day 1 if heparin exposure within past 30–100 days	< Day 4 (no recent heparin)
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
Other causes of thrombo-cytopenia	None evident	Possible	Definite

Score	Probability	Risk of HIT
0–3	**Low**	<1%
4–5	**Intermediate**	~10%
6–8	**High**	~50%

Source: Lo GK, *et al.* J Thromb Haemost 2006 Apr;4(4):759-65.

Table V: IMPROVE bleeding risk assessment method for calculating bleed risk on anticoagulants

IMPROVE BLEED RAM	
Risk Factors	**Point**
Moderate renal failure (CrCI 30–50 mL/min)	1
Male sex	1
Age 40–84 years	1.5
Active cancer	2
Rheumatic disease	2
Central venous catheters	2
Admission in intensive care	2.5
Severe renal failure (CrCI < 30 mL/min.)	2.5
Liver insufficiency (INR > 1.5)	2.5
Age ≥ 85	3.5
Thrombocytopenia (<50 × 10^9 cell/L)	4
Recent (3 months) bleeding	4
Active gastrointestinal ulcer	4
High bleeding risk when total score ≥ 7	4

Score	Risk	Implication
<7	**Low**	Has a major bleed risk of approximately 0.4%
≥7	**High**	Has a major bleed risk of 4.1%

INR: International normalized ratio; CrCI: Creatinine clearance.
Source: Adapted from Decousus H *et al.* IMPROVE Investigators. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011 Jan;139(1):69-79.

Table VI: Caprini scoring systems for VTE prophylaxis in surgical patients

Caprini score			
-35 points	**3 points**	**2 points**	**1 point**
• Stroke (in the previous month) • Fracture of the hip, pelvis, or leg • Elective arthroplasty • Acute spinal cord injury (in the previous month)	• Age 75 years • Prior episodes of VTE • Positive family history for VTE • Prothrombin 20.210A • Factor V Leiden • Lupus anticoagulants • Anticardiolipin antibodies • High homocysteine • Heparin-induced thrombocytopenia • Other congenital or acquired thrombophilia	• Age 61–74 years • Arthroscopic surgery • Laparoscopy lasting >45 minutes • General surgery lasting >45 minutes • Cancer • Plaster cast • Bed bound for >72 hours • Central venous access	• Age 41–60 years • BMI > 25 kg/m^2 Minor surgery • Edema in the lower extremities • Varicose veins • Pregnancy • Postpartum • Oral contraceptive • Hormonal therapy • Unexplained or recurrent abortion • Sepsis (in the previous month) • Serious lung disease such as pneumonia (in the previous month) • Abnormal pulmonary function test • Acute myocardial infarction • Congestive heart failure (in the previous month) • Bed rest • Inflammatory bowel disease

BMI: Body mass index; VTE: venous thromboembolism.

Score < 2	Low risk
Score 3–4	Moderate risk
Score ≥ 5	High risk

Source: Caprini JA, *et al.* Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost 1991;17(Suppl 3):304-12.

Table VII: Khorana scoring systems for VTE prophylaxis in oncology patients

Khorana Score	
Patients' characteristics	**Risk score**
Site of cancer	
• Very high risk (stomach, pancreas)	2
• High risk (lung, lymphoma, gynecological, bladder, or testicular)	1
Pre chemotherapy platelet count ≥ 350 × 10^9/L	1
Pre chemotherapy hemoglobin level < 100 g/L or use of red cell growth factors	1
Pre chemotherapy leukocyte count > 11 × 10^9/L	1
Body Mass Index ≥ 35 kg/m^2	1

Score 0	**Low risk**
Score 1–2	**Intermediate risk**
Score > 2	**High risk**

VTE: venous thromboembolism.
Source: Dutia M, White RH, Wun T. Risk assessment models for cancer-associated venous thromboembolism. Cancer 2012 Jul 15;118(14):3468-76.

Table VIII: HESTIA criteria
HESTIA Criteria
If any of the below are answered "Yes," the patient should NOT be treated as an outpatient.
1. Hemodynamically unstable?
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?
4. Oxygen supply to maintain oxygen > 90% > 24 hours?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. In severe pain needing IV pain medication > 24 hours (or multiple doses in the ED)?
7. Medical or social reason for treatment in hospital > 24 hours?
8. Creatinine clearance less than 30 mL/min?
9. Severe liver impairment or disease?
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?
Source: Adapted from Zondag W, *et al.* J Thromb Haemost 2011 Aug;9(8): 1500-7.

Table IX: HAS-BLED score for bleeding risk assessment on anticoagulant use	
HAS-BLED-Score	
Risk-factor	**Scores**
Hypertension	1
Abnormal-renal/liver function	1 or 2
Strokes	1
Bleeding tendency	1
Labile-INR	1
Age (e.g., >65)	1
Drugs-(e.g., concomitant aspirin, NSAIDs,) or alcohol	1 or 2
Maximum-score	9
Notes: Hypertension is defined as a systolic blood pressure >160 mmHg. 1 point is awarded for each of abnormal renal or liver function, and drugs or alcohol. INR: International normalized ratio; NSAID: Nonsteroidal anti-inflammatory drugs.	

Score	**Risk of Bleeding**
0–2	**Low risk**
Score ≥ 3	**High risk**
Source: Adapted from Pisters R, *et al.* Chest 2010 Nov;138(5):1093-100.	

ANNEXURE 4

DIAGNOSIS OF VTE

Ineffectively managed lower extremity DVT has risks associated with it (e.g., pulmonary emboli) as also the inherent risks of anticoagulation (e.g., resultant major or life-threatening bleeding); hence, the accurate diagnosis of VTE is essential [Figure 1]. Features of lower extremity DVT are usually nonspecific, and many patients are asymptomatic.

History: DVT should be suspected in patients who present with leg swelling, pain, warmth, and erythema. Information that should be sought from patients and informants include:

(a) History of immobilization or (prolonged) hospitalization
(b) Recent surgery or trauma (typically within 12 weeks of surgery or trauma)
(c) Obesity
(d) Previous VTE
(e) Malignancy or symptoms suggestive of malignancy
(f) Use of oral contraceptives or hormone replacement therapy
(g) Pregnancy or postpartum status
(h) Stroke with hemiplegia or immobility
(i) Age > 65 years
(j) Family history of VTE
(k) Heart failure
(l) Inflammatory bowel disease

Physical examination—A thorough physical examination of the legs, abdomen, and pelvis should be performed in patients with suspected DVT to look for the following by the "Look–Touch–Measure" technique:

(a) Dilated superficial veins
(b) Unilateral edema or swelling with a difference in calf or thigh diameters
(c) Unilateral warmth, tenderness, erythema
(d) Pain and tenderness along the course of the involved major veins
(e) Local or general signs of malignancy.

Note: Initial diameters should be recorded at presentation to maintain a baseline. A larger calf diameter is the most useful finding in the presentation. Subsequent measurements are not of much significance, with pain and tenderness being a more reliable indicator. Homans' sign (calf pain on passive dorsiflexion of the foot) is unreliable for the presence of DVT.

Laboratory Routine laboratory tests (e.g., complete blood count, routine biochemistry tests, liver function tests, coagulation studies) are not useful diagnostically but may provide clues as to the underlying cause and may influence treatment decisions if DVT is confirmed.

Young patients (<40 years) with an episode of unprovoked VTE in unusual sites (cerebral venous sinuses and splanchnic circulation) and those with a history of VTE in the family or recurrent VTE will warrant a screen for inherited thrombophilia. The duration of anticoagulation varies from long term in recurrent VTE to short term (3 months) in the presence of reversible risk factors like surgery. All non genetic tests for thrombophilia (PC, PS, AT, APC-R) should be done after withdrawal of anticoagulation for a period of 4 weeks. However, genetic tests such as FVL,

prothrombin gene mutation, and Methylenetetrahydrofolate reductase (MTHFR) gene mutations can be tested during anticoagulation.

In the Indian population, most of the studies have been limited to certain variants only. Many Indian studies have reported the role of MTHFR polymorphisms in VTE risk; however, a recently published report suggests MTHFR polymorphisms should not be a part of inherited thrombophilia testing and eliminating MTHFR from thrombophilia testing will reduce patient concerns and decrease healthcare costs.

Suspected first DVT (risk stratification)

An approach that incorporates clinical assessment of the pretest probability (PTP) and D-dimer testing in selected patients is recommended. This approach allows for the strategic use of US for diagnosis or alternative imaging modalities such as CT or MRI. The goal of diagnostic testing is to "rule-in" (>85% posttest probability of DVT) or "rule out" DVT (<2 % posttest probability of VTE in the next 3 months) with an acceptable level of certainty, thereby justifying instituting or withholding anticoagulant therapy, respectively.

Assessment of clinical PTP In patients with suspected first DVT, we recommend estimation of the clinical PTP. Subsequent measurement of the D-dimer level and compression US are dependent upon the assigned PTP of DVT. We may use the Wells score for the purpose of estimating PTP. Some experts, due to reproducibility, prefer the revised Geneva system as it also overcomes the interobserver variability.

Table I: Wells criteria for the prediction of deep vein thrombosis (DVT)

Wells Score	
Clinical feature	**Score**
Active cancer (treatment ongoing or within previous 6 months or palliative care)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for >3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non varicose)	1
Alternative diagnosis as likely or more likely than that of DVT	–2

Score	Classification
3–8	High probability
1–2	Moderate probability
≤0	Low probability

Source: Modi *et al.* World Journal of Emergency Surgery (2016) 11:24.

Table II: Revised Geneva Score

Items	Points
Previous PE or DVT	1
Heart Rate	
75–94 BPM	1
≥95 BPM	2
Previous surgery or fracture	1
Hemoptysis	1
Active cancer	1
Unilateral leg pain	1
Pain on lower limb palpation and unilateral edema	1
Age > 65 Years	1

PE: Pulmonary embolism; DVT: Deep vein thrombosis; BPM: Beats per minute.

3 Point Score	Clinical Probability
≥5	High
2–4	Intermediate
0–1	Low

2 Point Score	Clinical Probability
≥3	PE Likely
0–2	PE Unlikely

Source: Le Gal G, *et al.* Ann Intern Med 2006 Feb 7;144(3):165-71.

In patients with suspected first DVT, it is recommended that based on the clinical PTP, further action should be taken:

(a) Low probability—In patients with a **low** PTP for DVT, we recommend that D-dimer levels be obtained. Patients in whom the D-dimer level is normal (e.g., <500 ng/mL) do **not** need further testing, while those in whom the D-dimer is positive (e.g., ≥500 ng/mL) should have US of the lower extremities. Patients can proceed directly to US if the D-dimer is expected to be positive due to another condition. DVT is diagnosed

if US is positive; no further testing is required if US is negative.

(b) Moderate probability—In patients with **moderate** PTP for DVT, we recommend that D-dimer levels be obtained. Patients in whom the D-dimer level is normal do **not** need further testing, while those in whom the D-dimer is positive should have US of the lower extremities. Patients can proceed directly to US if the D-dimer is expected to be positive due to another condition. DVT is diagnosed if US is positive. When neither proximal nor distal DVT is identified on the whole leg US, no further testing is required; in contrast, in those in whom the proximal US is negative, repeat proximal US should be performed at one week to detect extension of distal DVT into the proximal veins.

(c) High probability—For patients with a **high** PTP for DVT, we suggest that US be performed. DVT is diagnosed if US is positive. If DVT is not identified, options include high sensitivity D-dimer level measurement (if not expected to be positive due to another condition), repeat proximal compression ultrasonography (CUS) at one week (off anticoagulation), whole leg US (if not already performed), or iliac vein US (when iliac vein DVT is suspected). Choosing among these options should be individualized. In general, if one or more of these tests are negative in a patient without proximal DVT on ultrasound, then no further testing is required.

D-dimer

D-Dimer is a degradation product of cross-linked fibrin and is elevated in nearly all patients with acute DVT. However, it is nonspecific since elevated levels are found in many other conditions (e.g., malignancy, sepsis, recent surgery or trauma, pregnancy, renal failure), i.e., D-dimer has high sensitivity but poor specificity for VTE. Hence a negative result (e.g., <500 ng/mL) is useful for ruling out DVT, particularly in those with a low or moderate PTP for thrombosis; however, a negative test is obtained in about 30% of outpatients (lower in inpatients or if there has been a previous VTE). A positive result (e.g., ≥500 ng/mL) is not diagnostic and indicates the need for further investigation. D-dimer testing is of limited value in patients with high PTP since the negative predictive value is lower in this population. In summary, D-dimer assay should not be used as a stand-alone test in patients suspected of having DVT but rather should be used in conjunction with clinical PTP and/or US.

Imaging

CUS with Doppler is the diagnostic test of choice in patients with suspected DVT. In general, the sensitivity and specificity of proximal CUS is greater than 95%. Duplex US has less accuracy than CUS since the specificity of an abnormal duplex ultrasonogram is lower than that of an abnormal compression ultrasonogram. Point-of-care-US is not recommended for diagnosis unless the situation is urgent or emergent.

Ultrasonography interpretation—Interpretation of CUS in patients with a first suspected DVT:

(a) ***Positive***
   (i) Using ultrasound probe pressure, the presence of thrombus is diagnosed by demonstrating the noncompressibility of the imaged vein. Veins that can be assessed for compressibility are proximal (e.g., the common femoral, femoral, and popliteal veins) and distal veins (e.g., peroneal, posterior and anterior tibial, and muscular veins); iliac veins often cannot be assessed for compressibility.
   (ii) Lack of compressibility of a vein with the ultrasound probe is the most sensitive (>95%) and specific (>95%) sonographic sign for **proximal** vein thrombosis.
   (iii) The addition of color flow Doppler does not improve the sensitivity but can provide supportive evidence of thrombus and also help to identify calf veins.
   (iv) Variation of venous size with the Valsalva maneuver has a low sensitivity and specificity for the diagnosis.
   (v) In contrast, CUS is less sensitive for the detection of calf vein and iliac vein thrombus since these veins are less readily compressed (particularly calf veins).

(b) **Negative**—A negative study is one that demonstrates full compressibility of all imaged veins.

(c) **Nondiagnostic**—A nondiagnostic study is one where there is uncertainty about whether DVT is present or absent.
   (i) Nondiagnostic findings are less common in outpatients compared with inpatients, with less than 5% of outpatients expected to have nondiagnostic findings of the proximal veins.
   (ii) Nondiagnostic findings are also less common when imaging the proximal veins compared with the distal veins (i.e., with whole leg US); however, nondiagnostic findings that are confined to the distal veins are also less important and can usually be managed by withholding anticoagulant therapy while doing serial ultrasound testing.

(iii) The main reasons for a nondiagnostic examination are:
  (aa) difficulty visualizing the deep veins because of morbid obesity, edema, recent surgery or trauma, skin lesions, contractures, or leg casts.
  (ab) although the deep veins are well visualized, small or atypical appearing abnormalities of uncertain significance may be identified.
  (ac) in patients with previous DVT, when a thrombus is present, it is often difficult to assess if it is acute or old (residual thrombosis can persist indefinitely).

Further investigation(s) (e.g., repeat proximal CUS at three and seven days) in those with nondiagnostic studies should be individualized and depend upon why the US is considered nondiagnostic, the extent and position of the venous segment (e.g., distal or proximal veins) that is nondiagnostic, clinical PTP, results of D-dimer testing, and the clinician's overall assessment of the risk associated with undiagnosed DVT.

Imaging at first occurrence

For patients who are not initially stratified according to clinical PTP of low, moderate, or high risk, the initial test of choice is US.

(a) When the whole leg US is negative, no further investigations are necessary unless iliac vein thrombosis is suspected.
(b) When the proximal CUS is negative, options include whole leg US (to detect distal DVT), repeat proximal CUS at 3–7 days (to detect extension of distal DVT into the proximal veins), measuring a high-sensitivity D-dimer level, or assessing clinical PTP (low PTP excludes DVT with a negative proximal CUS).

Diagnostic compressive US

(a) Proximal CUS—In most patients with suspected DVT, CUS with Doppler is the imaging test of choice. The presence of DVT is diagnosed by demonstrating noncompressibility of the imaged vein.
(b) Whole leg CUS—Both proximal and whole leg US have a high sensitivity for the detection of thrombus in the proximal veins (i.e., common femoral, femoral, and popliteal veins). Whole leg US additionally examines the veins in the calf (peroneal, posterior and anterior tibial, and muscular veins) and can, therefore detect isolated distal DVT.

Imaging in Recurrence

For most patients with suspected ipsilateral DVT recurrence, proceeding directly to US (proximal or whole leg US) or using an approach similar to that described for the first suspected DVT is appropriate. When an ultrasonographic abnormality is identified in patients with suspected recurrence, it may be difficult for the clinician to determine whether it is due to an old or new thrombus. The availability of a previous ultrasound report that documents the extent of residual thrombosis greatly improves the accuracy of ultrasound for recurrent DVT. In the absence of a previous ultrasound report, magnetic resonance direct thrombus imaging (MRDTI) may be useful.

Alternative imaging modalities—For patients with suspected DVT, contrast-enhanced computed tomographic venography (CTV) and magnetic resonance venography (MRV) are rarely used diagnostically, unless there is uncertainty about iliac vein or IVC thrombosis after US. Ascending contrast venography, which was the earlier gold standard for DVT diagnosis, and impedance plethysmography are now not recommended to be used.

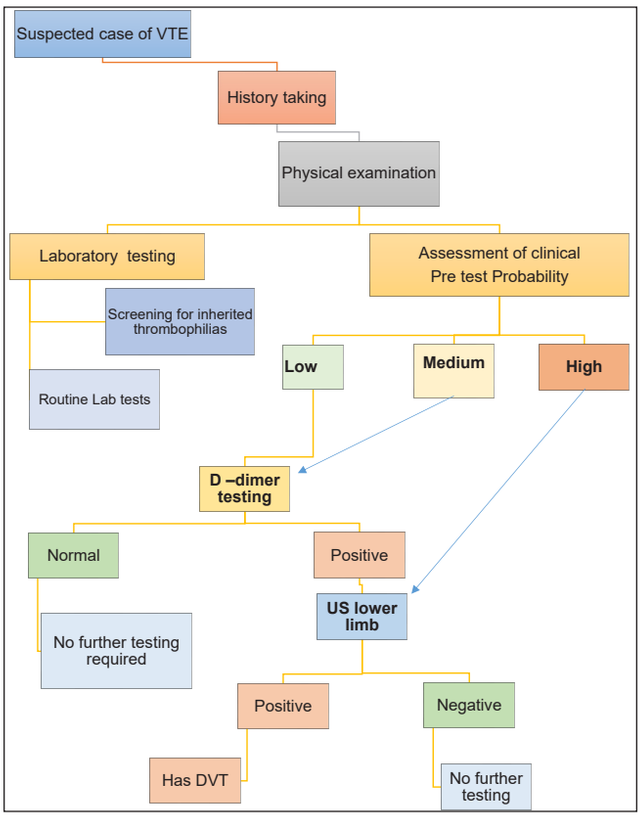

Figure 1: Clinical Decision Aid – Diagnostic workup of a suspected case of VTE
DVT: Deep venous thrombosis; VTE: Venous thromboembolism; US: Ultrasonography.

ANNEXURE 5

MOLECULAR ASPECTS AND GENETIC BACKDROP OF VTE

Ordering thrombophilia tests is easy; determining whom to test and how to use the results is not (Connors 2017).

To understand the Indian perspective of genetic risk factors in VTE, a literature review was undertaken to identify the genetic variants that have been reported in association with VTE [Table I].

Indian data depict that the established thrombophilia genetic markers FV Leiden and Prothrombin G20210A have a limited role from the Indian subcontinental perspective. Several studies have shown the role of FV Leiden in VTE risk, however, only with certain comorbidities in the Indian population. To understand this limited role, we reviewed the literature from other Asian countries also. The data show no role of established genetic markers in the Chinese and Thai populations as well. The prevalence of the FV Leiden phenotype, shown by Ridker *et al.* is 0.4% in an Asian population.

In the Indian population, most of the hospital-based studies have been limited to certain variants only. Many studies have reported the role of MTHFR polymorphisms in VTE risk; however, a recently published report suggests MTHFR polymorphisms should not be a part of inherited thrombophilia testing and eliminating MTHFR from thrombophilia testing will reduce patient concerns and healthcare costs.

Table I: VTE variants studied and reported in India

Variant	Association	Sample Size	Author & Journal
Factor V Leiden G1691A mutation and prothrombin G20210A	Significantly associated in the Kashmiri population	250 patients 250 controls	Shafia *et al.*, **Gene** (2018)
MTHFR C677T polymorphism	No significant association in the Kashmiri population		
EDN T1370G (endothelin gene)	Significant association with VTE occurrence	133 patients with VTE 164 controls	Kumari *et al.*, **Clinical and Applied Thrombosis/ Hemostasis** (2017)
CYP4F2 1347 G> A polymorphism	Significant association with PVT (portal vein thrombosis)	91 PVT cases 136 controls	Kalpana *et al.*, **Medicine** (2019)
JAK2V617F mutation	May increase the risk of thrombosis in patients with Philadelphia negative chronic myeloproliferative neoplasms.	65 (46 males and 19 females) CMPN cases	Singh *et al.*, **Indian J Pathol Microbiol** (2018)
FV Leiden	Inherited APCR in patients with DVT—significant association	50 APCR + patients 50 controls	Sharma *et al.*, **Clinical and Applied Thrombosis/ Hemostasis** (2017)
Factor V leiden (FVL) mutation and PAI 4G/4G homozygosity	Increase DVT risk in pregnant women in Western India	Prevalence of DVT in 34,720 prenatal women	Vora *et al.* **Thrombosis** (2007)
Factor V Leiden	Significant Association with Myocardial Infarction Patients	120 patients of MI (age < 40) 100 controls	Khare *et al.*, **Indian Journal Of Medical Sciences** (2004)
MTHFR 677TT polymorphism	Increased risk of thrombosis in patients with hyperhomo-cysteinemia	124 patients with DVT	Paradkar *et al.*, **Indian Journal of Clinical Biochemistry** (2020)
MTHFR 677C/T	Contribute toward susceptibility to thrombosis	93 male patients 102 controls	Kumari *et al.*, **Thrombosis** (2014)
PAI-1 −844G/A, fibrinogen-β −455G/A	Protective role		
FVL (1691G/A), pro-thrombin (20210G/A), and TFPI (−536C/T)	Limited role in Indian population		
eNOS894G/T and 2479G/A polymorphisms	Possess the risk of VTE	100 cases of DVT 200 controls	Akhter*et al.*, **Clinical Laboratory** (2022)

Table I: Continued

Variant	Association	Sample Size	Author & Journal
MTHFR C677T and prothrombin G20210A mutation	No significant association in west Indian population	Cases of DVT 252 males 180 females	Ghosh *et al.*, **Clinical and Applied Thrombosis/ Hemostasis** (2001)
Variant allele 4G of PAI-1 4G/5G polymorphism	Significantly associated with ischemic stroke in young Indians	100 cases 100 controls	Akhter *et al.*, **Clinical and Applied Thrombosis/ Hemostasis** (2017)
TFPI polymorphisms (polymorphisms (33T > C, 399C > T, and 536C > T))	33T > C protective and 399C > T as risk factors	100 DVT patients 100 controls	Kamal *et al.*, **Blood Cells, Molecules, and Diseases** (2017)
CYP2C9 polymorphisms (rs1799853, rs1057910, rs1057909, and rs28371686), VKORC1 promoter polymorphism (rs9923231)	CYP2C9 and VKORC1 polymorphisms, suggested that an increase in the anti-coagulant drug dose may be necessary for Indian patients	124 patients with DVT	Arunkumar *et al.*, **Drug Discoveries & Therapeutics** (2017)

VTE: venous thromboembolism; PVT: Portal vein thrombosis; DVT: Deep vein thrombosis; MI: Myocardial infarction; APCR: Activated protein C Resistance; CMPN: Chronic Myeloproliferative Neoplasms.

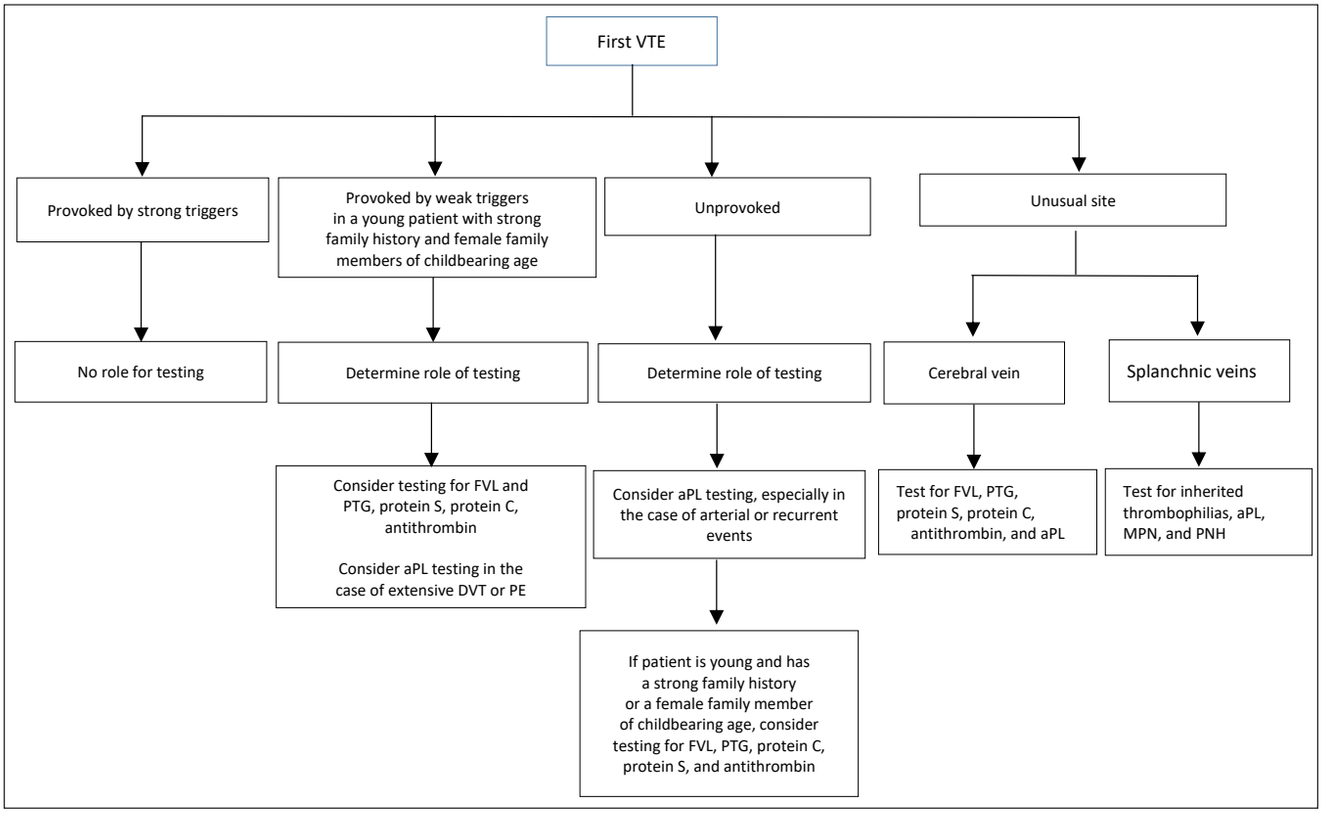

Figure 1: Algorithm for Selecting Patients with a First VTE episode for Thrombophilia Testing.
VTE: venous thromboembolism; FVL: Factor V leiden; PTG: Prothrombin gene mutation; MPN: myeloproliferative neoplasms; PNH: Paroxysmal Nocturnal Hemoglobinuria; aPL: Antiphospholipid antibody.
(Source: N Engl J Med 2017;377:1177–87)

We also reviewed the literature regarding European and American populations and a recently published trans-ancestry meta-analysis, and also another independent study that tested approximately 13 million DNA sequence variants for association with VTE and reported the variants associated with VTE [Figure 1]. A similar approach could be replicated in the Indian population, and validation of these variants in the context of different regional/ethnic population groups could be considered to identify a set of variants uniquely associated with Indian population (if at all).

Hence, a large-scale population-based genome-wide association study is recommended amongst the Indian population with representation from different regional and ethnic groups to identify the genetic associations with VTE.

ANNEXURE 6

PUBLIC HEALTH RESPONSE TO REDUCING DVT AND PE

DVT and PE are major public health problems across the world today. It is essential for policymakers to direct public health responses to reducing the burden of VTE, in various settings. The required set of actions is ideally organized by the CARE framework to be customized to the requirement and context on a regional basis:

(a) *Communication* refers to the provision of information to motivate and empower individuals and healthcare professionals in various settings to catalyze change that will lead to more effective prevention, diagnosis, and treatment of first-time and recurrent DVT/PE.
(b) *Action* refers to interventions and activities that will assist various stakeholders in preventing, screening, diagnosing, and managing medical conditions or diseases more effectively.
(c) *Research* into the various aspects of VTE that may be required to be addressed or investigated further.
(d) *Evaluation* refers to the ongoing assessment of the various activities and interventions for VTE to ascertain their practicality, feasibility, cost benefit, etc.

Note: The US Surgeon General's "call to action to prevent DVT and PE" (2008) provides an excellent framework which can be suitably adapted to the Indian context.

Setting: Communities

The community, which comprises individuals and their families, needs to understand DVT and PE as threats to their health and life; they need to understand the risk factors for these conditions and to learn how to reduce these risks. They need to recognize the signs and symptoms and to know about available medical management modalities. Patients and their family members should actively discuss these conditions when interacting with their healthcare providers. The goal is to raise awareness among patients and their family members and empower them to ask their healthcare providers about preventive treatment during hospitalization, after a traumatic event, or in other high-risk situations.

A broad-based health risk communication campaign can play a major role in raising awareness at the community level. From a public education and social marketing standpoint, communication campaigns can disseminate structured health messages aimed at educating individuals about DVT/PE. It is essential to harness social and other media to address gaps that exist in the availability of appropriate educational materials pertaining to VTE, among other medical conditions. Emphasis should be placed on opportunities for communication at the family and community level, with a specific focus on high-risk groups.

Communication

Policymakers and healthcare administrators need to take the following steps, among others:

(a) Increasing public knowledge of DVT/PE and the severity of the burden these disorders place on society.
(b) Educating people about the signs, danger signs, and precipitating circumstances, including medical procedures, hospital stays, and trauma.
(c) Educating the general public on genetic predispositions to DVT/PE.
(d) Supporting public education by letting people know how serious the issue is in terms of incidence and mortality/morbidity.
(e) Publication of specific patient tales via news channels and social media, as human interest stories frequently have a greater impact than statistics alone.
(f) Highlighting the substantial gap between what is understood about how to prevent and treat DVT/PE and what is happening in practice today.
(g) Facilitating the development and dissemination of uniform messages about DVT/PE that are consistent with existing guidelines.

Action

Actions that need to be initiated by policymakers and medical administrators include but are not limited to:

(a) Forming community coalitions to sponsor public awareness campaigns.
(b) Developing tools and materials that patients can use when talking with their physicians and other health professionals.
(c) Creating local networks and peer support programs for patients and their family members.
(d) Working with volunteer groups, professional societies, and the media as part of a national awareness campaign intended to educate both the public and health professionals about the incidence of the disease, along with its symptoms and risk factors.

(e) Making available to the media accurate messages about DVT/PE for news stories and media programming, including television shows or podcasts.
(f) Encouraging community-based advertising campaigns.
(g) Consider using a celebrity spokesperson to deliver messages about these conditions, especially a celebrity who may have had a personal experience related to either DVT or PE.

Research and Evaluation

It is recommended for policymakers and healthcare system administrators to assign priority to this often neglected aspect of interventions focused on medical conditions. This is essential to:

(a) Gain a better understanding of what the public already knows about DVT/PE, gaps in their understanding, and how best to address those gaps.
(b) Develop and test messages to determine which approaches work best to educate the public, inform them of when they are at risk, and empower them to raise issues proactively with their clinicians.
(c) Investigate, in a culturally and linguistically appropriate manner, why certain ethnic groups are more or less likely to develop these conditions.
(d) Investigate the causes of age- and gender-based variations in the incidence and recurrence of these diseases, including why men are more susceptible to a recurrence.
(e) Research the role (if any) that behavior modification (e.g., smoking cessation, increased physical activity, weight loss) plays in reducing risk.
(f) Conduct research to better understand why obesity increases risk.
(g) Investigate the role that prolonged immobility due to travel (air, car, rail), hospitalization, or confinement to bed plays in increasing risk.
(h) Conduct an analysis of the economic toll of DVT/PE on individuals, families, communities, and the nation as a whole. This analysis should include not only the direct costs (i.e., healthcare expenditures) but also indirect costs such as lost productivity and wages due to time away from work.
(i) Evaluate the impact of communication and social marketing programs, including pre- and post-evaluation levels of consumer awareness and knowledge.
(j) Conduct formative research to ensure that media messages are positive, realistic, relevant, consistent, and effective.

Setting: The Healthcare System

The healthcare system is uniquely positioned to implement interventions aimed at reducing the incidence and burden of DVT/PE, as the majority of cases occur within the healthcare system itself. There is a gap between the implementation of a required standard of care with broad compliance to evidence-based guidelines and ground realities.

Healthcare systems in the public and private sectors and also medical colleges have a crucial role to play in preventing and reducing the burden of DVT/PE. Much is left to be done—to apply evidence-based medicine in real-world settings and to investigate the gaps in knowledge related to the management of VTE.

Communication

Actions that need to be initiated by policymakers and healthcare administrators include but are not limited to:

(a) Informing healthcare professionals and administrators about the problem of DVT/PE in terms of mortality, morbidity, and direct and indirect costs.
(b) Promoting evidence-based practice by sharing existing guidelines with healthcare professionals on the prevention, diagnosis, and treatment in specific at-risk populations.
(c) Promoting the findings and recommendations from expert groups such as professional societies related to the importance of screening all hospitalized patients for risk for these diseases and providing appropriate preventive treatment based on those screenings.
(d) Educating healthcare professionals about the availability of genetic testing wherever feasible, about when it may be appropriate to discuss with and test patients, and the importance of counseling for those who test positive.
(e) Educating healthcare professionals at all levels about the relative risks of excessive bleeding from properly managed anticoagulation therapy versus the risks of not using such therapy.
(f) Informing healthcare professionals about the availability and appropriate use of treatment options, including anticoagulation therapy and clot dissolving/clot removal therapies.

Action

Actions that need to be initiated by policymakers and healthcare administrators include but are not limited to:

(a) Convening a TF, such as the NAMS TF, to forge consensus on a single set of clear, standardized, evidence-based guidelines in those areas where multiple and/or conflicting guidelines currently exist.
(b) Instituting formal systems related to risk assessment and the provision of preventive therapy (prophylaxis) to appropriate high-risk individuals in the healthcare system and community.

(c) Consistently tracking performance on current and future DVT measures that are endorsed by professional societies and developing quality improvement initiatives designed to improve performance on these measures over time.
(d) Developing and improving easy-to-use tools (such as Internet-based apps) that provide ready access to relevant data and information at the point of care. These tools will help healthcare professionals to follow existing evidence-based guidelines and assist in enhancing their patient care service delivery.
(e) Developing and/or refining tools and/or algorithms to determine who should undergo diagnostic imaging tests for DVT/PE. These tools could incorporate clinical manifestations, biomarkers and genetic profiles, patient and family history, the results of simple tests, and other information to determine who should be screened.
(f) Identifying and supporting healthcare professionals who can provide evidence-based preventive, diagnostic, and therapeutic care and serve as models in their respective hospitals.
(g) Encouraging medical and nursing colleges to provide adequate education and training to ensure that the new generations of doctors and nurses are aware of the magnitude of the problem and how to prevent, diagnose, and treat DVT/PE in accordance with the latest scientific evidence.
(h) Encouraging medical and nursing colleges, and other organizations to incorporate training into continuing medical education and recertification processes such as renewal of registrations.
(i) Supporting the development of hospital- and community-based support programs for patients with DVT/PE and their family members.

Research and Evaluation

It is recommended for policymakers and healthcare system administrators to assign priority to this often neglected aspect of interventions focused on medical conditions. This is essential to:

(a) Conduct further research into the benefits and risks associated with various strategies (pharmacological, mechanical, and surgical) for dissolving or removing clots and for determining which patients, if any, would benefit from these approaches (as an alternative to anticoagulation therapy).
(b) Conduct further research into the pathophysiology of DVT/PE, including the roles of inflammation, obesity, stasis, and the basic endothelial cell biology and vessel response to stasis and thrombosis. This research can lead to the development of novel prevention and treatment strategies.
(c) Investigate whether more biomarkers can be identified that will allow for the development of individualized risk profiles for primary and recurrent DVT/PE and chronic venous insufficiency. These biomarkers can possibly be used to help predict an individual's response to therapy.
(d) Investigate the role of prolonged air, car, boat, or rail trips (and other situations causing long periods of immobility) on raising risk, both for the general population and certain high-risk groups, such as women on oral contraceptives or individuals with a genetic predisposition to DVT/PE.
(e) Investigate the role of CUS in diagnosing isolated calf DVT, and study the benefits and costs associated with treatment.
(f) Continue to study the effectiveness of various tests, including the D-dimer and other tests, in diagnosing the recurrence of the disease.
(g) Investigate the safety and effectiveness of various approaches to diagnosing DVT/PE in pregnant women.
(h) Conduct further research into the best drugs, dosing strategies, and treatment regimens for anticoagulation therapy for certain patient populations, including children (from infancy through adolescence), obese individuals, and those with renal insufficiency.
(i) Conduct further research on the benefits and risks of preventive and therapeutic anticoagulation therapy for certain patient populations, including children, pregnant women, individuals with a genetic predisposition to DVT/PE (with or without prior events), cancer patients, and the elderly. Such research should also address how to treat individuals with multiple risk factors, such as pregnant women or children with genetic predisposition.
(j) Conduct further research into the appropriate duration of anticoagulation therapy in specific patient populations, including whether some high-risk groups should remain on the therapy indefinitely.
(k) Investigate the role that pharmacogenetics can play in determining optimal warfarin dosing in individuals.
(l) Investigate and evaluate the various approaches (e.g., pharmacological, mechanical, and/or a combination) to reduce the risk and impact of chronic venous insufficiency.
(m) Conduct research into when genetic testing is appropriate, including whether and when to test the asymptomatic family members of those with a genetic predisposition to DVT/PE.
(n) Conduct further research into optimal therapy for those with genetic predisposition and how that therapy might vary depending upon the number of genetic and other acquired risk factors or triggering events. Research should focus on the impact of specific thrombophilic disorders on anticoagulant therapy management and the identification of optimal prophylactic strategies for asymptomatic individuals during high-risk situations.

(o) Conduct research into how upper extremity DVT—a less common and less studied form than DVT in the legs—should best be evaluated, diagnosed, and managed.

Setting: Policymakers and Governments

Healthcare policymakers at the state and national levels have a crucial role to play in raising awareness and encouraging the development and use of evidence-based guidelines. The scientific community and professional societies, such as the National Academy of Medical Sciences (India), Indian Society of Hematology, Indian Public Health Association, and the Indian Medical Association, must seek to collaborate, partner, facilitate, and steer actions required for advocacy with all stakeholders. Governments at the state and the national level, along with the scientific community, must work together to focus on the following areas:

(a) **Communication**
   (i) Raise policymakers' awareness of DVT/PE and the magnitude of the problems caused by the disease, as well as the need to support research and infrastructure that are consistent with the provision of evidence-based care.
   (ii) Support public awareness campaigns.
   (iii) Support the education of health professionals, including the dissemination of evidence-based guidelines.

(b) **Action**
   (i) Review Ayushman Bharat reimbursement policies to ensure that they encourage the provision of evidence-based prevention, diagnosis, and treatment. Subsequently, to make recommendations to the Government of India for necessary action as may be required.
   (ii) Support the formation of community-based regional and national multi stakeholder coalitions dedicated to raising awareness about these VTEs.
   (iii) Form TFs, steering committees, or advisory committees dedicated to addressing the problems resulting from VTE.
   (iv) Support actions that lead to enhanced awareness about DVT/PE among healthcare professionals and obtain better adherence to evidence-based practices.

(c) **Research and Evaluation**
   (i) Support basic, clinical, and epidemiological research that is intended to fill critical gaps in the current knowledge about DVT/PE.
   (ii) Support translational research and the development of other tools that are intended to speed the adoption of new scientific knowledge into the everyday practice of medicine.
   (iii) Support the training of scientific investigators and healthcare professionals who are interested in VTE.

ANNEXURE 7

VTE TRAINING AND EDUCATION FOR HEALTHCARE PROFESSIONALS

It is recommended that an online training course for healthcare professionals be proposed by NAMS to be hosted on the Government of India website for training (www.igot.gov.in). This training course may be updated periodically as per evolving evidence and peer-reviewed best practices.

An outline template for such a training course may be taken from

https://www.cdc.gov/ncbddd/dvt/training.html#accreditation

Stop the Clot®: What Every Healthcare Professional Should Know

Course Overview: A self-paced, online course providing the most current foundational information on assessing, treating, and managing patients who have blood clots and clotting disorders.

Target Audience: Physicians, Nurses, and other healthcare professionals

Content:

1. Basics of blood clots
2. Thrombophilia and blood clots
3. Anticoagulation medications
4. Post-thrombotic syndrome
5. Pulmonary hypertension
6. Prevention of blood clots

Course Objectives

At the conclusion of this proposed training course, participants should be able to do the following:

1. Explain three signs and symptoms of DVT and pulmonary embolism (PE).
2. Describe three factors that increase the risk of developing a blood clot in the form of a DVT and/or PE.
3. Describe three management considerations for the use of anticoagulant medications.
4. Explain three signs and symptoms of post-thrombotic syndrome that providers should include in patient education plans for blood clot survivors.
5. Explain two facts about pulmonary hypertension and its relationship to PE.
6. Describe three appropriate treatment/management options to prevent blood clot recurrence and secondary complications.

ANNEXURE 8

Table I: Theoretical Framework: Prevention of VTE

<table>
<tr><td colspan="2">PERIOD OF PRE PATHOGENESIS</td><td colspan="3">PERIOD OF PATHOGENESIS
This is the stage when VTE has set in.</td></tr>
<tr><td>Disease Process</td><td>This is the stage when conditions within the body predispose to VTE, however VTE has not set in as yet.</td><td colspan="3">DEATH
Chronic State
Disability
Illness
Signs & Symptoms
Clinical Horizon
RECOVERY</td></tr>
<tr><td>LEVELS OF PREVENTION</td><td colspan="2">Primary Prevention</td><td>Secondary Prevention</td><td>Tertiary Prevention</td></tr>
<tr><td>MODES OF INTERVENTION</td><td>Health Promotion</td><td>Specific Protection</td><td>Early Diagnosis & Treatment</td><td>Disability Limitation</td><td>Rehabilitation</td></tr>
</table>

VTE: venous thromboembolism.

ANNEXURE 9

Comprehensive primary healthcare framework approach: prevention of VTE

Table I: Primary prevention

	Actions at - Level	Actions by	Remarks
Health Promotion	Community level	ASHA/ ANM	Conduct of community level Health Education campaigns *to promote healthy lifestyles and promote early healthcare seeking behaviour*
	Health & Wellness Centre level	CHO	Conduct of outreach health education for communities and support for ASHA/ ANM
	Primary Health Centre level	MO	Supervision and conduct of outreach health education activities for communities and patients, including support and guidance to CHOs
	Community Health Centre level	MO/ Specialist	Supervision and conduct of outreach health education activities for communities and patients, including support and guidance to MOs

	District Hospital level	Specialist	Supervision and conduct of outreach health education activities for communities and patients, including support and guidance to MOs and Specialists
	Medical College level	Specialist	Conduct of outreach health education activities, in rural / urban field practice areas, providing support and guidance to MOs and Specialists
	Tertiary Hospital level	Specialist / Sub Specialist	Conduct of health education activities for inpatients and relatives / caregivers, providing support and guidance to MOs and Specialists
Specific Protection			**Nil**

Table II: Secondary prevention

	Actions at - Level	**Actions by**	**Remarks**
Early Diagnosis	Community level	ASHA/ ANM	Early recognition of symptoms with prompt referral Training module (online) can be developed for early recognition at the community level
	Health & Wellness Centre level	CHO	
	Primary Health Centre level	MO	
	Community Health Centre level	MO/ Specialist	Early recognition of signs and symptoms , with a high degree of clinical suspicion Training module (online) can be developed for early diagnosis at the health care facility level
	District Hospital level	Specialist	
	Med College level	Specialist	
	Tertiary Hospital level	Specialist / Sub Specialist	

	Actions at - Level	Actions by	Remarks
Prompt Treatment	Community level	ASHA/ ANM	Referral without delay, and encouragement to patient to seek medical attention urgently.
	Health & Wellness Centre level	CHO	
	Primary Health Centre level	MO	Commence treatment as per Guidelines and referral as per criteria.
	Community Health Centre level	MO/ Specialist	
	District Hospital level	Specialist	
	Med College level	Specialist	
	Tertiary Hospital level	Specialist / Sub Specialist	Management as per Guidelines.

Table III: Tertiary prevention
This is the phase where long term anti coagulation is indicated, adhering to guidelines

	Actions at - Level	Actions by	Remarks
Disability Limitation	Community level	ASHA/ ANM	To brief patients in the domestic setting to comply with prescribed medications and follow up at required frequency, with self care as applicable. Referral as needed.
	Health & Wellness Centre level	CHO	To brief patients attending OPD in the HWC to comply with prescribed medications and follow up at required frequency, with self care as applicable. Referral as needed
	Primary Health Centre level	MO	To brief patients attending OPD in the PHC to comply with prescribed medications and follow up at required frequency, with self care as applicable. Referral as needed
	Community Health Centre level	MO/ Specialist	To undertake required investigations, and monitor patients for health status and ascertain compliance with prescribed medications. Referral as needed.
	District Hospital level	Specialist	
	Med College level	Specialist	
	Tertiary Hospital level	Specialist / Sub Specialist	To undertake investigations and management as needed.

	Actions at - Level	Actions by	Remarks
Rehabilitation	Community level	ASHA/ ANM	Counselling for maintenance of healthy lifestyle and risk reduction as applicable, with information on early recognition, and encouragement to health care seeking behaviour.
	Health & Wellness Centre level	CHO	
	Primary Health Centre level	MO	
	Community Health Centre level	MO/ Specialist	Advice on healthy lifestyle and risk reduction as applicable, with provision of physiotherapy services if available.
	District Hospital level	Specialist	
	Med College level	Specialist	Advice on long term rehabilitation as applicable , at the post VTE recovery stage
	Tertiary Hospital level	Specialist / Sub Specialist	

ASHA: Accredited Social Health Activist; ANM: Auxiliary Nurse Midwife; CHO: Community Health officer; MO: Medical Officer.

ANNEXURE 10

AREAS OF RESEARCH/FUTURE DIRECTIONS

Advances in technology and pharmacology have already improved our ability to predict and prevent VTE. However, the following major barriers to improving VTE prevention still exist:

(a) the limitations on the overall benefit to thromboprophylaxis inherent to current anticoagulant medications.
(b) the imperfect science of individualizing VTE risk stratification and the inherent complexity of predicting multifactorial and competing phenomena.

As per various position papers, future direction can be focused toward therapeutics and technology, including the importance of antithrombotic options with less bleeding and technological advances, including artificial intelligence and machine learning to refine risk stratification and facilitate their implementation.

A more pragmatic approach to pharmacologic prevention is what is necessitated in India today given the diversity in healthcare settings. Over the past decade, the tolerability, acceptability, and quality of life for patients at risk of VTE have changed with the advent of effective oral therapies for VTE treatment and prevention. In those with cancer, patient-reported quality of life is better with oral anticoagulant treatment compared to daily subcutaneous LMWH injection. While not as rigorously studied, quality-of-life improvements with oral therapies are likely similar in the prophylactic setting.

Novel agents for pharmacologic prophylaxis are currently being developed that target various factors. If these trials or other new agents are successful at reducing VTE without substantially increasing the risk of bleeding, existing approaches to VTE prevention could change dramatically.

Efforts to predict and prevent venous thromboembolic disease are predicated on our ability to accurately identify patients at risk. The benefits of thromboprophylaxis must be weighed against the financial costs and potential for increased bleeding. Understanding which patients are at greatest risk can help healthcare professionals and their patients to make informed decisions about the use of anticoagulants to prevent VTE. We must continue to collect and analyze large datasets on patient-specific and acquired risk factors and how they interact to improve existing risk assessment models.

The discovery and evaluation of novel biomarkers to risk-stratify patients may be an area of significant interest going forward, and serum biomarkers such as Vascular Endothelial Growth Factor (VEGF), Interferon-alpha, Interleukin-15 (IL-15), and Citrullinated histone H3 (H3cit) may see further investigation for this purpose.

The development and validation of prediction models should seek to increase the accuracy of prediction without sacrificing usability. As we seek to individualize preventive efforts, the primary obstacles that affect the implementation of risk assessment models will be the complications and complexity of any proposed algorithm. Scoring systems and other risk-assessment models can be implemented for use by healthcare professionals if they are easily accessible and understood, but developing sufficient predictive power for VTE often requires the combination of several variables. Scoring systems can quickly become time-consuming for use by physicians, and hiring additional data entry personnel adds significant cost. Predictive algorithms that appropriately consider and calculate bleeding risks for individual patients to avoid harm from VTE prophylaxis increase complexity and add additional workload. Scoring systems developed in the present times must not lose sight of the practical challenges of implementation by treating clinicians in busy hospital settings.

We have made tremendous progress in understanding the epidemiology and prevention of VTE and have transitioned from studies detailing the benefits of "mini-dose" unfractionated heparin given to postoperative patients to sophisticated algorithms that leverage patient-specific and acquired risk factors to determine which patients will derive the greatest benefit from VTE prophylaxis. As scoring systems and other decision support tools increase in accuracy and complexity, we risk overburdening overworked clinicians, and hence, we need to be aware of this pitfall.

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We are grateful to the tireless guidance and inspirational leadership provided by Lt Gen Velu Nair, Chairperson of the VTE TF in identifying, perusing and distilling a multitude of international guidelines focused on various aspects of VTE and developing an actionable and up-to-date guidance for the Indian context taking into consideration published Indian data on the subject.

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The TF Secretariat undertook extensive reviews of literature and evidence and collated them with an overarching view to present an easy-to-refer format for clinicians in the Indian context. The public health and health systems focus and orientation was maintained consistently through the proceedings of the TF and the resultant document by the efforts of the Secretary, Col MP Cariappa.

The contributions of various other Hemato-Oncologists and other domain experts are acknowledged.

OPERATIONAL DEFINITION OF TERMS USED

Pulmonary embolus refers to obstruction of the pulmonary artery or one of its branches by material (e.g., thrombus, tumor, air, or fat) that originated elsewhere in the body. Patients with ***acute PE*** typically develop symptoms and signs immediately after obstruction of pulmonary vessels. Some patients with PE may also present ***subacutely*** within days or weeks following the initial event. Patients with ***chronic PE*** slowly develop symptoms of pulmonary hypertension over many years (i.e., chronic thromboembolic pulmonary hypertension; CTEPH).

Symptomatic PE refers to the presence of symptoms that usually leads to the radiologic confirmation of PE, whereas ***asymptomatic PE*** refers to the incidental finding of PE on imaging (e.g., contrast-enhanced computed tomography performed for another reason) in a patient without symptoms.

LIST OF ABBREVIATIONS

ACCP: American College of Chest Physicians

AHA: American Heart Association

APLA: Anti-phospholipid antibody syndrome

ASCO: American Society of Clinical Oncology

ASH: American Society of Hematology

BMI: Body mass index

CrCl: Creatinine clearance

DOAC: Direct acting oral anticoagulant

DVT: Deep venous thrombosis

ENDORSE: Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting

ESA: European Society of Anesthesiology

ESC: European Society of Cardiology

HIT: Heparin-induced thrombocytopenia

IPC: Intermittent pneumatic compression

ISHBT: Indian Society of Hematology & Blood Transfusion

ITAC: International Initiative on Thrombosis and Cancer

IVC: Inferior vena cava

LMWH: Low molecular weight heparin

NICE: National Institute of Clinical Excellence

OSA: Obstructive sleep apnea

PAH: Pulmonary artery hypertension

PE: Pulmonary embolism

PICO: Population, intervention, comparator, and outcome

PTS: Post-thrombotic syndrome

RV: Right ventricle

SVT: Splanchnic vein thrombosis

TF: Task Force

UFH: Unfractionated heparin

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

VT: Venous thrombosis

SUGGESTED READINGS

1. Cohen H, Cuadrado MJ, Erkan D, Duarte-Garcia A, Isenberg DA, Knight JS, *et al*. 16th International Congress on Antiphospholipid Antibodies Task Force. Report on Antiphospholipid Syndrome Treatment Trends: Lupus 2020;29:1571–93.
2. Agarwala S, Bhagwat AS, Modhe J. Deep vein thrombosis in Indian patients undergoing major lower limb surgery. Indian J Surg 2003;65:159–62.
3. American Heart Association. The Postthrombotic Syndrome-Guidelines. Circulation 2014;130:1636–61.
4. American Society of Hematology. 2018 guidelines for management of venous thromboembolism: Venous thromboembolism in the context of pregnancy. Blood Adv 2018;2:3317–59.
5. American Society of Hematology. 2019 guidelines for management of venous thromboembolism: Prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898–944
6. American Society of Hematology. 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4:4693–738
7. American Society of Hematology. 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Adv 2021;5:927–74
8. Anghel L, Sascău R, Radu R, Stătescu C. From Classical laboratory parameters to novel biomarkers for the diagnosis of venous thrombosis. Int J Mol Sci 2020;21:1920.
9. American College of Chest Physicians. Antithrombotic Therapy and prevention of thrombosis, evidence-based clinical practice guidelines. Chest 2012;141:e419S–e494S
10. American College of Chest Physicians. Antithrombotic therapy for VTE disease guideline and expert panel report. Chest 2016;149:315–52
11. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Second update of the CHEST guideline and expert panel report. Chest 2021;160:2247–59
12. Anghel L, Sascău R, Radu R, Stătescu C. From classical laboratory parameters to novel biomarkers for the diagnosis of venous thrombosis. Int J Mol Sci 2020;21:1920.
13. Bagaria V, Modi N, Panghate A, Vaidya S. Incidence and risk factors for development of venous thromboembolism in Indian patients undergoing major orthopaedic surgery: Results of a prospective study. Postgrad Med J 2006;82:136–9.
14. Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, *et al*. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol 2010;149:209–20.
15. Basavanthappa RP, Vivek Vardhan JP, Gangadharan AN, Desai SC, Anagavalli Ramswamy C, Luthra L, *et al*. RAVS Study: An Indian single center analysis of patients with VTE. Ann Vasc Dis 2019;12:205–9.
16. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715–22.
17. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, *et al*. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): A multinational cross-sectional study. Lancet 2008;371:387–94.
18. Dantkale SS, Dalal SK, Gunaki RB. Is thromboprophylaxis really justified among Indian population with femur shaft fractures treated with IM nailing? Int J Orthop Sci 2018;4:492–5.
19. Dhillon KS, Askander A, Doraismay S. Postoperative deep-vein thrombosis in Asian patients is not a rarity: A prospective study of 88 patients with no prophylaxis. J Bone Joint Surg Br 1996;78:427–30.
20. Duranteau J, Taccone FS, Verhamme P, Ageno W, ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis. Eur J Anaesthesiol 2018;35:142-6.
21. Jain V, Dhal AK, Dhaon BK. Deep vein thrombosis after total hip arthroplasty in Indian patients with and without Enoxaparin. J Orth Surg (Hong Kong) 2004;12:173–7.
22. Jakhetiya A, Shukla NK, Deo SVS, Garg PK, Thulkar S. Deep vein thrombosis in indian cancer patients undergoing major thoracic and abdomino-pelvic surgery. Indian J Surg Oncol 2016;7:425–9.
23. Kamerkar DR, John MJ, Desai SC, Dsilva LC, Joglekar SJ. Arrive: A retrospective registry of Indian patients with venous thromboembolism. Indian J Crit Care Med 2016;20:150-8.
24. Kapoor CS, Mehta AK, Patel K, Golwala PP. Prevalence of deep vein thrombosis in patients with lower limb trauma. J Clin Orthop Trauma 2016;7(Suppl 2):220–4.
25. Lee AD, Stephen E, Agarwal S, Premkumar P. Venous Thrombo-embolism in India. Eur J Vasc Endovasc Surg 2009;37:482–5.
26. Mavalankar AP, Majmundar D, Sudha R. Routine chemoprophylaxis for DVT in Indian patients. Indian J Orthop 2007;41:188–91.

27. Nair V, Kumar R, Singh BK, Sharma A, Joshi GR, Pathak K. Comparative study of extended versus short term thromboprophylaxis in patients undergoing elective total hip and knee arthroplasty in Indian population. Indian J Orthop 2013;47:161–7.
28. Nair V, Singh S, Ashraf MZ, Yanamandra U, Sharma V, Prabhakar A, *et al*. Epidemiology and pathophysiology of vascular thrombosis in acclimatized lowlanders at high altitude: A prospective longitudinal study. The Lancet Regional Health - Southeast Asia 2022;3:100016
29. NICE (UK). Venous thromboembolism Guidelines; 2018 & 2020.
30. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. J Clin Med 2020;9:2467.
31. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). The surgeon general's call to action to prevent deep vein thrombosis and pulmonary embolism. Rockville (MD): Office of the Surgeon General (US); 2008.
32. Parakh R, Kakkar VV, Kakkar AK; Venous Thromboembolism (VTE) Core Study Group. Management of venous thromboembolism. J Assoc Physicians India 2007;55:49–70.
33. Pawar P, Ayyappan MK, Jagan J, Rajendra N, Mathur K, Raju R. Analysis of patients with venous thromboembolism in a multi-specialty tertiary hospital in South India. Indian J Vasc Endovasc Surg 2020;7:29–33.
34. Pinjala R, ENDORSE-India Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE), a multinational cross-sectional study: Results from the Indian subset data. Indian J Med Res 2012;136:60-7.
35. Prabhudesai A, Shetty S, Ghosh K, Kulkarni B. Dysfunctional fibrinolysis and cerebral venous thrombosis. Blood Cells Mol Dis 2017;65:51–5.
36. Sahoo DR, Dorairajan G, Palanivel C. Risk stratification for venous thrombosis in post–partum women in a tertiary care setup in south India. Indian J Med Res 2020;152:523–6.
37. Saket R, Aggarwal S, Kumar V, Kumar P, Patel S. Acute venous thromboembolism in Indian patients of isolated proximal femur fractures. J Clin Orthop Trauma 2019;10:917–21.
38. ESC Working Group. Second consensus document on diagnosis and management of acute deep vein thrombosis: Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. Eur J Prev Cardiol 2022;29:1248–63
39. Sehrawat A, Mittal GS, Sundriyal D, Chaturvedi A, Gupta D. Cancer–associated venous thromboembolism in ambulatory solid organ malignancy patients: Experience from a cancer research institute. Indian J Surg Oncol 2021;12:246–50.
40. Sen RK, Kumar A, Tripathy SK, Aggarwal S, Khandelwal N, Manoharan SR. Risk of postoperative venous thromboembolism in Indian patients sustaining pelvi–acetabular injury. Int Orthop 2011;35:1057–63.
41. Shrikhande SV, Verma M. A prospective observational study to determine rate of thromboprophylaxis in oncology patients undergoing abdominal or pelvic surgery. Indian J Surg Oncol 2021;12:279–85.
42. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. Arch Intern Med 1998;158:585–93.
43. Singh G, Rathi AK, Singh K, Sharma D. VTE in cancer patients – magnitude of problem, approach, and management. Indian J Cancer 2017;54:308–12.
44. Singh S, Kapoor S, Singh B, Tandon R, Singla S, Singla T, *et al*. Real world data on clinical profile, management and outcomes of venous thromboembolism from a tertiary care centre in India. Indian Heart J 2021;73:336–41
45. Spirk D, Sebastian T, Hans Beer J, Mazzolai L, Aujesky D, Hayoz D, *et al*. Role of age, sex, and specific provoking factors on the distal versus proximal presentation of first symptomatic deep vein thrombosis: Analysis of the SWIss Venous Thrombo Embolism Registry (SWIVTER). Intern Emerg Med 2022;17:799–803.

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Task Force Report

NAMS task force report on Organ donation and transplantation

National Academy of Medical Sciences (India), New Delhi, India.*

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*A list of Task force members of the Venous thromboembolism can be found in the report.

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PREFACE

Organ transplantation is known to save lives. There is a huge unmet need for organs and there is a widening gap between the requirement of Organs and transplants in patients with end stage organ failure. While live donor Organ donation is well established in India, despite an enabling law, deceased Organ donation has not been picked up across the country except for states in the south and west because of the proactive action taken by individual state authorities along with non-government bodies. While there is wide publicity on Organ donations, the awareness is far from optimum. In fact, the reluctance of clinicians to identify and certify brain stem death (BSD) and counseling the families for organ donation has been a major factor that has hampered the growth of deceased Organ donation in our country. Hence there is an urgent need to take an audit of all deaths including brain stem deaths that occur in the hospitals. It is imperative to highlight that with advancements in medical skills and technology, patients in need of Organ transplants should be given another chance in life to live and contribute to the society. We must recognize that Organs donated by families are a national asset.

EXECUTIVE SUMMARY

To promote deceased organ donation, the Government of India enacted the Transplantation of Human Organs and Tissues Act, 1994 (THOTA) to regulate Organ retrieval, storage, and transplantation for therapeutic purposes and prevent commercial dealing in human Organs and tissues. Since 2011, the Government of India also implemented the National Organ Transplant Program (NOTP) through states/union territories (UTs), to provide an organizational and financial framework for promoting deceased organ and tissue donation and transplantation in the country.

However, there is a enormous shortage of availability of Organs as compared to the number of patients who require Organ transplantation, resulting in a wide gap between demand and supply.

The National Academy of Medical Sciences (NAMS) of India formed a Task Force to identify the current status of Organ donation and transplantation, the exact deficiencies in the system, and to recommend ways to improve Organ donation and transplantation in India.

The Task Force formed a consensus among the members based on their expertise, experience, and extensive review of up-to-date published literature from India and abroad and made the following key observations and recommendations:

- The committee felt that Organs donated are a national asset and Organ transplantation should be a national priority.
- The Ministry of Health and Family Welfare assessed that there is an estimated need for 175,000 kidney, 50,000 liver, heart, lung, and 2500 pancreas transplants in India per year. The Organ donation rate in India has remained stable at less than 1 per million population (PMP) from 2013 till date. To achieve self-sufficiency in Organ donation the estimated rate would be around 124 PMP.
- The committee noted that the southern and western states in India have been doing better in the field of deceased Organ donation and the Task Force suggested a need to duplicate their best practices to increase momentum in other parts of the country.
- They also noticed a lack of information and training on brain stem death identification, certification and maintenance of Organ donor coupled with a shortage of manpower, suboptimal utilization, and lack of infrastructure in government as well as private hospitals. Hence, dedicated Department of Intensive Care Medicine, Non-Transplant Organ Retrieval Centers (NTORC), and Organ Transplantation should be created in all medical colleges and major government hospitals.

- The committee felt that all deaths in the hospital's ICU should be identified and communicated to the concerned State Organ & Tissue Transplant Organization SOTTOs or health authorities. The declaration of "Brain Stem Death" should be made mandatory for all government and private hospitals, as provided in the THOTA Rules.
- Hospitals with more than 200 beds should be involved in Organ donation.
- Widespread recognition of NTORC should be implemented using the Hub and Spoke model and simplifying requirements in Form 13 of the THOTA Rules of 2014.
- Dedicated infrastructure and Organ transplant department/unit manned by trained dedicated faculty must be created in at least one public sector hospital in each state for Organ transplantation on the lines of Institute of Kidney Diseases and Research Center – Institute of Transplantation Sciences (IKDRC-ITS), Institute of Liver and Biliary Sciences (ILBS), New Delhi and Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, which can function as Organ retrieval centers in the first phase. Multi-Organ Retrieval teams should be formed in all major hospitals. In fact, all Institute of National Importance (INI) should be made Organ transplantation centers and respective departments supporting them should be made, e.g., Department/Division of Hepatology, Division of Pancreatology.
- To maximize the utilization of deceased Organs, particularly Extended Criteria of Organs should be adopted, and provision should be made to do Machine Perfusion of Organs. For that, a clause should be added in THOTA Rules 2014 or a circular be issued by GoI.
- Ancillary tests for BSD certification should be permitted when the Apnoea test cannot be performed.
- A Standard Operating Procedure (SOP) is to be prepared for Organ donation after donation after circulatory death (DCD).
- Creation of an Independent State Appropriate Authority to exclusively look after issues related to Organ transplantation.
- Aν advisory committee should be formed to promote service, education, and research in Organ transplantation.
- Organ donation pledges have significantly increased in the country, but awareness and ease of doing should be publicized. In fact, all driving licenses should include a provision for pledging of Organs.
- National Organ & Tissue Transplant Organization (NOTTO) should be made administratively and financially robust.
- There should be more manpower and budget in the NOTTO office for service, education, and research in Organ donation and transplantation.
- Appointment of Director of NOTTO/Regional Organ & Tissue Transplant Organization (ROTTO)/State Organ & Tissue Transplant Organization (SOTTO) by a central agency and lateral entry to be permitted for these appointments with no age bar.
- Regular review of the performance of ROTTO/SOTTO by an independent audit committee of NOTTO.
- Linking of all hospitals with SOTTO/ROTTO/NOTTO through One Digital Platform with daily updates of the information.
- Revision of general and Organ-specific listing and allocation policies.
- Rules for Organ donation from deceased donors and living donors to be separated.
- Rules for tissue donations to be separate from deceased Organ donations.
- Research on Organ Preservation and Organ Resuscitation using modern technology should be permitted using discarded/unutilized deceased donor Organs and for that amend the law/rules.
- There is a need for more guidelines and consensus statements from NOTTO with inputs from transplant professionals and societies such as the Indian Society of Organ Transplantation (ISOT) on common clinical practice issues.
- Reporting of long-term Transplant Recipient and Donor outcomes to NOTTO should be mandated.
- Legal hurdles like the hierarchy of consent, post-mortem permissions throughout the day, and SOPs for donation in medico-legal cases should be clearly defined.
- Pradhan Mantri Jan Arogya Yojana (PMJAY) – Ayushman Bharat Scheme has included kidney and bone marrow transplantation. There is a need to widen its ambit to include the heart, lungs, liver, pancreas, and other Organs, and the amount should be increased.

INTRODUCTION

Organ transplantation gives a new lease of life to patients with end stage Organ failure. While in India, over the years living donors had been the primary source of kidneys for transplantation, the last decade and a half has seen live donors being the main source of livers also. However, there is a need to reverse this trend.

Almost 160,000 fatal road traffic accidental (RTA) deaths happen in India, and almost 60% have associated head injury (almost 90 per million possible brain deaths from RTA). Similarly, Cerebro Vascular Accident (CVA) is another common cause of BSD in India (prevalence rate of CVA ranging from 44.54 to 150 per 100,000 population) and 30 days case fatality rate ranging from 18% to 46.3%,[1,2] and these are also part of deceased donor pool in our country. A large number of Organs from these patients could be harvested for transplantation.

The number of persons donating Organs after death in India is less than one per million population, which is almost similar to some Asian countries like Japan but far less than most Western countries. [In 2020, the United States and Spain had the highest rates of deceased Organ donors in select Organisation for Economic Co-operation and Development (OECD) countries, with almost 38 people per million population, whereas Greece (4.6), Russia (3.9), and Turkey (3) had the least donation rate].[3]

Surprisingly, according to an Ipsos survey in 2018 about people's willingness to donate organs after death, Colombia and India, with 75% and 74%, respectively, had the highest percentage of willing people to donate organs after death, ahead of Spain (72%), UK (67%), and Germany (53%).[4] This may be due to the campaigns undertaken by non-government organizations in the country. Mass media, religious, and political leaders may be involved to maximize awareness about Organ donation. Thirty-two percent of the study participants believe that there is a danger that donated Organs could be misused, abused, or misappropriated.[5]

Organ transplantation represents the final choice for life, as without a transplant, the patient will die. Thus, Organ transplantation is a field of medicine with extremely huge stakes. In this huge stake area, the transplant community should be constantly looking at mechanisms to boost the Organ supply. This also includes maximizing the utilization of brain deaths, diminishing the missed opportunities for donation, and also considering expanded criteria of donor Organ.

Barriers to donation: While the need for Organ donors is high in the Indian population, the actual number of donors remain low to help the number of recipients on the waiting list. Reluctance to donate Organs is not only within Indian borders but also extends to the Indian population in the UK and Canada.[6]

Societal issues: In certain regions of the country, there is less reluctance when it comes to donation in comparison to other regions. A study in north India found that the majority of individuals who were suffering from renal failure and on dialysis were unlikely to be an Organ donor since their families had not initiated any conversation on Organ donation. Such conversations play an important role in decision-making during consent. Many have been unaware of how to register, which means campaigns for Organ donation registration should be improved. Fear and mistrust are also the main roadblocks due to media news items appearing of illegal Organ donation and transplant practices. Body disfigurement was the least reason for Organ donation. Though no religion is against Organ donation, many donors use this as a reason for not giving consent. It was also found that nuclear families agreed more rapidly for Organ donation.[7] In a survey from South India involving 300 participants to a questionnaire on Organ donation, less than half of the study participants were knowledgeable about the definition of brain death and the existence of organ donation law. Although they were in favor of organ donation, there were still some doubts related to family support.[8]

Hospital issues: A recently published study showed a lack of knowledge on clinical criteria for brain death and legal issues pre-intervention, which improved post-intervention, after they participated in an interactive educational module. This intervention significantly improved the tendency of doctors and nurses to promote Organ donation, pledging their Organs, and for counseling patients/attendants on this cause.[9] There is no magic bullet to increase the Organ donation rates. Addressing donor shortages requires a multipronged strategy considering barriers to Organ donation as they manifest across a society.

Spain's achievements of a high Organ donation rate are attributed to its systems in place and wide government support. It has a vast transplant coordination network of doctors and nurses specially trained in reporting and approaching family members for Organ donation. They also stress education/health care infrastructure and human resources, forming a multipronged approach that is tailored to develop transplants in that country.[10]

As part of a national network, the National Organ & Tissue Transplant Organization (NOTTO) and five regional organizations, namely Regional Organ & Tissue Transplant Organization (ROTTO) at Mumbai, Kolkata, Chandigarh, Chennai, and Guwahati cover Western, Eastern, Northern,

Southern, and North-Eastern regions of the country, respectively, were established. It was envisaged to set up one State Organ & Tissue Transplant Organization (SOTTO) in each state, with 14 SOTTOS already sanctioned so far. These organizations integrate efforts of the states, institutions, healthcare professionals, non-government organization, and members of the community.

The National Organ Transplant Program was first conceived in 2011–2012 and its detailed guidelines entitled "Highlights of National Organ and Tissue Transplant Programme & Operational Guidelines for its implementation" were first published in 2015. After the inception of the program, the total number of Organ transplants in the country increased from 4990 in the year 2013 to 12,746 in the year 2019 and Organ donation rate (no. of deceased donors per million populations) increased from 0.16 in the year 2012 to 0.65 in the year 2018.

TERMS OF REFERENCE (TORS) FOR THE TASK FORCE

The Executive Council of the National Academy of Medical Sciences (India) assigned the following terms of reference for the Task Force on Organ donation and transplantation in April 2022.

a. To identify the current status of Organ donation and transplantation in India.
b. Identify the exact deficiencies.
c. To suggest and recommend ways of improvement in the area of Organ transplantation.

METHODOLOGY

The Task Force conducted meetings using a virtual platform and Focused Group Discussions were held. In addition, the Chairperson co-opted expert members as and when required to facilitate the discussions. The relevant technical documents, published papers, reports, like NOTP Guidelines and various State Guidelines, were used as background materials.

The key recommendations were arrived at by consensus of the members based on their expertise and experience.

BACKGROUND: HOW MANY TRANSPLANTS ARE CONDUCTED IN INDIA PER MILLION?

The current status of Organ donation and transplantation in India is shown in Figure 1–7:

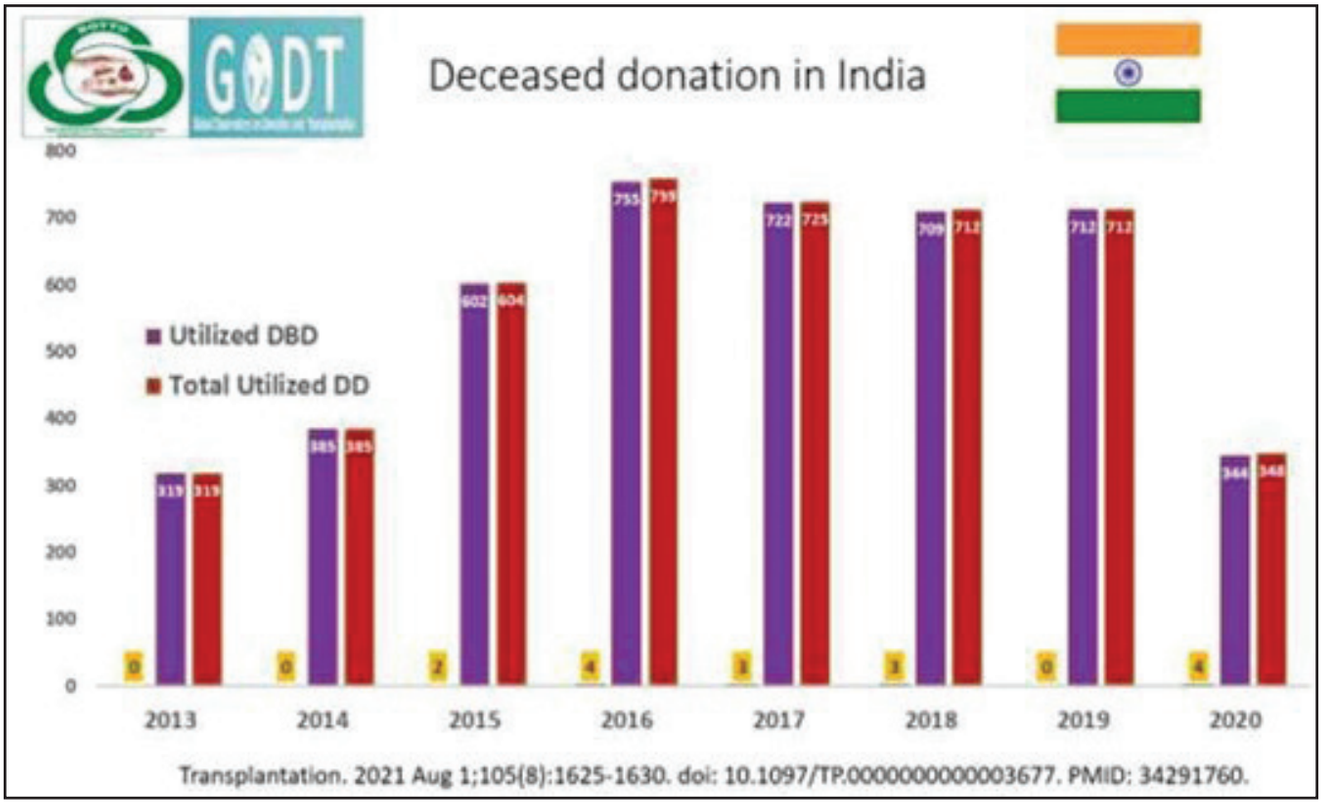

Figure 1: DD: Deceased donor; DBD: Donation after Brain Death.
Source: National Organ & Tissue Transplant Organization (NOTTO)

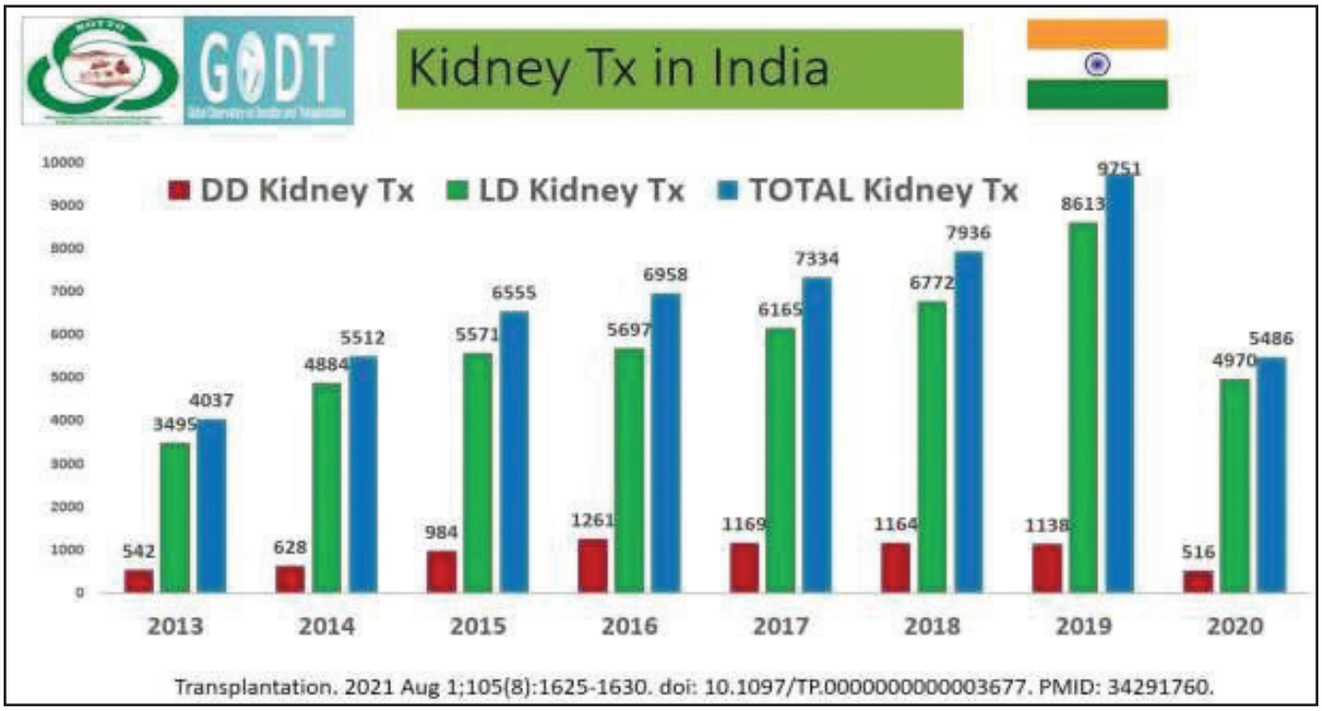

Figure 2
DD: Deceased Donor; LD: Live Donor; Kidney Tx: Kidney transplant.
Source: National Organ & Tissue Transplant Organization (NOTTO).

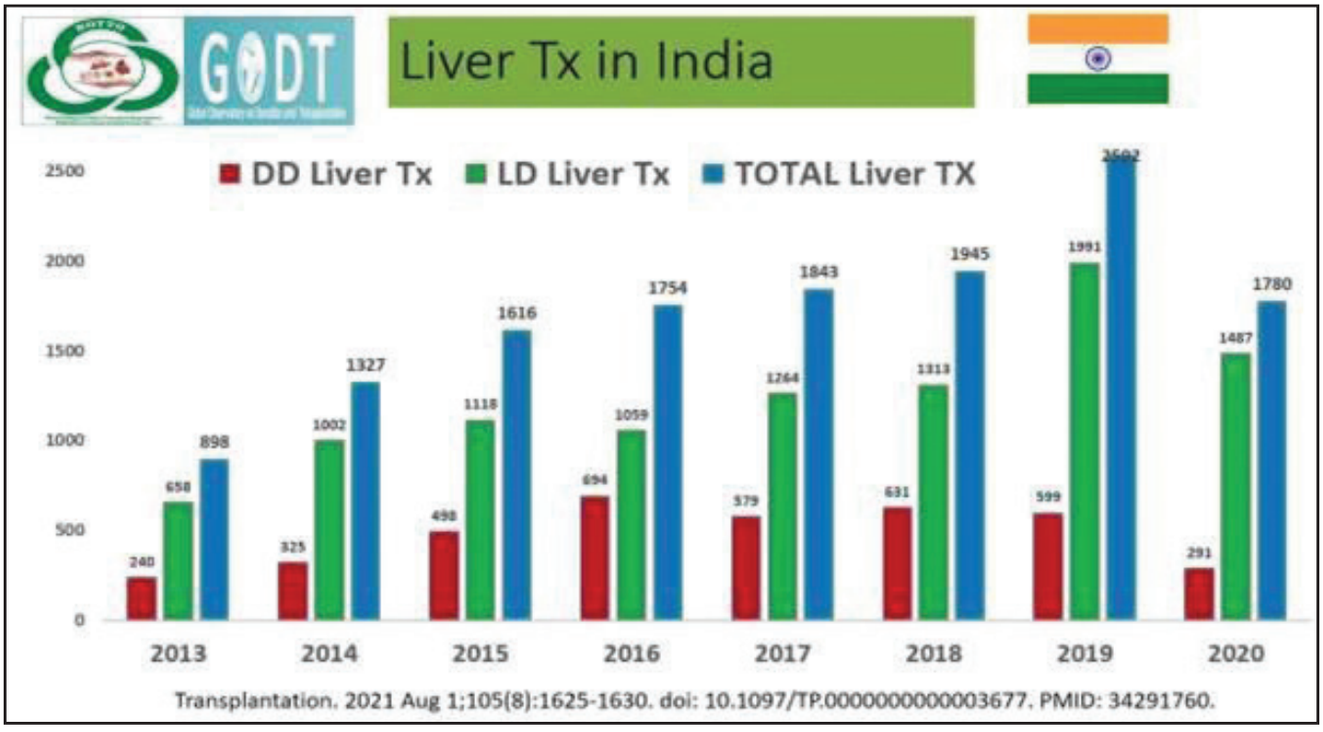

Figure 3
DD: Deceased Donor; LD: Live Donor; Liver Tx: Liver transplant.
Source: National Organ & Tissue Transplant Organization (NOTTO).

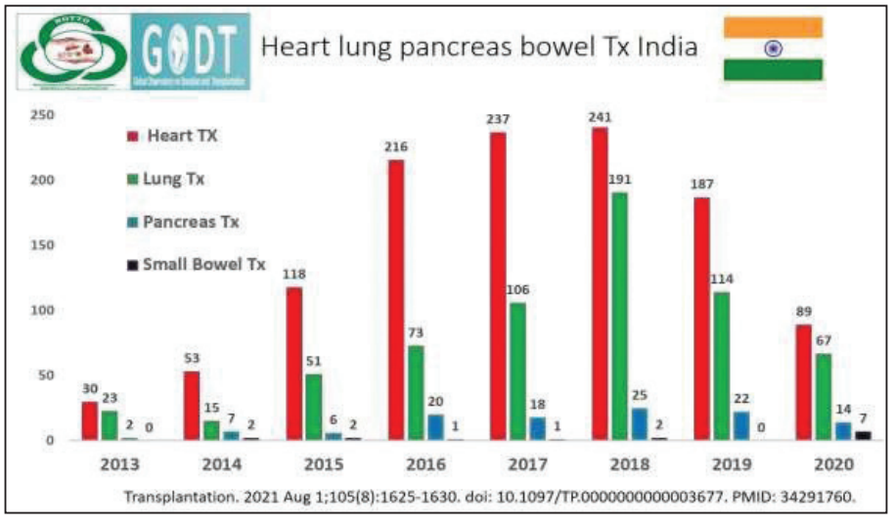

Figure 4: Transplantations done from 2013 to 2020 of Heart, Lungs, Pancreas & small bowel.
Tx: Transplant.
Source: National Organ & Tissue Transplant Organization (NOTTO).

Organ Deceased Donor Organ Donation & Transplantation (DDOT)

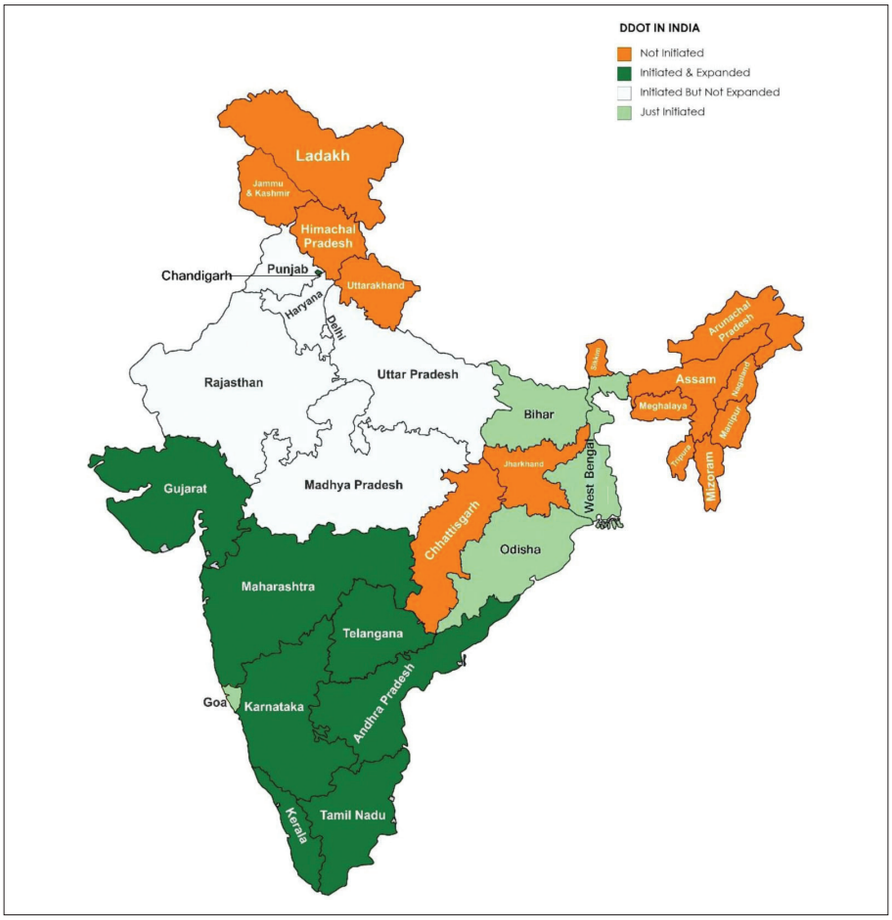

Figure 5
States shown in green have well-established Deceased Organ Donation programs (dark green states) to expand DDOT in emerging states (light green, orange states).
Source: National Organ & Tissue Transplant Organization (NOTTO).

Total Transplants in India (2020)

Figure 6: Distribution of total transplantation in Different Regions of India 2020
Source: National Organ & Tissue Transplant Organization (NOTTO).

Total Transplants in India (2021)

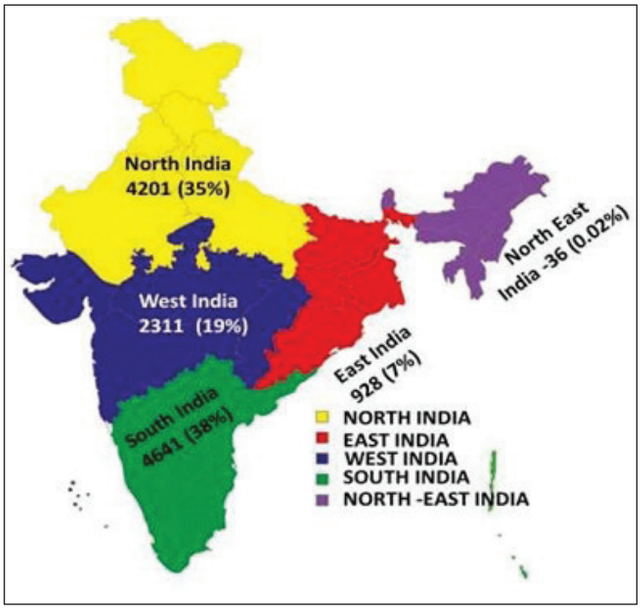

Figure 7: Distribution of total transplantation in Different Regions of India
Source: National Organ & Tissue Transplant Organization (NOTTO).

*2021 data is tentative (before submission to WHO-GODT 2021) as some of the states may make minor changes in their data.

Organ Donation Statistics

Organ donation statistics				
	2020*		2021**	
	Public	Private	Public	Private
Deceased	118	458	171	521
Living	492	4152	827	6029
Total	610	4610	998	6550

Data shared by NOTP
Note: Public facilities include Autonomous Hospitals and Private facilities include Trust Managed Hospitals.
**Data as per the survey conducted in January 2022 for 618 hospitals that are the part of National Registry.

OBSERVATION

Current situation in the country

- About 160,000 deaths happen annually due to road traffic accidents in India – even if 10% (16,000) of these are converted as Organ donors, that will generate an average of 3 Organs per donor (as per Zonal Transplant Coordination Centre (ZTCC) Mumbai data), resulting in 45,000 Organ transplantations (livers, kidneys, hearts, lungs, pancreas, and small bowel).
- CVA is another common cause of BSD in India, and these could also add to the deceased donor pool in our country (ZTCC Mumbai donor data).
- The Organ donation rate (the number of deceased donors per million population) in the country increased from 0.27 in the year 2013 to 0.65 in 2018, however, it dipped to 0.52 in 2019. And are far less than compared to a maximum of around 48 in Spain.
- There is an estimated need for 175,000 kidney and 50,000 each liver, heart, and lung transplants in India. 80% of kidney and liver transplants and 95% of heart, lung, and pancreas transplant services are in private hospitals where the cost is prohibitive for the common man with end-stage Organ failure.
- Currently, it is estimated that only 10% of kidney failure patients get some form of renal replacement therapy (dialysis or transplant) due to the problems of access to tertiary care and financial constraints. However, the growth of healthcare and provision of dialysis facilities in all the 773 districts in the country by GoI, would mean a spurt in the patients requiring access to transplants.
- India is the third country in the world after the USA and China, in terms of the total number of transplants done in a year.
- The total number of transplants done in the country has increased from 4990 in 2013 to 12,666 in 2019, indicating a marked improvement in infrastructure for undertaking transplants in the country and this was mostly due to the growth of private healthcare.

- Organ transplantation in India to date relies predominantly (80.3%) on living donor procedures for kidney and liver transplantation. Heart, lung, pancreas, and small bowel transplants are therefore less frequent.

Current infrastructure, facilities, technologies, policies, programs, etc. in the country in context of the problem/ health issue

- A total of 618 hospitals undertaking transplantation or retrieval in the country are now registered with NOTTO for networking and National Registry. This indicates significant progress in the establishment of an organized system in the country for Organ procurement from deceased donors and their distribution and transplantation to the needy citizens of the country. However, the data entry by the hospitals in the National Registry remains incomplete.
- The number of persons who have pledged for Organ and/or tissue donation with NOTTO is now more than 1.4 million, out of which more than 300,000 have been registered online. This indicates a significant improvement in awareness about Organ donation.
- Capacity for undertaking rare transplants, e.g., pancreas, intestine, hand, limbs, lung, and uterus has developed within the country, besides a significant enhancement in capacities for undertaking relatively common transplants of kidney, liver, and heart.
- Some transplant centers, including PGIMER Chandigarh, have also developed capacities for undertaking donation after cardiac death.

Current budget

The following is the grant in aid under the National Organ Transplantation Program (NOTP) available for the promotion of Organ transplantation.

	Amount
ROTTO: Recurring Grant per annum	**Rs. 1.05 crore**
SOTTO: 1. Non-Recurring grant for setting up of SOTTOs 2. Recurring grant for manpower.	**Rs. 36 lakh** **Rs. 48 lakh**
RETRIEVAL CENTRE: for setting up	**Rs. 75 lakh**
TRANSPLANT CENTRE: For setting up	**Rs. 1.50 Cr.**
UPGRADATION of existing retrieval/transplant unit	**Rs. 75 lakh**
TRANSPLANT COORDINATORS:: Govt. institutions-2 TCs, PVT. Centres- 1 TC Identified Govt. Trauma Centres- 1 TC	**Rs. 35,000/PM per transplant coordinator**
Bio-material Centre (only for ROTTO)-	**Rs. 1.0 Cr.**
IMMUNO-SUPPRESSANT THERAPY to BPL transplant recipients in Govt. hospitals	**Rs. 10,000/month**
DIGNIFIED FUNERAL OF DECEASED DONOR	**Rs. 10,000/per deceased person**
MAINTENANCE OF BODIES OF DECEASED DONOR	**Rs. 1,00,000/- per donation**

ROTTO: Regional Organ & Tissue Transplant Organization; SOTTO: State Organ & Tissue Transplant Organization; TC: Transplant Coordinator.

Summary of total budget for Organ donation and transplantation

(Tentative year-wise distribution for 2021–2022 to 2025–2026 as per proposed outlay in lakhs of rupees)

S.No.	Component	(2021–2022) Proposed outlay	(2022–2023) Proposed outlay	(2023–2024) Proposed outlay	(2024–2025) Proposed outlay	(2025–2026) Proposed outlay	Total in Rs. (Lakh)
1	IEC Activities	129	129	114	114	114	600
2	National THOA and NOTP Cell	25	40	45	45	45	200
3	NOTTO including National Biomaterial Centee	300	325	325	375	400	1725
4	ROTTO and SOTTO (5)	109	114.25	119.76	125.55	131.63	600.19
5	SOTTO (20)	450	480	534	588	600	2652

(*Continued*)

S.No.	Component	(2021–2022) Proposed outlay	(2022–2023) Proposed outlay	(2023–2024) Proposed outlay	(2024–2025) Proposed outlay	(2025–2026) Proposed outlay	Total in Rs. (Lakh)
6	Bio-material Centers -3 at ROTTOs/SOTTOs	100	-	100	-	100	300
	States at 100 lakh per center						
7	Govt. supported online system of networking	150	50	50	25	25	300
8	Training	50	75	75	100	100	400
9	Skill center(s)	50	50	50	50	-	200
10	Support for immune-suppressants	75	75	100	125	125	500
11	Coordination with trauma centers	10	10	10	10	10	50
12	Coordination with goverment medical colleges and good performing private centers	50	50	50	75	75	300
13	New retrieval/transplant facility and strengthening old transplant facility in government medical colleges/ institutions	200	300	200	200	200	1100
14	Support for maintenance of Cadavers in retrieval centers at Rs. 100,000 per cadaver for 5 cadavers per year	5	5	5	5	5	25
15	Support for Organ transportation through ROTTO and NOTTO at 1 crore per year	10	10	10	10	10	50
16	Grant to cover expenses for dignified funeral of deceased donor (support of Rs. 10,000 to each donor family)	40	50	60	70	80	300
17	Outcome monitoring	2	2	2	2	2	10
18	International cooperation	30	30	30	30	30	150
19	Evaluation	0	0	0	0	30	30
	Grand total	1785	1795.25	1879.76	1949.55	2082.63	9492.19

Total Proposal for 5 years = 9492.19 Lakh = 94.92 Crore; data given by NOTTO.
THOA: Transplantation of Human Organs and Tissues Act 1994; NOTP: National Organ Transplantation Program; ROTTO: Regional Organ & Tissue Transplant Organization; SOTTO: State Organ & Tissue Transplant Organization; NOTTO: National Organ & Tissue Transplant Organization

KEY ISSUES/GAPS IDENTIFIED IN THE CURRENT SITUATION IN THE COUNTRY IN THE CONTEXT OF THE PROBLEM/HEALTH ISSUE

Deficiencies in the program

- Lack of brain stem death identification, certification and maintenance of Organs for donation
- Shortage of manpower in government as well as private hospitals.
- Lack of infrastructure/suboptimal utilization of infrastructure in the government sector.
- The provision of Non-Transplant Organ Retrieval Centers (NTORC) in the law has also not been optimally utilized.
- Guidelines related to donation after circulatory death are lacking.
- Non-utilization of the grant under various heads of the National Program.
- There is a regional imbalance. The Organ donation should happen in all the regions and should not remain concentrated in any geographical region. This creates problems with equity and the allocation of Organs.
- Manpower working in SOTTO/ROTTO is having additional charge of SOTTO/ROTTO so adequate time cannot be devoted to Organ donation-related activities. It would be better to have such posts on full-time basis to devote more time to Organ donation rather than just giving additional charge of SOTTO/ROTTO posts.

Recommendations made to bridge the critical gaps/ deficiencies in this aspect

a. Brain death

- There should be a uniform declaration of death with a mode of death being brain stem death (BSD)/ cardiopulmonary death (circulatory death).

- The declaration of "Brain Stem Death" should be made mandatory for all hospitals, both private and government. The THOTA Rules provide for the same, however, the rule is not being followed in letter and spirit.
- The hospital staff in medical colleges, district hospitals, and other retrieval centers that have ICU and ventilator facilities should be trained in the concept of BSD. There should be regular training programs on BSD for staff from medical colleges, district hospitals, and major corporate hospitals.
- All BSD certifying specialists should be registered with local authorities.
- The procedure for the donation of Organs in Medico Legal Case (MLC) should be streamlined and nation/state wise SOPs to be made.
- Monthly audit of BSD must be done regularly by the concerned SOTTOs. The data pertaining to the declaration of BSD should be online as well as re-certification process should have a mandatory review of the number of brain deaths identified and audit reports of such activities from the ICU.
- Training of ICU staff in family conversation for end-of-life care should be regularly conducted. The number of trained staff in the ICU for end-of-life conversations should be introduced in a phased manner. SOP for donation procedure within the hospital should be a mandatory requirement for certification

b. Regulatory bodies

- There are around 618 registered transplant centers and only 140 non-transplant retrieval centers. The retrieval centers must proportionally be increased by incentivizing them.
- Registration of Non-Transplant Organ Retrieval Centers (NTORC): The process for registration of NTORCs should be simplified. The hub and spoke model can be followed with big hospitals as hubs and NTORCs as spokes. Registered transplant hospitals can be tied up with trauma centers. In fact, all the trauma centers in the country should be registered.
- All the medical colleges and hospitals can be identified as NTORCs.
- Written SOPs with clear guidelines regarding manpower and equipment requirements should be shared with these NTORCs.
- Apex National Body: Empowered and robust NOTTO with more financial powers should be there to work in the field of Organ donation and transplantation.
- The Appropriate Authority should be a designated senior official only handling Organ donation and transplant on a full-time basis.
- Independent oversight committee with representation of Appropriate Authority (AA) & Apex National Body.
- Monthly activities of NOTTO, SOTTO, and ROTTO should be notified on the website including future workshops.
- The performance of SOTTOs should be assessed on a regular basis with a possibility of transfer if found unsatisfactory.

c. Hospitals and ICU*:*

Death audits

- Monthly audits of death, including BSD must be done on a regular basis by the concerned SOTTOs to find out the missed opportunities and possible solutions. The data pertaining to the declaration of BSD should be reported online on a central NOTTO interface.
- Training of ICU staff in family conversation for end-of-life care should be regularly conducted and made mandatory.
- SOP for donation procedure within the hospital should be a mandatory requirement for certification.
- Re-certification process for a transplant license should have a mandatory review of
    - Number of brain deaths identified and audit reports of such activities from ICU.
    - SOPs for Organ donation pathways.
    - Family conversation for end-of-life care workshops conducted.
    - The number of trained staff in ICUs for end-of-life conversations should be introduced in a phased manner. Re-certification should consider the performance in this aspect.

Grief counselors/Transplant coordinators

- At least four existing staff in the hospitals can be identified, trained, and designated as transplant coordinators.
- The transplant coordinators for deceased donor family counseling should be different from those handling transplant recipients.

Role of police

- The police must designate nodal officers to coordinate Organ donation-related activities.
- The investigating officers/station house officer of the police station under which the hospital falls should be directed to assist in Organ procurement as mandated in the THOTA Act.
- The respective governments must be directed to instruct police chiefs to hold regular awareness meetings for all investigating officers/station house officers.
- The police also need to be sensitized about the importance of Organ donation and medico-legal issues should be eased.

Education and training

- Organ transplant units should be there in all medical colleges and All India Institute of Medical Sciences (AIIMS) institutions. Such units should have faculty with expertise in the field of Organ transplantation and at least should become Organ retrieval centers in the first phase and have a brain death certification committee wherever possible. Multi-organ retrieval teams should be available in all major hospitals.
- State governments should identify one medical college in their state that can become a center for excellence as a multi-organ transplantation hospital to help with the training of manpower and growth of the program.
- Advanced transplant centers should be there in all INIs with individual Organ subdivisions. These centers should have a common ICU so that it could be managed with less logistics and manpower. Specialized departments for cardiac, lung, and Hepato Pancreato Biliary (HPB) surgery, and liver transplants should be created in all INIs to enhance the seriousness of multi-organ transplants. Stress must be laid on the recruitment of people with passion in the field of Organ transplantation to give a fillip to the program.
- Training related to Organ transplant and prospective donors after the declaration of BSD should be given to all concerned physicians/surgeons.
- All postgraduates should be trained in BSD like they are being trained in BLS and ALTS regularly. It would increase awareness and strengthen the concept of BSD, and make the foundation strong.
- More consultants should be systematically trained in the field of Organ transplantation.
- Transplant Societies and non-government organizations could help in the training of ICU professionals and surgeons in multi-Organ transplants. The competence of the transplant surgeons and the team should be objectively assessed.
- A letter from the Secretary of Health, Director General of Health Services (DGHS), or National Medical Commission (NMC) may go to different states and medical colleges to start donor action programs.
- Trauma centers should be better equipped to handle brain deaths (ventilators, Arterial Blood Gas (ABG) machines, and other equipment). This would help in both saving lives and early identification of brain deaths.
- Fellowships as well as short-term attachments should be available/started at transplant centers.
- A pool of certified transplant surgeons must be created for capacity building in the field of Organ donation and transplantation.
- The curriculum/training on BSD should be imparted to all residents, faculty, and nurse staff. Organ donation chapters should be included in the curriculum. Besides, public awareness should be increased.

Infrastructure

- All medical colleges, district hospitals, and trauma centers should be actively involved in transplant-related fields.
- INIs should have transplant departments for multi-organ transplants and have permission for fellowships training in transplant.
- A dedicated Department of Intensive Care Medicine should be created in all medical colleges and major government hospitals.
- Dedicated infrastructure must be created in the Public Sector for Organ Transplantation on lines of IKRDC-ITS Ahmedabad, ILBS New Delhi, and PGIMER: Chandigarh. Few ICU beds can be dedicated for Organ donation in government hospitals. In all INIs dedicated ICUs and HDUs should be made as per standard protocol. This will strengthen the infrastructure for Organ transplantation from the beginning and new AIIMS will have accountability for Organ transplantation.
- To maximize the utilization of deceased Organs, particularly extended criteria Organs, a provision should be made to do machine perfusion of Organs and for that, a clause should be added in THOTA Rules 2014 or a circular should be issued by GoI.
- Organ transplant units should be formed in all medical colleges and AIIMS-like institutions. At least they should become Organ retrieval centers in the first phase and have a brain death certification committee. Such units should have faculty with expertise in the field of Organ transplantation and plan to have multi-organ retrieval team in all major hospitals.
- Separate departments for multi-organ transplantation need to be created in one medical college of each state to promote Organ donation and transplantation. Advanced transplant centers should be there in all INIs with individual Organ subdivisions. These centers should have a common ICU so that it could be managed with less logistics and manpower. Departments of HPB Surgery & Liver Transplant and Department of Hepatology should be created in all INIs to enhance the seriousness towards liver transplant. The same should be adopted for other Organs as well. Stress must be laid on the recruitment of people with passion in the field of Organ transplantation.

Challenges and Solutions for Deceased Donor Organ Transplantation (DDOT) in India.	
Challenges	**Solutions for Deceased Donor Organ Transplantation (DDOT) in India**
Awareness	• Prime Minister highlighted DDOT in "Mann Ki Baat" radio program • "Mobile caller tune, festival celebration, walkathon" on Organ donation theme • Religious/faith leaders and non-government Organization support to overcome religious, socio-cultural barriers • Social media, TV, and digital reforms are quicker, easier, and more cost-effective to disseminate DDOT in large populations in India • Implementing options to Organ pledges while applying for a driving license in all states • Include Organ donation in the education system syllabus, developing information, education, and communication materials as per regional need • Facility for offline and online pledging for donation of Organ
Grief counseling	• Mandatory dedicated grief counselors in emergency rooms and ICU doctors, treating, and primary care doctors should initiate GC/DDOT
Brain Stem Death (BSD) declaration	• BSD declaration needs to be separated from DDOT • Uniform guidelines for BSD declaration by government authority • Mandatory BSD declaration and reporting to state authority • Donor pledge form (form 7) requires a legal status
ICU Team	• All transplant hospitals must have a team headed by an intensivist and supported by a team of ICU nurses, counselors, and coordinators • Early and proactive donor identification and management • The highest standard for donor care with no out-of-pocket expenditure • Increase donor conversion rate with regular e-learning modules
Registry, Allocation, Transplant Team	• Uniform data collection and data management systems should be developed at the national level and state level organizations should have admin access to state data • Government priority and support to develop self-sufficiency in transplant • The commitment of authorities, institutions, and individuals for the pledge, waiting list, and transplant outcome registry • Non-transplant Organ retrieval centers license on priority • Government guidelines for donation after circulatory death donors • "One Nation One Policy" for digital Organ allocation: must be localized to the state and when the state declines, it goes to the regional and national level
Nonfinancial incentives	• Honoring family members on Organ Donation Day and World Kidney Day • Memory tree plantation in honoring Organ donors • Social support (cremation rituals), government health cards to dependent family members of Organ donors and educational support to children of a sole bread earning deceased donor
Collaboration, Advisory Committees	• Government authority, transplant collaboration with related national societies including The Transplantation Society • State- and national-level advisory committees of experts should be engaged in policy making and revisions • A 24/7 call center has been made operational with the provision of a toll-free helpline by the National Organ and Tissue Transplant Organization (NOTTO) • NOTTO apex technical committees developed broad guiding principles for allocation
Expand DDOT in Public Sector Hospitals	• Leadership and dedicated transplant team • Use key features of successful DDOT model (dark green states in Figure 1) to expand DDOT in emerging states (light green and orange states in Figure 1) • Initiate and expand DDOT for heart, lung, and pancreas • Living and deceased donors advocate to decrease waiting time on DDOT
Training, Capacity building	• Organ transplant fellowships • Local multi-organ retrieval team to avoid delay in multi-organ retrieval by multiple teams
Audit	• Audit of counseling, brain death declaration, Organ donation, utilization rate, and transplant outcome • Accountability of hospitals getting licenses for Organ donation and transplantation and outcome registry • Regulatory oversight of the entire transplant program is the responsibility of the state authority • Root cause analysis of social distrust and lack of awareness
Future	• Machine perfusion to reduce discard rates • There is a need for "One Nation and One deceased donor allocation policy" and "One Nation and One Digital platform" for SOTTO/ROTTO/NOTTO website and data reporting
DDOT: Deceased Donor Organ Donation & Transplantation; NOTTO: National Organ & Tissue Transplant Organization; ROTTO: Regional Organ & Tissue Transplant Organization; SOTTO: State Organ & Tissue Transplant Organization.	

NOTTO and financial aspect

- The Government of India has earmarked funds for setting up a transplant center but this needs to be widely publicized and centers pushed to accept these funds with financial accountability. The fund utilization in this field is sub-optimal.
- The grant allocated for various components should be visible at the level of NOTTO, ROTTO, and SOTTO. There should be a separate finance officer at the national or regional level for the grant and processing of the payments.
- NOTTO could be made more robust by recruiting new officers with varied backgrounds like finance, etc. and SOPs should be made for the use of grants allocated for various components under NOTTO.
- A full-time designated official in top positions (at NOTTO, ROTTO, and SOTTO) with a keen interest in Organ transplantation and donation should be appointed. Lateral entry for suitable candidates with experience in the field should be allowed with no age bar.
- Audit should be conducted at the level of NOTTO to evaluate the work done by ROTTO and SOTTO and they should be made accountable.
- There is an urgent need to make Organ donation and transplantation affordable. Drugs like immuno-suppressants, preservative solutions for Organ transportation, and other consumables required for Organ transplantation should be made tax-free.
- The inclusion of Organ transplantation under Ayushman Bharat PMJAY by GOI is a good step and financial support from corporates through Corporate Social Responsibility and Crowd Funding should be encouraged for poor patients. The post-transplantation expenditure should also be taken into account.
- States that have not adopted Transplantation of Human Organs and Tissues Act 1994 (THOA) should be requested to do so. Letters from Director Genertal of Health Services (DGHS) enumerating all funds should be sent to all state Directorate of Health Services (DHS) for setting up SOTTO in their states and registering all licensed transplant centers and retrieval centers. Enhancement and improvement of the National Registry into computerized data collection and automatic computerized allocation to have a transparent allocation.
- Incentives to hospitals – who provide complete data to health authorities such as SOTTO/NOTTO.
- Regular meetings by AA for reviewing the progress from time to time of SOTTO/ROTTO and NOTTO.
- Regional Directors of the Government of India Health and Family Welfare should be involved in facilitating the operationalization and implementation of various schemes of NOTP.
- Greater involvement of the neuro critical care team of hospitals to enhance donor identification and Organ donation. They may be the preferred nodal officers of the hospital for all Organ donations and transplant-related matters.
- Conferences of these specialties should have a session on Organ donation and transplantation.
- Annual conferences should be organized by NOTTO/ROTTO/SOTTO and widely published.

National THOTA and NOTP Cell

- It has the role of representing and renewal of all Organ and tissue transplant centers and monitoring transplants and retrieval in respective states and UTs.
- Give consultancy on transplant law and program-related matters.
- Facilitating National Organ Donation/World Organ Donation Day.
- Looking after technical, administrative, and financial matters of NOTP, implementation and monitoring of its various components.

Organ transportation

- Organ transportation by air can be taken up as a Corporate Social Responsibility (CSR) by corporates, the Indian Airforce can be involved in addition to the Ministry of Civil Aviation. Organ transportation by drones can also be considered.
- Facilities for Organ transportation by road/air ambulances should be available at subsidized rates.

Tissue donation

- Tissue donation has to be promoted. The tissue donation needs to be looked at by an independent Apex Technical Committee constituted for this purpose.

Best practices

- Best practices from state Government Orders (G.O.) to facilitate deceased organ donation may be compiled and evaluated, and later adopted based on merit.
- A modified The United Network for Organ Sharing (UNOS) model has been in practice in Maharashtra for over 20 years should be looked into and implemented.

Recommendations made to bridge the critical gaps/ deficiencies in this aspect in THOTA rules of 2014

Current problem in Form 13: The requirements for infrastructure and manpower are almost similar to those

for registration of a transplant center. There is no need to change Form 13 for recognition of NTORC. There is a need to simplify the process and a MoU can be signed.

- All BSD certifying specialists should be registered with local authorities.
- If there is a deceased donor in a non-registered hospital and the family is willing to donation of Organs and or tissues, then "In such non-registered hospital the death will be certified by two certified specialists from the registered transplant hospital or NTORC and retrieval of Organs and tissues can be done at the same hospital by teams from registered transplant hospital or shifted to a registered NTORC or transplant hospital". In such cases, donor-specific/time-specific permission by Appropriate Authority may be granted when the family comes forward to donate the Organs.
- Alternatives/Ancillary tests to Apnea test. BSD certification in a person where either:
  a. Apnoea test cannot be done due to hemodynamic instability or
  b. Cranial nerve reflexes cannot be tested due to eye/facial injuries, where actions to be taken.

Use ancillary tests to document the absence of cerebral blood flow as per international practices: BSD certifying specialist to decide the tests to be performed e.g., 4-vessel cerebral angio/CT cerebral Angio/MR angio/Trans Cranial Doppler/Isotope scan, depending on availability of facilities.

Any other

- In all cardiac deaths, the option of tissue donation should be offered.
- Role of digitization: the digitization of the Organ Donation Registry to avoid man-made errors.
- 24-hour call center at NOTTO.
- Tree plantation drives in the name of donors and other ways to honor their families.
- Awareness in schools and colleges on Organ donation.
- National Health Insurance for Organ Transplantation.
- Orientation and sensitization of various stakeholders like judges, legal experts, police, and traffic personnel, etc. on Organ donation and transplant centers.

WAY FORWARD

It is a well-known fact that Non Governmental Organisation (NGO) in the past have played a pivotal role in the promotion of eye and blood donation. An inclusive working group is required to be created from all regions to include all the stakeholders from both public and private bodies including medical societies such as Indian Society of Organ Transplantation (ISOT) and NGOs.

Increasing awareness:

- More full-time manpower and budget should be allocated to NOTTO and NOTP.
- Creation of modified UNOS model of Organ Procurement and Transplantation Network (OPTN) and Organ Procurement Organisations (OPOS) as being practiced in Maharashtra (ZTCCs) having financial self-sufficiency to be looked into.
- There is a need to increase awareness about Organ transplantation among medical professionals.
- Awareness posters about Organ donation should be installed at all hospitals (trauma center and ICU) and prominent places (such as shopping malls, railway stations, government offices, and banks). The "Ang Daan Jeevan Daan" posters having toll-free numbers should be installed at important places in all hospitals.
- If any Organ donation and transplantation is being performed, such an event may be displayed on LED or as a blinking light on dashboards at NOTTO, ROTTO, SOTTO offices, and other prominent places to sensitize the public at large.
- There should be a provision in the driving license about willingness to donate Organs in all states.
- Smart cards should be issued to Organ donors.

Key actions

- Adoption of THOTA by states who have not accepted as yet.
- Establish SOTTO in each state to develop an effective and organized system of Organ procurement.
- Govt institutions – augment infrastructure for Organ donation and transplant (identify medical colleges without infrastructure).
- Register all trauma centers as Organ retrieval centers.
- Have transplant coordinators in each hospital.
- Make intensivists and critical care doctors as Nodal officers.
- Creation of independent AA in each state.
- Reporting of long-term transplant recipient and donor outcomes to NOTTO should be mandated.
- Organ transplantation from deceased donors after cardiac death is underutilized in India and should be promoted.

ACKNOWLEDGMENTS

The contributions made by various domain experts in the field of "Organ" donation and transplantation, NOTTO, Ministry of Health & Family Welfare Government of India (GOI), and the support provided by the National Academy of Medical Sciences (India) and MOHAN Foundation are acknowledged.

OPERATIONAL DEFINITION OF TERMS USED IN THE REPORT

Brain stem death: Transplantation of Human Organs and Tissues Act (THOTA) defines brain stem death (BSD) as "the stage at which all functions of the brain stem have permanently and irreversibly ceased" and is so certified under Section 3 (6) of the Act. The BSD can be certified only by a board of Medical experts nominated from the panel of names approved by the Appropriate Authority (AA).

Circulatory death or cardiac death: Irreversible cessation of circulatory and respiratory functions.

Deceased donation: Organ donation by an individual who has been certified as deceased either due to brain stem or cardiac death.

Living donation: Organ donation by a living donor is generally limited to renal and hepatic donation.

Organ transplantation: This involves a surgical procedure to implant Organs or composite tissue from the donor into a recipient. Not all donations result in actual transplantation.

Organ procurement process: This involves:

A. Identification of potential BSD patient in ICU, family counseling about the criticality of the clinical situation by treating clinicians and intensivist, followed by confirmation of BSD by the expert clinical team as per the THOTA, discussion with family about Organ donation by clinicians and transplant coordinator and seeking consent for Organ donation from the family of a deceased individual.
B. Communication with local Organ Distribution Organizations in the state for organ allocation to recipients as per the organ-specific allocation guidelines.

Organ retrieval, preservation, and transportation: This involves a surgical procedure of retrieving various Organs, their cold preservation, and transportation to transplant centers.

LIST OF ABBREVIATIONS

THOTA: Transplantation of Human Organs and Tissues Act, 1994

NOTP: National Organ Transplant Program

NOTTO: National Organ & Tissue Transplant Organization

ROTTO: Regional Organ & Tissue Transplant Organization

SOTTO: State Organ & Tissue Transplant Organization

DDOT: Deceased Donor Organ Donation & Transplantation

WHO-GODT: WHO Global Observatory on Donation and Transplantation

TC: Transplant Coordinator

NTORC: Non-Transplant Organ Retrieval Centers

BSD: Brain Stem Death

MLC: Medico Legal Case

AA: Appropriate Authority

IKDRC-ITS: Smt. G.R. Doshi and Smt. K.M. Mehta Institute of Kidney Diseases and Research Center and Dr. H.L. Trivedi Institute of Transplantation Sciences (IKDRC-ITS), Ahmedabad

PMJAY: Pradhan Mantri Jan Arogya Yojana

CSR: Corporate Social Responsibility

INI: Institute of National Importance

UNOS: The United Network for Organ Sharing

ZTCC: Zonal Transplant Coordination Centre

DCD: donation after circulatory death

ILBS: Institute of Liver and Biliary Sciences, New Delhi

PGIMER: Postgraduate Institute of Medical Education & Research, Chandigarh

GOI: Government of India

REFERENCES

1. Vincent BP, Randhawa G, Cook E. Barriers towards deceased organ donation among Indians living globally: An integrative systematic review using narrative synthesis. BMJ Open 2022;12:e056094.
2. Khurana S, Gourie-Devi M, Sharma S, Kushwaha S. Burden of stroke in India during 1960 to 2018: A systematic review and meta-analysis of community based surveys. Neurol India [serial online] 2021 [cited 2022 Aug 2];69:547–559. Available from: https://www.neurologyindia.com/text.asp?2021/69/3/547/317240
3. Organ transplantation number worldwide 2020 – Available from: Statista https://www.statista.com, State of Health.
4. Organ Donation: Where are the Most People Willing? HEALTH by Martin Armstrong, Sep 6, 2018. Available from: https://www.statista.com, State of Health.
5. Deceased Organ donor rate in selected countries 2020; Health, Pharma & Medtech, State of Health Published by John Elflein, Oct 4, 2021.
6. Li AH, Lam NN, Dhanani S, Weir M, Prakash V, Kim J, *et al*. Registration for deceased organ and tissue donation among Ontario immigrants: A population-based cross-sectional study. CMAJ Open 2016;4:E551–E561.
7. Balwani MR, Kute VB, Patel H, Shah PR, Goswami J, Ghule P, *et al*. Awareness and beliefs towards organ donation in chronic

kidney disease patients in western India. J Nephropharmacol 2015;4:57–60..
8. Vincent BD, Kumar G, Parameswaran S, Kar SS. Knowledge attitude & perception on organ donation among undergraduate, medical & nursing students at a tertiary care center hospital in some other part of India: A cross sectional study. J Educ Health Promo 2019:9:161.
9. Mahagam P, Koushal V, Chhabra R, Dhaliwal N, Pandey N, Kaur R. Effectiveness of international strategies in modulating knowledge & attitude of health care professionals for promoting organ donation. A study in a tertiary care hospital in North India. Ann Neursui 2020:27:242–58.
10. Matesanz R, Domminiquez GR, Coll E, Mahíllo B, Marazuela R. How Spain reached 40 deceased organ donation per million population. Am J Transpl 2017:17:1447–54.

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Task Force Report

NAMS task force report on Alcohol, substance use disorders, and behavioral addictions in India

National Academy of Medical Sciences (India), New Delhi, India.*

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PREFACE

Substance use disorders and behavioral addictions are now recognized as an important public health issue. Many psychoactive substances are being used in India, including alcohol, tobacco, opioids, cannabis, sedative-hypnotics, volatile solvents, etc. These are associated with multiple health problems, diseases, and disability, which can progress on to an early death. The use of psychoactive substances additionally result in a burden on the family members and also has social costs. In recent times, behavioral addictions have emerged as another related problem needing initiatives on the part of health professionals and policymakers. Subjects with substance use disorders, as well as behavioral addictions, need help and treatment. In India, a range of services are available for helping patients with substance use disorders and behavioral addictions. However, more concerted efforts are required to improve the outcomes of patients with these illnesses. The report of the Task Force on Alcohol, Substance Use Disorders, and Behavioral Addictions of the National Academy of Medical Sciences (India) provides a roadmap and recommendations to improve upon the availability and delivery of treatment for substance use disorders and behavioral addictions in India.

EXECUTIVE SUMMARY

Substance use disorders are a growing concern in India. In the last decade, behavioral addictions have also emerged as a key mental health challenge. Community-based surveys have suggested that substance use disorders affect a significant proportion of the population. These disorders cause impairment of physical, psychological, social, and financial health. The burden attributable to the use of substances at the population level is considerable.

The high magnitude of substance use disorders and behavioral addictions calls for a multipronged and multifaceted action. The approaches to addressing substance use disorders can generally be categorized into supply reduction (reduction of availability of substances), demand reduction (effective treatment of substance use disorders and awareness to reduce initiation of substance use), and harm reduction (reducing the harms associated with substance use, without necessarily targeting cessation of substance use). Acute treatment phase of detoxification is followed by maintenance treatment and rehabilitation. All of these interventions and approaches have their role. From a public health perspective, substance use disorders and behavioral addictions are commonly observed in the primary care clinical setting (outpatient, inpatient, and emergency), and empowering a range of medical professionals for screening and providing treatment for addictive disorders can be an important step in improving the availability of services. There is a distinct role of prevention, whereby preventive measures can be instituted at schools, colleges, workplaces, and communities. There is a need for convergence to jointly address the problem of substance abuse under a coordinating body.

Medical professionals can play an important role in mitigating the effect of substance use disorders and behavioral addictions in the general population. The National Academy of Medical Sciences (India) (NAMS), can play a key role by offering considered views for addressing substance use disorders and behavioral addictions in the Indian population. In pursuance of the meeting of NAMS held on 21st April 2022, a Task Force was constituted on Alcohol and Substance Use Disorders and Behavioral Addictions. The Task Force has the mandate to develop a white paper to be submitted to the Government of India for improving the health intervention activities in the area of alcohol and substance abuse disorders and behavioral addictions. The Task Force reviewed the current reports and data pertaining to alcohol and substance use disorders and behavioral addictions in India. It then developed a consensus on the key observations and key recommendations, taking into consideration the healthcare services and the varied social-cultural-economic contexts across the Indian landscape.

The key takeaways and recommendations are as follows:

Policy

- A national alcohol policy is required in India in line with the WHO global strategy to reduce the harmful use of alcohol.
- Relocation of all health-related activities for alcohol, drugs, and behavioral addictions within the Ministry of Health and Family Welfare.
- Legislative policies to divert patients with substance use disorders with small quantities of recovered substances toward medical care in lieu of criminal proceedings and incarceration; sensitizing important stakeholders, including law enforcement authorities and judiciary, on the need to distinguish users from drug dealers.
- Telemedicine rules and guidelines should facilitate the treatment of substance use disorders and behavioral addictions.

Services and training

- Sensitization and education of primary healthcare providers about the detection of substance use disorders and behavioral addictions and their treatment. Screening, brief intervention, and referral to treatment can be more frequently done in primary care.
- Optimum utilization of online training mechanisms for the training of medical professionals about substance use disorders and behavioral addictions. As a long-term goal, there is a need to incorporate the Ministry of Health and Family Welfare-approved addiction psychiatry curriculum at the MBBS level.
- Expanding the healthcare services available and making a basket of services available to cater to the different needs of the population.

Education and Awareness

- Enhancing awareness about substance use and the harms associated with it, especially in the younger population and educational institutions.
- Health promotion measures to enhance prosocial behaviors to reduce substance use experimentation among the younger population.

INTRODUCTION

Substance use disorders and behavioral addictions are growing public health problems all over the world, including India.[1-4] Substances that are commonly used in India include tobacco (both smoked and smokeless forms), alcohol (beer, wine, spirit, toddy, etc.), cannabis (bhang, ganja, charas, etc.), and opioids (heroin, raw opium, *Doda,* pharmaceutical opioids, etc.). While many people use substances, some of them suffer adverse health consequences, develop dependence, and/or require help and treatment. Sometimes, certain rewarding behaviors like playing video games and gambling may become excessive and can lead to serious social, financial, and legal consequences. These excessive behaviors are manifestations of behavioral addictions, as the person finds it difficult to stop indulging in these behaviors despite acknowledging the harms caused by these behaviors.

Community-based surveys have suggested that substance use disorders and behavioral addictions affect a substantial proportion of the population. Among the substance users, some become regular users, exhibit problematic patterns of use, and a minority also develop substance dependence as depicted in Figure 1. Similarly, behavioral addictions may also affect a considerable proportion of the population, though a larger proportion may indulge in the behaviors in a nonaddictive manner.[5,6] Many factors play a role in the development of problematic substance use among users. It is seen that the onset of substance use generally starts in adolescence, and multiple biological, psychological, and social factors play a role in the genesis of substance use disorders.

Substance use disorders and behavioral addictions can cause impairment of physical, psychological, social, and financial health at both individual and societal levels. The profile of substances being used has changed over time, as evidenced by the changing profile of patients.[7] There has also been an increase in behavioral addictions, reflected by an increase in the number of adolescents presenting with addiction to Internet/gaming disorders.

Substance use is a risk factor for many noncommunicable diseases (NCDs) like hypertension, mental health problems, and malignancies.[8,9] Thus, substance use and substance use disorders are likely to be encountered by a range of healthcare professionals and in various settings like routine outpatient, inpatient, wellness clinics, and emergencies. Injection drug

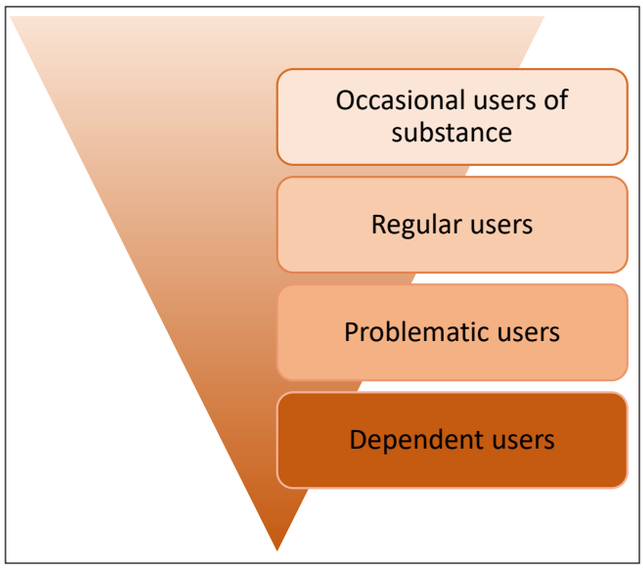

Figure 1: Continuum of substance-related issues.

use (IDU) is associated with increased rates of transmission of the human immunodeficiency virus (HIV), Hepatitis B, and Hepatitis C. Substance use disorders and behavioral addictions are found to be more commonly present along with other mental health conditions than expected by chance, and substance use disorders can worsen the course and outcomes of psychiatric disorders.

The high magnitude of substance use disorders and behavioral addictions call for a multipronged and multifaceted action. The approaches to addressing substance use disorders can generally be categorized into **supply reduction** (reduction of availability of substances), **demand reduction** (effective treatment of substance use disorders and awareness to reduce initiation of substance use), **harm reduction** (reducing the harms associated with substance use, without necessarily effecting cessation of substance use), and **rehabilitation** of individuals who have quit substance use to ensure they return to the mainstream of society. Services can be provided at the primary, secondary, and tertiary levels of care. Apart from therapeutic efforts, preventive efforts also have a major role in reducing the burden of substance use disorders and behavioral addictions. However, different organizations and entities are involved in addressing different aspects of addictive disorders. Hence, there is a need for convergence to jointly address the problem of substance abuse under a coordinating body.

Despite preventive approaches and availability of services, substance use disorders and behavioral addictions remain a serious problem at the community level in India. There is a need to further plan about means and measures to address the issue more coherently and effectively. Medical professionals have the expertise and responsibility to chalk out the manner in which addictive disorders can be better addressed in India. Thus, the present white paper, under the auspices of the National Academy of Medical Sciences (India), discusses the manner in which substance use disorders and behavioral addictions can be tackled better.

BACKGROUND

Medical professionals can play an important role in mitigating the effect of substance use disorders and behavior addictions in the general population. The NAMS, India, has taken the initiative to constitute a task force in this area to develop guidelines for various stakeholders for addressing the problem of substance use disorders and behavioral addictions in the Indian population. In pursuance of the meeting of NAMS held on 21st April 2022 and the constitution of a Task Force on Alcohol and Substance Abuse to develop a white paper to be submitted to the Government of India for improving the health intervention activities in the area of Alcohol and Substance Abuse, the objectives of the task force were laid out.

This white paper document discusses the extent of substance use disorders and behavioral addictions in India and offers a roadmap for policymakers to address these more effectively with the help of medically oriented interventions.

TERMS OF REFERENCE (TORS) FOR THE TASK FORCE

The main objectives of the Task Force are:

1. To identify the current status in the area of alcohol and substance use disorders and behavioral addictions
2. To identify the deficiencies that need to be addressed
3. To recommend the prevention of alcohol and substance use disorder and behavioral addictions and to make improvements in this field.

METHODOLOGY

The Task Force reviewed the current reports and data pertaining to substance use disorders and behavioral addictions in India. It then developed a consensus on the key observations and recommendations, taking into consideration the healthcare services and the varied social-cultural-economic contexts across the Indian landscape. The initial working draft was circulated among the Task Force members, and comments were sought. The working draft was modified based on the suggestions. Subsequently, an online meeting was held on 21st Sept 2022, in which the experts deliberated on the various aspects of the document. Further modifications were made to the document based on the inputs received from the experts.

OBSERVATION/CRITICAL REVIEW

Current situation in the country

Alcohol and other substance use and behavioral addictions constitute an important public health issue all around the world, including India. Several research endeavors have estimated the prevalence of substance use and substance use disorders in India. In this section, we present the magnitude of the problem based on reports from India.

The National Survey on Magnitude of Substance Use in India (2019), conducted by the National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi, has estimated the national and state-wise prevalence of substance use in the country.[1] The survey has reported that alcohol is the most common psychoactive substance used by the Indian population. Nearly 15% of the population aged between 10 and 75 years consume

alcohol. Converting these to absolute numbers, about 16 crore persons consume alcohol in India. The prevalence rate of alcohol use is much higher among men (about 27.3%) as compared to women (1.6%). The states with the highest prevalence of alcohol use, as per this survey, are Chhattisgarh, Tripura, Punjab, Arunachal Pradesh, and Goa. The types of alcohol commonly consumed in India include both country liquor and Indian-made foreign liquor. Among the 16 crore alcohol users, about 5.7 crore individuals were found to be problem users (i.e., experiencing some problems with the use of substances), and about 2.9 crore individuals were identified as dependent users [Figures 2 and 3]. This suggests that there are a large number of individuals with alcohol use disorders.

Cannabis use was reported by about 2.8% of the population. This translates to about 3.1 crore individuals reporting cannabis use in India. Different forms of cannabis used have also been assessed in this survey. About 2% of the population uses *bhang* (translating to about 2.2 crore individuals), and 1.2% of the population uses *ganja* and *charas* (translating to about 1.3 crore individuals). The states with the highest reported prevalence of cannabis use were Uttar Pradesh, Punjab, Sikkim, Chhattisgarh, and Delhi. There were about 72 lakh problem users and 25 lakh dependent users of cannabis across the country [Figure 4].

Opioids were the next common substance of use. About 2.26 crore individuals, translating to about 2.1% of the country's population, consume opioids. Heroin (1.14%), followed by pharmaceutical opioids (0.96%) and raw opium (0.52%), were the commonest opioids being used in India. The states with the highest prevalence of opioid use were Sikkim, Arunachal Pradesh, Nagaland, Manipur, and Mizoram (the prevalence of use in the general population was more than 10%). It was

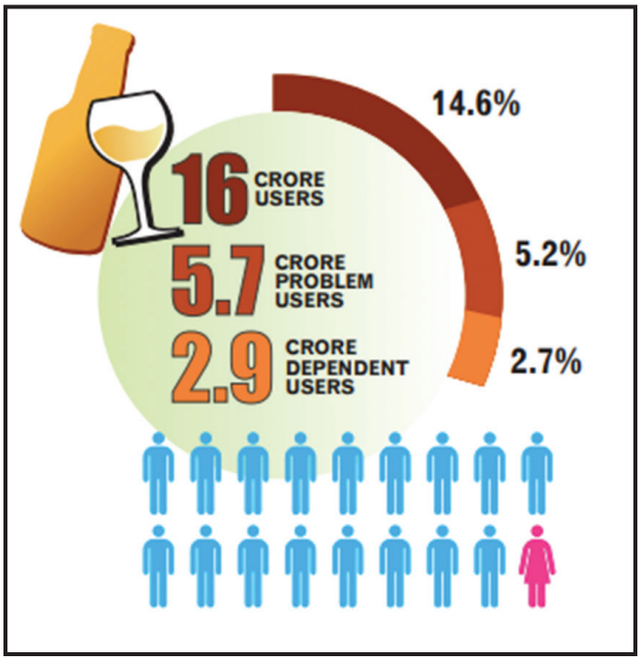

Figure 2: Alcohol use in India.
(**Source**: Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India. 2019.)

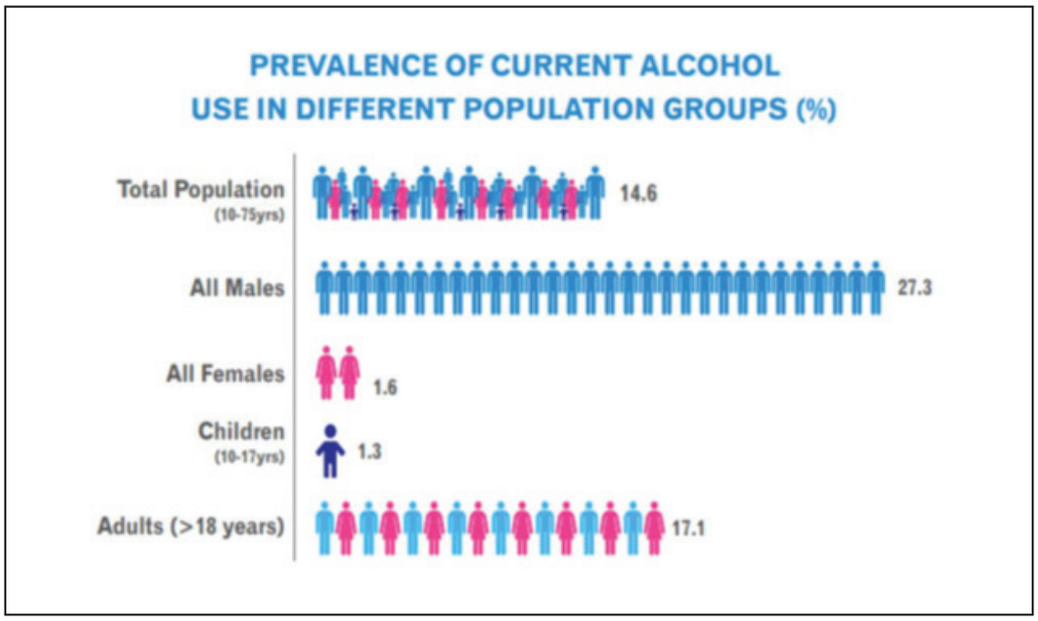

Figure 3: Alcohol use in different population subgroups.
(**Source**: Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India. 2019.)

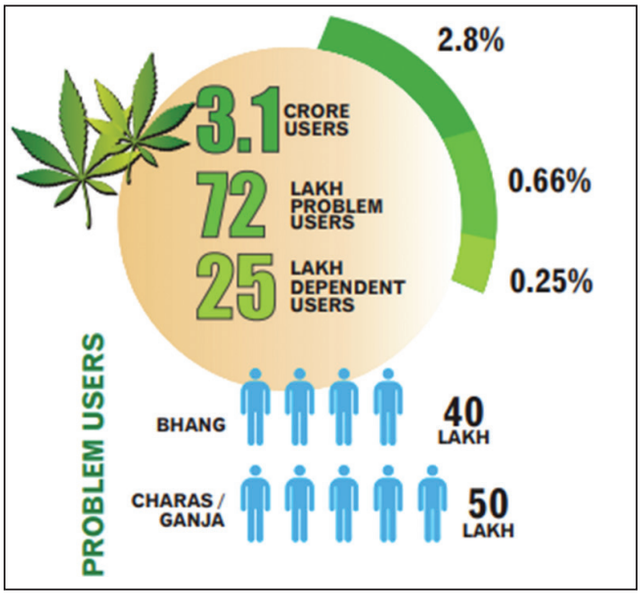

Figure 4: Cannabis use in India.
(**Source**: Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India. 2019.)

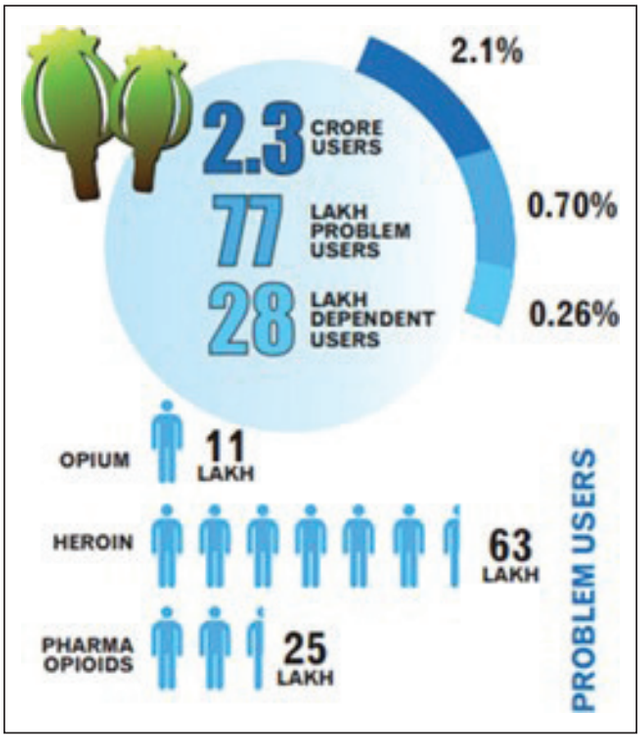

Figure 5: Opioid use in India.
(**Source**: Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India. 2019.)

estimated that there were 77 lakh problem users of opioids, and about 28 lakh dependent users [Figure 5].

The survey estimated 1.08% of the population (translating to about 1.18 crore people) as current users of nonmedical and nonprescription sedatives. Sikkim, Nagaland, Manipur, and Mizoram have the highest prevalence of such sedative usage. Inhalant use was more common among children and adolescents (1.17%) than adults (0.58%). Other categories of drugs, such as cocaine (0.10%), amphetamine-type stimulants (0.18%), and hallucinogens (0.12%), were reported to be used by a smaller proportion of the population.

The National Mental Health Survey of India conducted in the years 2015–2016 has also presented the data on harmful and dependent use of alcohol and other substances.[4] The prevalence of alcohol use disorders was found to be 4.7%, and the prevalence of other substance use disorders (apart from tobacco) was found to be 0.6%. The prevalence of tobacco use disorders was 20.9%. These findings also suggest a high prevalence of substance use disorders in the country.

The rates of tobacco use according to National Family Health Survey - 5 was found to be 38.0% among men and 8.9% among women, though this survey did not present the prevalence of tobacco use disorders per se.[3] Similarly, the prevalence rate of alcohol use among men and women was reported to be 18.3% and 1.3%, respectively.

Of late, behavioral addictions have emerged as an important consideration in India as well.[10] Among them, Internet addiction has drawn research attention across the different states of India.[6] It has been estimated that about 20% to 40% of college students in India are at risk of Internet addiction. Similarly, gambling-related problems have been studied in the Indian context and there is evidence to suggest that 7.4% of college students indulged in problem gambling.[5] Thus, behavioral addictions also need to be addressed from a policy and healthcare perspective in India. However, the literature on behavioral addiction has been limited, and representative national surveys are yet to be conducted on behavioral addictions.

Substance use disorders and behavioral addictions cause adverse health consequences, which result in disability and death. Ramalingam *et al.* (2022)[8] showed that alcoholic liver disease led to more than 8,000 deaths in the National Capital Territory of Delhi in a single year starting in March 2017.[8] The health-related expenditure due to alcohol was estimated to be about two times the revenue generated due to the sale of alcohol. Similarly, the Bangalore study suggests that alcohol use was associated with several familial and social adverse consequences, and the costs incurred due to alcohol use exceeded the revenue generated from alcohol.[2,11]

Taken together, there seems to be a high prevalence of substance use and substance use disorders in the country.[12] Problematic substance use not only affects the person from a health perspective but also causes a burden to the family and society. Substance use can cause both direct and indirect harm to individuals and communities.

Current infrastructure, facilities, technologies, policies, programs, etc., in the country in the context of the problem/health issue

Care of people with substance use disorders can be at various levels, including primary, secondary, and tertiary care [Figure 6]. Primary care has the widest approach and is most easily accessible to individuals with substance use disorders.

A larger number of individuals can be helped at a lower level of care. As the severity of problems increases, the individual may need to be referred to a higher level of care.

Brief interventions at the primary care level can be of much use to elicit problematic substance use and to use the medical/clinical encounter for suggesting behavioral change and discussing methods of reducing or ceasing substance use.[13] For example, a clinical encounter in the medicine/emergency department with a medical health problem can provide an opportunity to discuss cessation of alcohol use, which has led to gastritis/accident. Screening, brief intervention, and referral to treatment (SBIRT) can be utilized to screen and refer patients with more severe substance use disorders to the secondary level of care, and patients with complex needs can be referred to the tertiary levels of care.

Provisions of care can be through various approaches and settings:[14-18]

- **Public institutions** – There is a wide array of medical and mental health services at primary, secondary, and tertiary care. Generally, patients with substance use disorders and behavioral addictions would have closer access to primary care. Much of the treatment of patients with substance use disorders, especially screening and identification, can be conducted in primary care.[19]
  There are also specialized center and psychiatry departments in medical colleges for helping people with substance use disorders and behavioral addictions. NDDTC Ghaziabad, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh; National Institute of Dr. RML Mental Health and Neurosciences (NIMHANS), Bengaluru; RML Hospital, New Delhi; AIIMS, Bhubaneswar; and Central Institute of Psychiatry (CIP), Ranchi, are among the centrally supported institutions. Apart from that, there are several drug treatment clinics (DTCs) and addiction treatment facilities (ATFs) across the country. Medical colleges (centrally supported or supported through state governments) also provide care.
- **Private medical facilities** – Many private medical facilities (both inpatient and outpatient) provide care for patients with substance use disorders. These facilities may be dedicated mental health facilities or general medical facilities. Counseling is also provided by independent practitioners from across the country. Alcohol, tobacco, and other substance-related harms may make individuals visit general healthcare facilities, and this can be an opportune moment to discuss cessation/reduction of substance use.
- **Nongovernmental organization (NGO) and not-for-profit sector** – This sector also aims to reach out to patients with substance use disorders and provide care for them. There are a range of models of providing care, and these services tend to provide low-threshold services in the community. NGO and not-for-profit sectors provide a wide range of services varying from outpatient counseling services to long-term residential rehabilitation services. In addition, Alcoholics Anonymous and Narcotics Anonymous also provide mutual self-help 12-step facilitation among substance users.
- **Traditional and alternative systems of medicine –** Many patients with substance use disorders approach traditional and alternative systems of medicine as well. Several interventions, like yoga, have demonstrated efficacy for patients with substance use disorders.

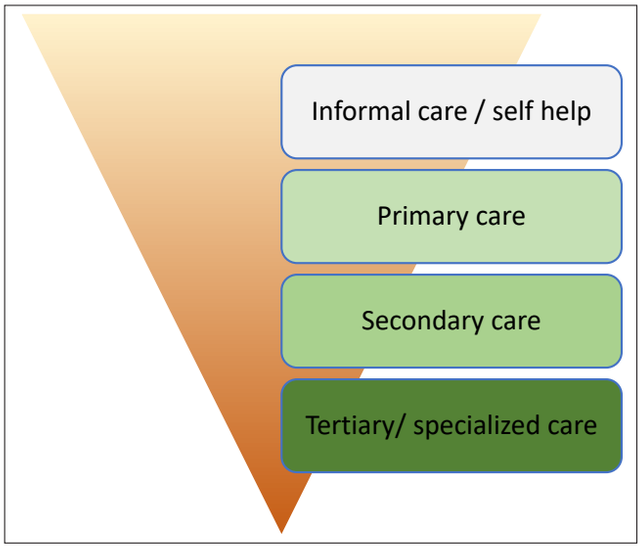

Figure 6: Care levels for people with substance use and behavioral problems.
(Source: Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India. 2019.)

- **Digital and tele services** – In the recent past, telephone and digital platforms have expanded in India. These offer an opportunity of reducing costs and make care more easily and immediately available. mHealth-based applications can be used through smartphones and can help in the reduction of substance use. Similarly, quitlines can provide counseling for the cessation of tobacco.

Figure 7 summarizes the range of services available for substance use disorders and behavioral addictions.

Apart from services, prevention forms an important component of the approach to substance use and substance use disorders at the community level.[20-25] Prevention aims at both educating the younger population about harms associated with substance use and emphasizing the measures available for addressing substance use. Other approaches for prevention rely on improving prosocial behaviors in the school setting, which has been shown to reduce substance use initiation. Workplace-based interventions have also shown promise for reducing substance use. Prevention measures can be universal, selective, or indicated, though universal approaches may have a wider reach and show greater impact. Prevention approaches that have shown a reduction in substance use among adolescents and young adults include increasing taxes on alcohol, brief alcohol screening, and intervention for college students, and workplace interventions.

Supply control measures may also have an impact on the use of substances like alcohol. Restrictions on the sale below a certain age, prohibition of the sale of alcohol in a particular area, control on the number of outlets, and taxation may also limit the consumption of alcohol, and hence the consequent harms.

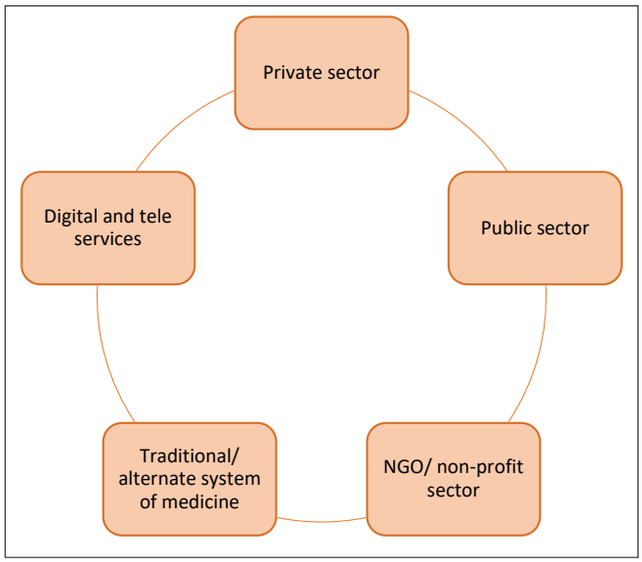

Figure 7: Treatment service provisions.

Current policies:

National Policy on Narcotic Drugs and Psychotropic Substances

Current programs:

- Drug De-Addiction Program under the Ministry of Health and Family Welfare, Government of India.
- National Action Plan for Drug Demand Reduction under the Ministry of Social Justice and Empowerment, Government of India.
- Nasha Mukt Bharat Abhiyaan under the Ministry of Social Justice and Empowerment, Government of India.

Current Budget

Ministry of Health & Family Welfare is running a National "Drug De-Addiction Program (DDAP)" with the objective of providing affordable, easily accessible, and evidence-based treatment for all substance use disorders through the government healthcare facilities and of building the capacities of healthcare staff in recognition and management of substance use disorders. The program is implemented through the health institutions under the Ministry of Health and Family Welfare (MoH&FW), viz., AIIMS, Dr.RML New Delhi; PGIMER, Chandigarh; NIMHANS, Bengaluru; RML Hospital, New Delhi; AIIMS, Bhubaneswar; and CIP, Ranchi. Out of these six, the center at AIIMS, New Delhi (NDDTC), is functioning as the National/Nodal center. The Ministry of Health and Family Welfare (MoHFW) has released the "Standard Treatment Guidelines for the Management of Substance Use Disorders and Behavioral Addictions".[18] The average annual budget of Rs. 45–53 crores has been allotted for DDAP Program for these above-cited DDAP Institutes in the last three years.

Ministry of Social Justice and Empowerment (MoSJE) implements the National Action Plan for Drug Demand Reduction (NAPDDR), which is an umbrella scheme under which financial assistance is provided to:

(i) 'State governments/union territory (UT) administrations for preventive education and awareness generation, capacity building, skill development, vocational training, and livelihood support of ex-drug addicts, programs for drug demand reduction by states/UT, etc.'
(ii) "Non-Government-Organizations/Voluntary Organizations for running and maintenance of Integrated Rehabilitation Centers for Addicts (IRCAs), Community-

based peer Led Intervention (CPLI) for early Drug Use Prevention among Adolescents and Outreach and Drop In Centers (ODIC) and Addiction treatment facilities (ATFs) in Government Hospitals".

RECOMMENDATIONS

Key issues/gaps identified in the current situation in the country in the context of the problem/health issue

Despite having a considerable substance-using population, there is a large unmet treatment need pertaining to substance-use disorders in India. The National Survey on Magnitude of Substance Use in India suggests that only one in four persons with dependence on illicit substances receive treatment. For alcohol dependence, the rates were even abysmal, with only one in 38 individuals with alcohol dependence ever receiving treatment. **The National Mental Health Survey of India found the treatment gap to be 86.3% for alcohol use disorders, 91.8% for tobacco use disorders, and about 73% for other drug use disorders (overall 90%).** This emphasizes the fact that there is a much larger number of individuals with substance use disorders than those who seek treatment.

In addition, among those who seek treatment, many drop out of treatment due to various reasons. There could be many causes of drop-out from treatment, including inaccessibility of treatment, lack of motivation, logistical difficulties, peer pressure for discontinuation, and other reasons. Drop-out from treatment may be associated with relapse to substance use and recurrence of the problems associated with substance use. Thus, unplanned treatment cessations need to be focused upon so that the duration of abstinence from substances can be prolonged.

Treatment facilities for substance use disorders need to be expanded. Treatment for substance use disorders is provided through dedicated services through various channels. There is a need to expand the services so that it is accessible to individuals who need it. Providing such treatment at subsidized costs or free of cost or bringing it under the ambit of insurance coverage may make the care affordable to the patients.

There is also a **need to expand the training and teaching in addiction psychiatry among medical graduates.** Since alcohol dependence and substance use disorders are a common presentation in the clinical medical setting, clinicians need to be empowered to deal with these disorders. However, as of present, the attention to substance use disorders in the medical curriculum is limited. This forces medical graduates to "learn on the go" when they practice. Greater training of the medical graduates about substance use disorders and behavioral addictions is warranted.

There is a need to empower primary care physicians and other health professionals through training to enable them to screen substance use disorders and treat them. This might be done by providing clinical experience through case discussions and handholding in the initial period so that they become more attuned to the care of patients with substance use disorders in a routine manner.

Apart from training medical graduates, there is a need to train specialists in the field of addiction to provide care for patients with complex needs. Specialized training is also needed to develop a workforce of those who are able to train personnel for the treatment of addictive disorders.

Services of clinical psychologists, professionals from psychiatric social work, and professionals from psychiatric nursing can be utilized for the purpose of awareness, identification, and counseling of persons with substance use disorders.

Short-term courses (for example, under the Indira Gandhi National Open University-IGNOU) can be designed to increase human resources for counseling services and work at the community level. This would enable services to be provided at a larger scale to those who use substances or have issues related to behavioral addiction.

Furthermore, there needs to be **efforts to enhance knowledge about substance use disorders in the general population**. More awareness about these disorders, putting in the context of harms associated with them and the help available for treatment, would be helpful. Coupled with this, stigma reduction measures would help to de-stigmatize substance use disorders and enable greater acceptability of treatment.

While drawing and implementing policies, one has to consider the social needs and expectations. The perceptions of the community and their expectations should be factored while framing programs and implementation. Social marketing and social engagement need to be implemented to improve the outcomes of policies. The experience from previous programs has suggested that corrective measures may be required to improve community engagement and delivery of services.

Key issues/gaps identified in the current infrastructure, facilities, technologies, policies, programs, etc., in the country in the context of the problem/health issue

Key gaps in the current infrastructure, facilities, technologies, policies, and programs include:

1. Lack of adequate facilities and evidence-based treatment available to provide treatment for substance use disorder.

2. Lack of knowledge and skills in medical personnel to address substance use disorder
3. Different agencies to deal with different aspects of substance use disorders
4. Non uniform policies on alcohol
5. Lack of awareness regarding available treatment for substance use disorders and behavioral addiction
6. Lack of community support for treatment, support, and aftercare for people with substance use disorders
7. Lack of regulation of some centers that cater to people with substance use disorders resulting in the mistreatment of people with substance use disorders
8. Lack of due emphasis/focus on substance use disorders at the state level (which is responsible for health) in the midst of competing priorities.

Key issues/gaps identified in current financial inputs, etc., in the country in the context of the problem/health issue

While financial inputs are being provided for the treatment of substance use disorders, there needs to be a greater emphasis. Some of the further measures could be:

- Dedicated outlays for evidence-based preventive measures
- Greater government expenditure for sustaining services in the government sector
- Dedicated budget for substance use disorders through telemedicine
- Financial incentive for the provision of care to patients with substance use disorder in the NGO sector
- Dedicated funds for incentivizing capacity development – trained primary care physicians, medical professionals, counselors, nurses, and other health professionals.
- Funds for research need to be earmarked to find contextual solutions to the problems of substance use and behavioral addictions in India

WAY FORWARD

The way forward should include both preventive and curative aspects to address the problems of substance use and behavioral addictions. There is a need for clearly demonstrated efficacious measures, especially those that have been shown to be implementable in the country. Due to cultural and linguistic differences across the country, a multiple set of approaches might be useful to address the concerns of substance use disorders and behavioral addictions [Figure 8].

Addressing substance use and behavioral addiction in India.

Suggested policy activities and advocacy for policy makers

- Working further toward a national alcohol policy in line with the WHO Global Strategy to reduce the harmful use of alcohol.
- Relocation of all health-related activities for tobacco, alcohol, drugs, and behavioral addictions within the Ministry of Health and Family Welfare.
- Framing policies to divert patients with substance use disorders with small quantities of recovered substances toward medical care in lieu of criminal proceedings and incarceration.
- Sensitizing important stakeholders, including law enforcement authorities, and judiciary, on the need to distinguish drug users from drug dealers.
- Telemedicine rules and guidelines should also facilitate the treatment of substance use disorders.
- Enabling provisions to ensure the physical safety of healthcare providers at the workplace.
- Advocating with policymakers on the need to ease the availability of medicines that are otherwise regulated under the Narcotic Drugs and Psychotropic Substances (NDPS) Act of 1985 and the need to protect the medical fraternity from inadvertent lapses in following processes/ procedures in prescribing and dispensing medicines. This includes benzodiazepines that are needed for patients with mental illnesses.

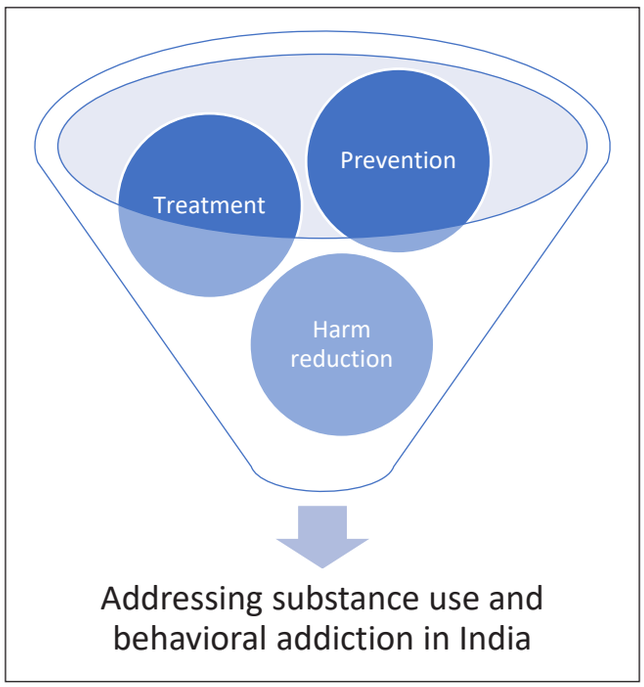

Figure 8: Addressing substance use disorders and behavioral addictions in India.

- Fund policy-related research activities on existing policies on substance use disorders and behavioral addiction, for example, the impact of banning alcohol in some regions/states, whether criminalization/decriminalization of some substances is the way forward, etc.

Recommendations for health/medical professionals

- Training medical professionals and other healthcare providers about substance use disorders to enable screening and detection of substance use disorders and behavioral addictions at the primary/emergency care level.
- Every patient who visits any health center or tertiary care center and has any of the above listed addiction habits should be counseled by the doctor at first instance and necessary referral should be provided by a psychiatrist in case a need arises.
- Greater utilization of brief intervention and referral to the treatment of patients encountered in the medical setting who have problematic substance use at the primary level of care.
- Optimum utilization of online training mechanisms for the training of medical professionals about substance use disorders and behavioral addictions. As a long-term goal, incorporate the Ministry of Health and Family Welfare-approved addiction psychiatry curriculum at the MBBS level.
- Enable provision of basic treatment of substance use disorders and behavioral addictions at the primary care level.
- Making a basket of services available to cater to the different needs of the population.
- Greater access to treatment services like opioid substitution treatment for those who need such treatment.
- Integrate psychosocial rehabilitation with medical treatment of patients with substance use disorders.
- Training about addictive disorders at postgraduate levels in mental health and allied disciplines.

Suggestions to create awareness among general public, NGOs, and community stakeholders

- Enhancing the awareness about substance use and the harms associated with it at the school and college levels. This includes not only medical harms and health deterioration but also mental health concerns and social consequences of substance use disorders.
- Strengthening, implementation and monitoring of "Nasha Mukt Bharat Abhiyaan" could hold promise in preventive aspects.
- Initiate workplace interventions for substance use problems in the workforce.
- Sensitizing teachers in educational institutions about substance use for early identification and referral.

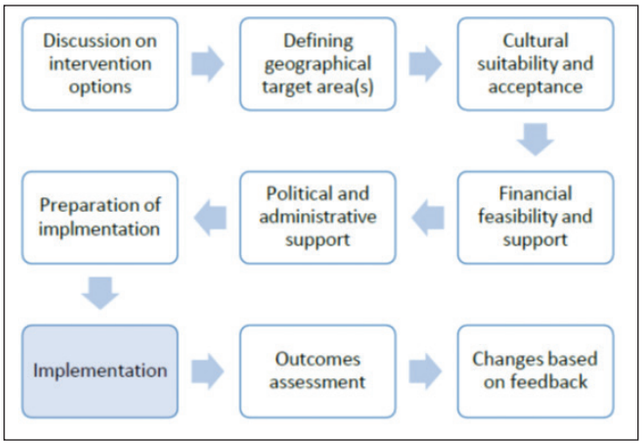

Figure 9: Key thrusts at policy, professional, and awareness levels.

- Target school and college students toward enhancing prosocial behaviors, to reduce substance use experimentation.

The key thrusts at policy, professional, and awareness levels are given in Figure 9.

The implementation plan would need more thorough deliberations with not only medical experts but also a multi-stakeholder approach, including individuals with substance use disorders, those with programmatic and administrative experience, financial experts, and others. The choice of strategies to be prioritized should be based on the evidence base and also the unique cultural, social, economic, and political landscape of the country. Social marketing should be considered while planning and implementing programs that address substance-related problems and behavioral addictions (Tiwari, 1998). The strategies selected should be linked to measurable outcomes evaluated on a suitable time frame basis. The objectives being defined by being specific, measurable, achievable, reliable, and time-bound would help to know whether the strategies have the intended effects. This would be beneficial in directing resources and better utilization of the inputs.

Further implementation plan is given in Figure 10.

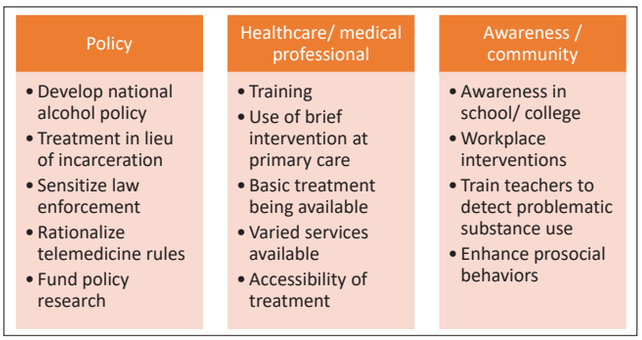

Figure 10: Further implementation plan.

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OPERATIONAL DEFINITIONS OF THE TERMS USED IN THE REPORT

Behavioral addiction – Syndromes related to repetitive rewarding behaviors that cause distress or interference with functioning.

Demand Reduction – Demand reduction means trying to prevent people from wanting to and taking illicit drugs.

Harm reduction – An approach to reduce the harmful consequences of drug use without necessarily reducing drug consumption.

Prevention (in the context of substance use disorder) – Process that attempts to prevent the onset of substance use or limit the development of problems associated with using psychoactive substances.

Substance use disorder – Involves patterns of symptoms caused by using a substance that an individual continues taking despite its negative effects.

Supply reduction – Supply reduction means using various strategies to disrupt the production and supply of illicit drugs.

LIST OF ABBREVIATIONS

AIIMS: All India Institute of Medical Sciences

ATF: Addiction Treatment Facility

CIP: Central Institute of Psychiatry

DTC: Drug Treatment Clinic

GOI: Government of India

IRCA: Integrated Rehabilitation Centers for Addicts

MoHFW: Ministry of Health and Family Welfare

MoSJE: Ministry of Social Justice and Empowerment

NAPDDR: National Action Plan for Drug Demand Reduction

NGO: Nongovernmental Organization

NIMHANS: National Institute of Mental Health and Neurosciences

ODIC: Outreach and Drop in Centers

PGIMER: Postgraduate Institute of Medical Education and Research

SUD: Substance Use Disorder

REFERENCES

1. Ambekar A, Agrawal A, Rao R, Mishra AK, Khandelwal SK, Chadda RK. Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India; 2019.
2. Gururaj G, Murthy P, Girish N, Benegal V. Alcohol related harm: Implications for public health and policy in India, Publication No. 73, NIMHANS, Bangalore, India, 2011.
3. National Family Health Survey – 5. 2019-21. India Fact Sheet. International Institute for Population Sciences. 2022 [accessed 2021 Jan 19]. Available from: http://rchiips.org/nfhs/NFHS-5_FCTS/India.pdf
4. Gautham MS, Gururaj G, Varghese M, Benegal V, Rao GN, Kokane A, *et al*. The National Mental Health Survey of India (2016): Prevalence, socio-demographic correlates and treatment gap of mental morbidity. Int J Soc Psychiatry 2020;66:361–72.
5. George S, Ts J, Nair S, Rani A, Menon P, Madhavan R, *et al*. A cross-sectional study of problem gambling and its correlates among college students in South India. BJPsych Open 2016;2:199–203.
6. Joseph J, Varghese A, Vijay VR, Dhandapani M, Grover S, Sharma S, *et al*. Prevalence of internet addiction among college students in the Indian setting: A systematic review and meta-analysis. Gen Psychiatr 2021;34:e100496
7. Basu D, Aggarwal M, Das PP, Mattoo SK, Kulhara P, Varma VK. Changing pattern of substance abuse in patients attending a de-addiction centre in north India (1978-2008). Indian J Med Res 2012;135:830-36.
8. Ramalingam A, Pasupuleti SS, Nagappa B, Sarin SK. Health and economic burden due to alcohol-associated liver diseases in the Union Territory of Delhi: A Markov probabilistic model approach. Indian J Gastroenterol 2022;41:84–95.
9. Sarkar S, Nebhinani N, Gupta S, Parakh P, Basu D. Self-reported medical co-morbidity among 400 substance using patients at an addiction unit in India. Journal of Substance Use 2016;21:41–7.
10. Balhara YP, Bhargava R, Chadda R. Service development for behavioural addictions: AIIMS experience. Ann Natl Acad Med Sci (India) 2017;53:130–38.
11. World Health Organization. Burden and Socio-Economic Impact of Alcohol — The Bangalore study. World Health Organization, Regional Office for South-East Asia, 2006.
12. Murthy P, Manjunatha N, Subodh BN, Chand PK, Benegal V. Substance use and addiction research in India. Indian J Psychiatry 2010;52:S189.
13. Sarkar S, Pakhre A, Murthy P, Bhuyan D. Brief interventions for substance use disorders. Indian J Psychiatry 2020;62:S290–8.
14. Chadda RK. Substance use disorders: Need for public health initiatives. Indian J Soc Psychiatry 2019;35:13.
15. Chadda RK, Chatterjee B. Need for psychosocial interventions: From resistance to therapeutic alliance. Indian J Psychiatry 2018;60:S440.

16. Tiwari SC. Social marketing: A new approach in mental health research. Indian J Psychiatry 1998;40:311–21.
17. Chadda RK, Lal R, Basu D, Gupta N, Balhara YPS, Bhargava R, *et al*. Standard Treatment Guidelines. Management of Alcohol Dependence. Ministry of Health & Family Welfare Government of India, New Delhi; 2017.
18. Standard Treatment Guidelines for the Management of Substance Use Disorders and Behavioural Addictions. In: Murthy P, Dhawan A, Basu, D, Gupta M, Chandra M, Chand PK, Mahadevan J, Bhatia G, Nirwan H, Sharma N, Singh S, Singh VV, editors. New Delhi: Tobacco Control & Drug De-Addiction Programme Ministry of Health and Family Welfare, Government of India, 2020.
19. Dhawan A, Rao R, Ambekar A, Pusp A, Ray R. Treatment of substance use disorders through the government health facilities: Developments in the "Drug De-addiction Programme" of Ministry of Health and Family Welfare, Government of India. Indian J Psychiatry 2017;59:380.
20. Kaur J, Jain DC. Tobacco control policies in India: Implementation and challenges. Indian J Public Health 2011;55:220.
21. National Policy on Narcotic Drugs and Psychotropic Substances. 2012 [accessed 2021 Jan 19]. Available from: http://dor.gov.in/sites/uploadfiles/revenue/files/NationalPolicyonNDPS.pdf.
22. Substance Abuse and Mental Health Services Administration: Substance Misuse Prevention for Young Adults. Publication No. PEP19-PL-Guide-1 Rockville, MD: National Mental Health and Substance Use Policy Laboratory. Substance Abuse and Mental Health Services Administration; 2019.
23. World Health Organization. Global strategy to reduce the harmful use of alcohol. World Health Organisation: Geneva; 2010.
24. World Health Organization. Regional Office for the Eastern Mediterranean. Summary report on the regional technical consultation on the working document for development of the action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority, virtual meeting, 23 February 2021. World Health Organization. Regional Office for the Eastern Mediterranean; 2021 [accessed 2021 Jan 19]. Available from: https://apps.who.int/iris/handle/10665/351532
25. World Health Organization. International Standards for the Treatment of Drug Use Disorders: Revised edition incorporating results of field-testing. World Health Organization and United Nations Office on Drugs and Crime, 2020.

IMPORTANT DATA, STATISTICS RELATED TO THE ISSUE

Relevant data available from:

- Ambekar A, Agrawal A, Rao R, Mishra AK, Khandelwal SK, Chadda RK. Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India. 2019.
- Murthy P, Manjunatha N, Subodh BN, Chand PK, Benegal V. Substance use and addiction research in India. Indian J Psychiatry. 2010;52(Suppl 1):S189.
- National Family Health Survey – 5. 2019–21. India Fact Sheet. International Institute for Population Sciences. 2022. Available at http://rchiips.org/nfhs/NFHS-5_FCTS/India.pdf

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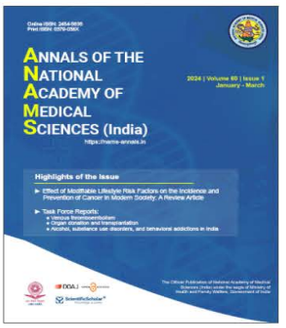

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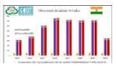

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