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School Age Immunization: The Need of the Hour

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It has been forty-three years since the WHO declared the complete eradication of smallpox in the world – a tremendous victory attributed entirely to the intensified, large-scale vaccination programs across the world. Polio has been similarly eliminated from many countries in the world, including India, and occurrence of other vaccine preventable diseases (VPDs) has dramatically reduced over the last few decades in the country. Unfortunately, some of these diseases continue to exist in large numbers in the developing world. India is one of the ten countries where a measles outbreak was reported in late 2022, and early 2023 [1]. Other VPDs, such as enteric fever, hepatitis A, diphtheria, chickenpox and cervical cancer continue to exist in alarming numbers in our country. In fact, a third of all global deaths due to VPDs occur in India [2]. While we have made rapid strides to catch up with the developed countries on several parameters, time has come to also focus on the vaccination of children beyond two years. Even in our NFHS data collection the emphasis is given on vaccination status of infants and toddlers only up to 12-23 months of age and I find it extremely disheartening that we lag behind on large scale immunization beyond the age of toddlerhood. Although, vaccine uptake amongst infants is widespread in the private sector in India, it is a known fact that vaccine immunity wanes over time and thus, booster shots are required in the successive years of childhood. India lacks a comprehensive strategy to improve coverage of childhood immunization beyond infancy and toddlerhood, and this is a significant deterrent to eliminating, or at least reducing, the incidence of VPDs in India.

As is the case for most public health issues, delay in immunization is the consequence of both demand and supply side limitations, and is a more severe issue in remote geographies and impoverished populations, migrants and urban slums, which rely on public health facilities for healthcare. On the demand side, parental resistance due to religious beliefs, lack of awareness and community-level fear-mongering (more so on social media these days) are all documented factors behind vaccine delays. Although India's Universal Immunization Program (UIP) provides free vaccination for children aged below 12 years, there are significant vaccination delays compounded by the reporting and monitoring on immunization data at the ground level. Government initiatives incentivizing institutional births have indirectly improved the administration of the BCG vaccine, Hepatitis B and birth dose of OPV, which has more promising data as opposed to the DPT-1 vaccine, which is given six weeks after birth. Once the infant leaves the facility, it becomes more logistically taxing to ensure subsequent vaccinations. ANMs at the village level are expected to go through birth records and prepare lists of all children due for vaccinations, and handover these lists to ASHA workers to mobilize them at the Village Health Nutrition and Sanitation Day. This process is labor intensive and prone to human error. It is also a well-known fact that frontline health workers such as ASHAs and ANMs are already overburdened as they execute several other health initiatives of the government, immunization only being one of them. Despite these hardships, considering the huge geographical area and population cohort, the efforts of the state and central governments for successfully implementing Mission Indradhanush over the past several years is certainly laudable. Immunization protects not only the vaccinated child, but also furthers herd immunity for the entire community. Thus, it is imperative to step up our immunization efforts.

School entry booster vaccination is the link between infant vaccination and adolescent vaccination. It boosts the immune response in these children and helps restore the immunity gap. Impact of introduction of pertussis containing DTP vaccine at school entry in Norway was seen with 65% reduction in pertussis cases from a median of 204 per 100,000 cases between 1997 and 2005, to 71 per 10000 cases between 2008 and 2016, in 5- to 11-year-old children [3]. The same has been concluded from a clinical effectiveness study of influenza vaccination in Japan in children aged 1 to15 years, where influenza vaccines were very effective in reducing its secondary complications. In India, schools and anganwadis are the perfect touchpoint for monitoring immunization status, and improving the coverage for consecutive rounds of post-infancy vaccination. Checking vaccination status of each child

during admission to school allows an opportunity to identify children that have missed their first dose of BCG or DPT or any other routine vaccine, especially from amongst those born at home, or from hard-to-reach geographies. Through greater collaboration between the Ministries of Women and Child Development and Health and Family Welfare, the former can collect data through checks at entry, while the latter can plan for mop-up vaccination drives in the areas where the data on immunization is particularly worrisome. Parent-teacher meetings at schools are also a great platform for health workers to disseminate accurate and scientific information about vaccines, allowing for detailed discussions and myth-busting with a larger audience as opposed to one-on-one counselling in a clinical set up, which is rarely sufficient. Checking of vaccination status at entry or milestones at childcare, pre-school or primary school is a strategy that has been widely recommended by the World Health Organization (WHO) and others as a way to improve coverage of routine vaccinations. A comprehensive school-based approach to deliver immunization services and improve vaccination coverage in school-aged children is consistent with the Global Vaccine Action Plan (GVAP) [4] and Immunization Agenda 2030 (IA2030) [5] strategic priorities to establish platforms for life course vaccination.

India currently does not have a national or state level policy to involve schools in routine immunization programs. Of the 194 member states at the WHO, 135 implement a vaccination check at entry to, or during, at least one level of school in 2018 [6]. I recognize that there could be a small but unwanted side-effects to such a policy, such as an increase in the rate of out-of-school children, where parents chose to keep the children at home rather than get them vaccinated. As socio-cultural beliefs still play a big role in day-to-day decision making in India, I would recommend that the policy be tweaked: instead of making vaccination a barrier to entry, we use it exclusively as a way to improve data and monitoring of immunization history. Similarly, instead of referring the child to a health facility, we use this data to improve follow-up at VHND (village health and nutrition days) or through a regular immunization outreach program at the school. We have many vaccines available for the school aged children which are not part of the national UIP as of now, like influenza, hepatitis A, varicella, mumps, HPV, TdaP, typhoid etc. Though many parents can afford to give these time-tested vaccines to their children, probably they are not as aware of them as the other well-known vaccines. School authorities checking the vaccination status at the preprimary, primary and secondary school or a pediatrician addressing a school parent teacher meeting, can definitely make an attempt to increase the mass awareness on VPDs.

India has undoubtedly made significant strides in reducing child mortality. However, hundreds of thousands of toddlers still die every year of preventable and treatable diseases. Taking lifesaving vaccines to every child is logistically feasible, if the right will be shown at the policy level. IAP, through its SAKSHAM program, is also incentivizing school drives for vaccinations. With immense gains for child health, and public health immunity at large, it is time we step up the focus on vaccinations from birth till 18 years of age and make other VPDs a word of the past, much like we did with smallpox and polio.

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INVITED COMMENTARY

Let's Start At the Very Beginning: The Importance of Registries in Childhood Cancer

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Childhood cancer is widely considered a success story, with over 80% of children in high-income countries (HICs) and high-resource settings being cured [1]. However, in low-income countries and low- and middle-income countries (LICs and LMICs), where most children with cancer reside, as few as 20% may be cured [1]. There are multiple causes for the disparities in childhood cancer outcomes in LMICs, starting with co-morbid conditions, delays in detection/diagnosis, advanced presentations, misdiagnosis, poor access to care, inappropriate and incomplete treatment, treatment abandonment/delays, and undue toxicities [1].

There are many unknown entities in LMICs like India including the true burden of the disease itself. While HICs are able to provide accurate estimates of childhood cancer incidence and mortality by means of well-established population-based cancer registries (PBCRs) linked with death records, there is a paucity of comprehensive PBCRs as well as health-record linkages in LMICs [2]. Crucially, in order to reach the stage of accrual into hospital-based registries (HBCRs), children and families need to pass the sequential, and often interlinked, stages of symptom recognition, primary care access, clinical diagnosis, referral to secondary/tertiary centre and confirmation of diagnosis [2]. This tedious process might not be completed by many patients, thus making both PBCRs and hospital-based cancer registries (HBCRs) complemen-tary and essential.

It is estimated that close to 50,000 children 0-14 years and 75,000 children 0-19 years will develop cancer annually in India [3]. However, a recent simulation-based analysis found that close to 50% of children with cancer in south Asia (including India) are undiagnosed, leading to a huge 'incidence gap' [4]. Additionally, mortality data are not generally available or complete due to poor linkages with the Civil Registration System. A study [5], which used data from the Million Death Study to estimate mortality due to childhood cancer in India, found it to be 37 per million population per year in India, far exceeding prior estimates.

Considering the size, heterogeneity and complexity of health systems in India, establishing and maintaining cancer registries is an uphill task, but there has been tremendous progress. The Indian Council for Medical Research (ICMR) National Cancer Registry Program (NCRP) has been collating data on cancer incidence from PBCRs and HBCRs since 1982. Most registries are based in cities, leading to referral bias and under-representation of rural areas. The most recent ICMR analysis in 2020 was representative of 10% of the Indian population but was unable to include data from the some of the more populous states [6].

The manuscript by Arora, et al. [7] in this issue of the journal is a welcome step in this direction. The authors describe the epidemiology and survival in children registered over nearly 9 years in their hospital-based cancer registry. Amongst 705 newly diagnosed children (36.2% female), most were leukemia, central nervous system tumors and bone tumors, similar to the epidemiology across India. The 5-year overall survival (OS) and event-free survival (EFS) were 66% and 57.5%. As the authors point out [7], this is the first registry-based data to provide 5-year survival rates by diagnosis, especially EFS, within the limitations of a HBCR in a private setting. Similar detailed analysis from other HBCRs/PBCRs would be of great value. The importance of quality combination registry data was further emphasized by a recent pooled report of PBCRs and HBCRs from several centers in India, which confirmed the worrisome feature of referral bias against female children [8].

Childhood cancers constitute less than 5% of all cancers across all ages, are far less of a public health concern than other causes of under-5 and other childhood mortality, and are not a national health priority; although, recently brought under the Ayushman Bharat scheme [9]. However, there is a gradual epidemiological shift world-over from communicable to non-communicable disease, with the recognition that childhood cancer mortality and long-term morbidity are best measured in terms of disability-adjusted-life-years rather than mere numbers. Having the best estimate of children who develop cancer will help inform public

health policies and national childhood cancer programs [9]. Additionally, strengthening of diagnostic referral pathways, making cancer a notifiable disease, linkage of registry data with Ayushman Bharat and civil registration systems are steps thought to improve cancer registration, follow-up, and outcome data [6].

Currently, only about 13% of the world's population of children is covered by cancer registries. The Targeting Childhood Cancer through the Global Initiative for Cancer Registry Development (ChildGICR), as part of the World Health Organization Global Initiative for Childhood Cancer (WHO-GICC) aims to ensure a greater focus on childhood cancer registration systems in LMICs, and India is an active partner in this initiative [10].

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INVITED COMMENTARY

Reducing Radiation Dose in Neonates: Small Efforts Make Big Changes

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Infants and children are particularly susceptible to the harmful effects of ionizing radiation, as they have rapidly dividing cells in their body, which are more prone to radiation induced damage. Also, they have a longer life expectancy to manifest the potential oncogenic effects of radiation [1], and have the possibility of transmitting radiation induced genetic mutations to the future generations. Hence, all possible efforts need to be made to reduce radiation exposure in pediatric patients. The concept of ALARA, the acronym for 'as low as reasonably achievable' is the principle followed worldwide to keep the radiation dose to the minimum possible level, at the same time striking a reasonable balance with the obtained image quality, which should be satisfactory and acceptable for the clinical question to be answered for which the radiological study has been performed.

X-ray is an indispensable imaging modality for the newborns admitted in the neonatal intensive care unit (NICU) facilities globally. In many of the modern and well-equipped centers, the conventional *X*-ray equipment working on traditional film-screen combination and even the computed radiography (CR) systems has been replaced by the more efficient portable bedside direct digital radiography (DR) equipment. Preterm neonates often require repeated follow up radiographs as part of their management [2], particularly those suffering from pulmonary disorders of prematurity and prolonged ventilation (respiratory distress syndrome of neonate and chronic lung disease of prematurity), infective lung conditions such as pneumonias, bowel dis-orders, and to assess whether the tubes and lines are positioned appropriately [3]. These little babies in the NICU are adversely affected by radiation to an even greater magnitude, as due to their small body size, their vital organs as thyroid, gonads and brain receive higher effective radiation dose, and targeted studies are often difficult to perform [4].

Radiation protection is based on the principles of justification, optimization, dose limitation [5], and protection of radio-sensitive organs. Justification in this scenario means that there should be a valid and justified indication for performing any *X*-ray on a baby, and that the same result is unlikely to be achievable with an alternative non-radiation modality such as ultrasound. The number of previously performed radiation studies also needs to be reviewed, and only essential repeat studies to be advised, in order to avoid cumulative radiation dose to the baby from multiple studies. For dose optimization and limitation, only the personnel with proper training and experience in radiography should be allowed to perform the procedure. Appropriate technical exposure parameters should be used, which maintain the delicate balance between radiation dose and image quality. Appropriate filtration and collimation should be used routinely, and every effort should be made that the *X*-ray beam exposes only the area of interest in the patient's body. Wherever possible, radiation-protection apparel as gonadal and thyroid shields may be applied to protect these radio-sensitive organs.

Efforts have been made by numerous researchers in the recent past to reduce the radiation dose to neonates in the NICU, without compromising on the image quality of bedside *X*-rays. Choi, et al. [3] published a study describing the formulation of a low dose *X*-ray proto-col for NICU using a new mobile DR system, and concluded that radiation dose can be reduced without significantly affecting image quality, by adding filtration and a new denoising technique on the DR system. Zhang, et al. [6] have recommended the use of a chest stabilization device during bedside DR for neonatal chest *X*-ray, the conclusion of their study being that movement control significantly improves image quality as well as reduces radiation dose. Armendariz, et al. [7] found that it was possible to reduce radiation dose in mobile chest *X*-rays performed in the NICU by adding 2 mm aluminum filtration and increasing the tube potential.

The research paper by Shrikant, et al. [8], published in this issue of *Indian Pediatrics*, is another desirable and beneficial step in this direction, which has included all principles of radiation protection in a holistic manner – by first documenting and justifying the actual need of *X*-ray in

the patient, then by applying principles of optimization and dose limitation by fixing the technical exposure parameters of tube potential, current and exposure time (kVP and mAs) to the minimum possible setting on their equipment, source to detector distance (still popularly known as focus to film distance or FFD) to 100 cm, and use of strict collimation for exposing the least possible body area of the baby. They also ensured use of gonadal shields in the NICU and finally utilized the post processing image enhancement options on the DR system, in order to reduce noise and obtain the best possible image quality, even with the reduced radiation dose levels [8]. Such active involvement of the treating clinician while performing bedside *X*-rays in the NICU is laudable, and will certainly prove to be of benefit for neonatal patients by successfully reducing radiation exposure while maintaining optimum image quality, in keeping with the spirit of ALARA!

More studies of similar nature conducted on neonates, including premature babies in the NICU, are the need of the hour, based on the evaluation and reduction of entrance skin dose to the babies who undergo *X*-ray examinations. Presently, there is a paucity of standardized technical *X*-ray parameters to be used for newborns, and the recommended reference dose limits for neonatal *X*-rays also do not take into consideration the premature newborns, or those admitted in the NICU [9]. Further similar research would assist to frame uniform protocols and imaging guidelines for *X*-ray on newborns, and would go a long way to help these little patients!

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INVITED COMMENTARY

Unmasking the Perils: A Critical Analysis of Advertising of Pre-Packaged Foods in India

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Ultra-processed foods are formulations of ingredients, mostly of exclusive industrial use, typically created by series of industrial techniques and processes (hence 'ultra-processed') [1]. Processes and ingredients used for the manufacture of ultra-processed foods are designed to create highly profitable products (low-cost ingredients, long shelf-life, powerfully branded). Their convenience (imperishable, ready-to-consume), hyperpalatability, and ownership by transnational corporations using pervasive advertising and promotion, give ultra-processed foods enormous market advantages. They are therefore liable to displace all other NOVA food groups, and to replace freshly made regular meals and dishes, with snacking anytime, anywhere.

The article in this issue of *the journal* on advertising of prepackaged foods in India [2] sheds light on the pervasive issue of advertising practices surrounding pre-packaged foods in India. The consistent evidence accumulated by studies with different design, undertaken in a number of countries, shows that the displacement of non-ultra-processed by ultra-processed foods increases the risk of obesity, diabetes, hypertension and several other diet-related non-communicable diseases [3,4], and also premature mortality.

The qualitative analysis conducted in the study [2] reveals the extent of deceptive marketing tactics employed by companies in promoting pre-packaged foods. The research emphasizes the targeting of vulnerable populations, particularly children and adolescents, who are easily influenced by advertising messages. This echoes global trends where the food industry utilizes similar strategies to perpetuate the consumption of unhealthy ultra-processed products.

One noteworthy aspect brought to light by the study [2] is the use of celebrities and sports personalities as brand ambassadors for prepackaged foods [5,6]. By associating popular figures with these products, companies create a sense of trust and credibility, leading consumers to believe that these foods are both nutritious and desirable. Such practices not only impact children but also influence adults, who may be swayed by the endorsements of their favorite celebrities. The implications of these advertising strategies are far-reaching, as they contribute to the normalization of unhealthy food choices and the escalation of diet-related diseases in the Indian population.

Furthermore, the study [2] highlights the prevalence of misleading health claims in the advertising of pre-packaged foods [7,8]. Labels such as "low fat," "high in fiber," or "nutritious" are used to create an illusion of healthiness, despite the actual nutritional content being subpar. This deceptive marketing tactic confuses consumers and undermines their ability to make informed choices about their dietary habits. It is crucial for regulatory bodies to strengthen labeling regulations and ensure that health claims are substantiated by scientific evidence, thereby protecting the public from falling victim to false advertising.

The qualitative analysis [2] also emphasizes the influence of digital media platforms, particularly social media, in the advertising of pre-packaged foods. With the rise of influencers and online celebrities, social media has become a powerful tool for the promotion of these products. Companies leverage the reach and impact of social media influencers to penetrate the market further and shape consumer preferences. This phenomenon is particularly concerning as it blurs the lines between genuine recommendations and paid advertisements, making it difficult for individuals to discern what is truly beneficial for their health.

In conclusion, the qualitative analysis presented in the article [2] reveals the advertising practices surrounding prepackaged foods in India. The findings highlight the urgent need for stricter regulations and heightened awareness regarding the deceptive tactics employed by food com-panies. Regulatory bodies must take decisive action to enforce transparent and accurate labeling practices, prohibit misleading health claims, and restrict the use of celebrities and influencers in promoting unhealthy food choices.

In addition to regulatory measures, public health campaigns and educational programs should be initiated to em-

power consumers, especially children and adolescents, with critical thinking skills necessary to navigate the on-slaught of persuasive advertising [9]. Parents also play a crucial role in educating their children about healthy food choices and developing their ability to scrutinize marketing messages.

It is imperative for all stakeholders, including policymakers, healthcare professionals, and parents, to work together to create an environment that prioritizes the well-being of the population over the profits of the food industry. By addressing the advertising practices surrounding pre-packaged foods, India can take a significant step towards safeguarding public health and promoting healthier food choices among its citizens. Only through collective efforts can we unmask the perils of advertising and pave the way for a healthier future for India's population.

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INVITED COMMENTARY

Pediatric Cancer in India

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A cancer registry is an important information system that collects vital epidemiological data for the use of oncologists. Registries have a role in cancer surveillance, and forming a platform on which important research can be conceptualized and implemented. This would have larger implications on cancer control, implementation and evaluation of public health programs, and patient care improvement [1-3].

Another important use of a cancer registry is the systematic compilation of clinical and epidemiologic data of cancer survivors. Such cancer registries may be either population or hospital-based; both have their respective advantages and limitations. Population-based cancer registries are considered the 'gold standard' for all aspects of cancer registry data capture [3].

Cancer is a notifiable disease in many developed countries. Such legislation at present is absent in India.India is reported to have the one of the highest incidence and mortality rates related to cancer.The earliest population-based cancer registry (PBCR) was started in Hamburg in 1926, in USA in 1935, and in Denmark in 1942, with the concept then spreading to many countries. The first cancer registry in India was initiated in 1963, in Mumbai. In 1982, India introduced the implementation of PBCRs and hospital-based cancer registries (HBCRs) under theNational Cancer Registry Programme (NCRP) – National Centre for Disease Informatics and Research (NCDIR) of the Indian Council of Medical Research (ICMR), Bengaluru [3-7]. Till date there are about 36 PBCRs and 236 HBCRs under the ICMR-NCDIR-NCRP [8-11]. However, such registries do not cover the entire country. Cancer registries cover approximately 21% of the world's population. Indian registries, mostly covering urban areas, are reported to cover about 15 -20% of India's population [3,11]. There are also deficits in data capture. This reflects the need to strengthen the system of cancer registries in India, especially population-based registries, which are lacking in many large Indian states.

The paper on pediatric cancer burden in different regions of India in this issue of the journal [12] discusses the burden as well as regional and epidemiologic characteristics of pediatric cancers, which constitute 1-2% of all cancers from PBCRs under the NCRP and Tata Medical Centre (TMC), Mumbai. The authors have collected cancer burden from 28 NCRP and five TMC PBCRs and rationally highlighted the need of pediatric registries to ascertain the precise burden of pediatric cancers [12]. The paper highlights the burden of pediatric cancers in relation to overall population, gender variations and disease-wise descriptions in relation to geographic areas. The age-standardized incidence rate (95% CI) for boys and girls is 95.1 (94.3-95.9) and 65.5 (64.8-66.2) per million population [12].The highest rate was reported from northern India and lowest from northeast India. Similar observations have been made by adult registry analysis as well [11].

Great caution is required to interpret data collected from registries [2,3,11]. Many factors like accuracy, completeness of data entry, geographical areas covered, referral bias, awareness for cancers, access to care with respect to diagnostics and treatment facilities, and many more, determine the effectiveness of the registry program. It may mean that a higher burden of a cancer may be reported from a geographic area simply because a large center may be the referral center for a particular malignancy. Additionally, India is a vast country with diverse cultural and social peculiarities that are region-specific, further compounding the problem. Each registry is expected to carry out certain consistency checks and quality control measures to ensure the reliability of the data. In addition, there is a need that statutory bodies like ICMR, NCDIR help implement accurate data collection.

Overall survival from childhood cancers is improving globally, though more so in high-income countries.With the launch of the Global Initiative for Childhood Cancer (GICC) and improving the outcomes of childhood cancer, two of the most important contributors will be ascertaining cancer burden and identifying gaps/action points that will help achieve the goal of increasing the survival rate of children with cancer globally to at least 60% by 2030, and reducing their suffering and improving their quality of life. High-quality and region-wise population-based cancer registries form one of the most

essential tools to define accurate burden, demographic/clinical/diagnostic characteristics and outcome of childhood cancers in LMICs like India for better policy-making and planning decisions.

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PERSPECTIVE

The Need for Food Fortification With Zinc in India: Is There Evidence for This?

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There has been recent advocacy for food fortification with zinc in India. However, there are three important conditions that should be established before fortifying food with any micronutrient, which requires that there should be *i*) Established high prevalence of biochemical or sub-clinical deficiency (≥20%), *ii*) Low dietary intakes that increase the risk of deficiency, and *iii*) Evidence of efficacy of supplementation from clinical trials. For zinc, all three conditions are not satisfied. The prevalence of low serum zinc concentrations in Indian children is well below 20% (~6%), signifying that zinc deficiency is not a public health problem. There is no risk of dietary zinc inadequacy in Indian populations where intake has been measured. Finally, there is no robust evidence that zinc-fortified foods improve functional outcomes, even if the serum zinc concentration is increased. Thus, contemporary evidence does not justify the need for food fortification with zinc in India.

Keywords: *Deficiency, Intake, Supplementation*.

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Zinc is an essential nutrient for growth [1-3]. Whole-body zinc content is stable over a wide range of dietary zinc intakes indicating its efficient homeostasis [2,3]. Zinc absorption takes place throughout the small intestine, but the duodenum contributes maximally to zinc absorption owing to the higher zinc concentration in the duodenal lumen after a meal [2,3]. Excess endogenous zinc is excreted in feces via pancreatic secretions. The balance of intestinal absorption and endogenous fecal zinc (EFZ) excretion are two important factors for zinc homeostasis [3]. During zinc deficiency, EFZ decreases, with a concurrent increase in intestinal absorption. On the other hand, during an excess zinc intake, EFZ increases while its absorption remains unaffected.

Physiologically, zinc is defined as a type 2 nutrient. During deficiency, its functional pools are maintained at the expense of growth, but severe dietary restriction (<1 mg/day) results in reduced concentrations in functional tissue pools, with clinical symptoms such as growth faltering and infectious morbidity [3]. Thus, except when serum zinc concentration (SZC) is reduced during severe dietary zinc restriction, there are no biomarkers of mild or subclinical zinc deficiency (like serum ferritin for iron deficiency). Therefore, other contextual deficiency indicators, such as dietary zinc inadequacy and the prevalence of stunting, are suggested for assessing the risk of zinc deficiency in populations [1,2].

As severe forms of malnutrition have reduced substantially in India over the years, the focus has shifted to finding and preventing subclinical micronutrient deficiencies, with potential deficits in functionality (growth, cognition, etc). This subclinical deficiency can be assessed by measuring either blood biomarkers or risk of inadequacy in dietary intake, with prevention by diverse dietary intakes and through suitable public health interventions. The World Health Organization (WHO) has suggested staple food fortification with micronutrients as a short-term approach to increase micronutrient intakes [4], as it is potentially sustainable, does not require behavioral modifications, and is relatively safer and cost-effective compared to therapeutic supplementation [4]. However, the WHO suggested documenting important information for introducing specific fortification programs. These were: *i*) Established high prevalence of biochemical or subclinical deficiency (≥20%), *ii*) Low dietary intakes that increase the risk of deficiency, and *iii*) Fortification will produce a health benefit [4].

We review these three core conditions from the Indian perspective, and highlight uncertainties that have direct implications for considering zinc fortification as a public health strategy. Additional considerations in the evidence to decision framework are beyond the scope of detailed examination. These include adverse effects, user perspective (values and acceptability), feasibility, resource requirements, and cost-effectiveness [5].

ASSESSMENT OF ZINC STATUS

The serum or plasma zinc concentration, collectively referred to as SZC subsequently, is the usual biomarker for assessment of zinc status, or elevated risk of zinc deficiency, in populations [1,2]. Although zinc intakes are not associated with SZC in the American population [6], possibly due to a ceiling effect, where at higher intakes the SZC response is blunted, a systematic review [7] indicates that doubling the zinc intake results in ~9% increase in SZC, and therefore, the SZC can reflect the zinc intake.

Age, gender, and fasting status specific SZC cutoffs are suggested by International Zinc Nutrition Consultative Group (IZiNCG) to assess the risk of zinc deficiency in populations derived from National Health and Nutrition Examination Survey (NHANES)-II [1]. These cutoffs are statistically derived as the 2.5th centile from the SZC distribution in the US population (**Table I**), and used in many countries, including India. Experimentally, severe zinc restriction (<1mg/day for 2-9 weeks) in human volunteers has shown a progressive and rapid fall in SZC, with the onset of non-specific clinical symptoms [8]. Zinc supplementation rapidly improved the SZC and resolved these clinical signs. In Receiver Operating Characteristic (ROC) analyses to derive a diagnostic cutoff of zinc deficiency, the highest specificity was observed at a cutoff SZC value of 70 µg/dL. This value was similar to the statistically defined IZiNCG adult cut-off, suggesting that the latter remains useful [8].

Using statistical methods identical to IZiNCG [1], SZC cutoffs for apparently healthy 1-19-year-old children and adolescents (selected after applying more stringent exclusion criteria) were recently reported [9]. Interestingly, these cutoffs were lower (by 10-18 µg/dL) than those of the IZiNCG. There could be several reasons for this. First, the SZC cutoffs are variable and depend on the statistical distribution of SZC they are derived from. The cutoffs derived from the recent NHANES (2011-14) data are lower than the IZiNCG value (66 vs 74 µg/dL). Second, the dietary intakes of the NHANES reference population were almost twice that of their requirements, resulting in a right shift of the SZC distribution with higher 2.5th centile cutoffs. Third, the lower Indian cutoff, without any functional deficit, could indicate a successful adaptation to low bioavailable dietary zinc. Fourth, there could be differences in body composition, particularly lower lean body mass in Indians [9]. Thus, a range of SZC that are compatible with good health exist, and local contextualization of these values is critical when assessing the risk of zinc deficiency.

Inflammation is a critical confounder, left-skewing the SZC distribution independent of zinc status. Isolated Indian studies have reported 25-50% prevalence of low SZC [10], but the majority did not adjust for underlying inflammation, which overestimated zinc deficiency prevalence. The Comprehensive National Nutrition Survey (CNNS, 2016-2018), which surveyed children across India, provided representative data on SZC values (along with measurement of inflammation by serum C-reactive protein concentration) in Indian children and adolescents. The inflammation-adjusted pre-valence of low SZC (or zinc deficiency), using the IZiNCG cutoffs, among preschool (17.4%) and school-age (15.8%) children was below 20%, meaning that zinc deficiency was not a public health problem in these age groups. In adolescents, the prevalence of zinc deficiency was higher at 31% [10]. However, when India-specific SZC cutoffs were used, the national prevalence of zinc deficiency was ≤6% among 1-19-year children and adolescents, and this was less than 20% across all geographic states [9].

Another indirect, distal indicator considered for assessing zinc deficiency is the prevalence of stunting [1]. However, stunting is multifactorial in origin and SZCs are not associated with height for age in Indian children [9], and zinc supplementation in settings with high prevalence of stunting was not associated with improvements [11]. Indeed, in a high income European country, the prevalence of low SZC was 31%, when the prevalence of stunting was

Table I India-specific and IZiNCG Cutoffs to Define Low Serum Zinc Concentration (SZC) and Prevalence Estimates of Low SZC in Indian Children and Adolescents (Aged 1-19 Year)

Age	*Gender*	*Serum zinc concentration*						
		India- specific cutoff [a]			*IZiNCG cutoffs* [b]			
		Morning fasting	*Morning non-fasting*	*Prevalence* [a] *(%)*	*Morning fasting*	*Morning non-fasting*	*After noon*	*Prevalence* [a] *(%)*
<10 y	Both	56	55	<5 y: 6.0 5-9 y: 5.7	-	65	57	<5 y: 17.4 5-9 y: 15.8
>10 y	Female	54	53	5.6	70	66	59	31.1
	Male	56	55		74	70	61	

All values in µg/dL. [a]Pullakhandam, et al. 2022 [9] and Pullakhandam, et al. 2021 [10]. [b]IZiNCG, Food Nutr Bull. 2004 [1].

just 1% [12]. Therefore, the use of stunting as an indicator in assessing zinc deficiency is not valid, and controversial.

ZINC REQUIREMENTS AND INTAKES IN INDIA

Assessing the dietary zinc intakes *vis-à-vis* their requirement is a critical component of quantifying the risk of zinc deficiency [13], as SZCs are not a robust diagnostic of mild deficiency [1,2]. This exercise requires data on both nutrient requirements and dietary intake.

The nutrient requirements of Indians, published by the Indian Council of Medical Research (ICMR) in 2020 [13], provided three important metrics of the zinc requirement (**Table II**) viz., the estimated average requirement (EAR, average population requirement), the recommended dietary allowance (RDA, 97.5% of the population will have a requirement less than this) and the tolerable upper level of intake (TUL, the intake at which the risk of adverse effects starts). The EAR is factorially computed, considering factors such as daily loss of zinc (EFZ, urine, sweat, semen and menstrual losses), losses due to lactation, and sequestration during tissue accretion in growing children and during pregnancy. The daily replacement of these combined daily losses are adjusted for by dietary bioavailability, to derive the final dietary requirement [13].

As explained above, EFZ loss and bioavailability are two most important factors in this requirement. Added to this complexity is the homeostatic adjustment of EFZ, influenced by both recent intake (absorbed zinc) and body status. Stable isotopic methods now allow the precise measurement of EFZ as well as fractional zinc absorption [2]. Therefore, in India [15], the combined excretion of zinc from all possible routes was regressed against absorbed zinc, to find the minimum amount of absorbed zinc that was required to match losses. This was then adjusted for bioavailability to derive the EAR. A coefficient of variation of EAR of 10% was assumed to derive the RDA, while the TUL value was adopted from the Institute of Medicine recommendation [14]. Still, more contextual data on EFZ excretion are required, with low zinc-density and high phytic acid cereal/pulse diets.

Table II Age- and Gender-based ICMR, 2020 Zinc Requirements and Tolerable Upper Intakes for Indians

Category /age	*ICMR, 2020 (mg/d)*		
	EAR	*RDA*	*TUL*
Men	14.1	17	40
Women[a]	11.0	13.2	40
Children			
7-12 mo	2.1	2.5	5
1-3 y	2.8	3.3	7
4-6 y	3.7	4.5	12
7-9 y	4.9	5.9	12
Adolescents[b]			
Boys 10-12 y	7.0	8.5	23
Girls 10-12 y	7.1	8.5	23
Boys 13-15 y	11.9	14.3	34
Girls 13-15 y	10.7	12.8	34
Boys 16-17 y	14.7	17.6	34
Girls 16-17 y	11.8	14.2	34

EAR: estimated average requirement; RDA: recommended dietary allowance (Indian Council of Medical research, 2020) [13]; TUL: tolerable upper intake (Institute of Medicine, 2021) [14]. [a]Women of reproductive age; [b]TUL for 9-13 year age group is 23 mg/d.

Next, the dietary inadequacy assessment requires representative dietary zinc intake data. This allows estimation of the risk of intake inadequacy as the proportion of population intakes below the EAR (by the EAR cut point method) or the probability of inadequacy against the entire requirement distribution [2,13]. Based on probability theory, this proportion is ≤50% in a normal population [15]. However, there is lack of good quality national dietary intake data in India. The IZiNCG categorized India as a high-risk country for zinc deficiency based on (in addition to stunting) inadequate absorbable zinc intakes (26%) that were derived from FAO food balance sheets [1]. Trends (from 1983 to 2012) from National Sample Survey Organization (NSSO) data indicate that prevalence of inadequate zinc intake has increased from 17.1%-24.6% between 1983 and 2012 [16]. However, it should be noted that these analyses were based on either food balance sheets or per capita household food purchases, with imputed intakes from other settings, and the absorbable zinc was based on estimated phytate/zinc molar ratios. Therefore, further confirmation of dietary assessment with representative and accurate dietary intake data across all physiological, gender groups and demographics is sorely needed to identify the potential variables linked with risk of dietary zinc inadequacy, verified with simultaneous SZC data. However, even in these analyses the dietary zinc inadequacy remained ~25%, implying that the intakes in 75% of the population are above the EARs.

EFFICACY OF ZINC SUPPLEMENTATION/FORTIFICATION

Most studies of zinc supplementation/fortification have investigated increments in SZCs, linear growth, diarrhea and morbidity. There is robust evidence that oral zinc therapy reduces the severity of diarrhea in children, and India has pioneered evidence in this regard [17-20]. Further, preventive zinc supplementation (≥10 mg) also reduced the incidence of diarrhea and pneumonia, and tended to reduce related mortalities [21,22]. Molecular evidence indicates that an ionic imbalance (Na^+ and Cl^- loss) enforces water loss during diarrhea, which can be offset by zinc via cAMP signaling

mechanisms [23], and that zinc may also inhibit viral replication [2]. However, on anthropometric indicators (stunting, underweight or wasting), zinc supplementation (mean dose ≥7.5 mg/day) had either modest or no effect, even in LMICs considered to be at high risk of zinc defeciency [11,24,25]. It is worth noting that the doses used in the majority of these studies were greater than 10 mg (2-3 times higher than EAR of under-five children, and higher than the TUL). Further, the effects of zinc on intestinal function in animal models appear to be independent of zinc status [2]. Therefore, while therapeutic zinc supplementation as adjunct therapy for diarrhea as recommended by WHO/ UNICEF is beneficial, preventive zinc supplementation with pharmacological doses of zinc to improve growth or reduce morbidity does not appear to be ideal, in context of the lack of impact of supplementation on anthropometric indicators [26].

Systematic reviews of zinc fortification trials (zinc alone or with other micronutrients) have shown a significant increase in SZCs or reduction in prevalence of low SZCs [27-29], where the effect was higher with zinc-alone fortification compared to when it was combined with other micronutrients [28]. However, this was the sole effect, with no reported evidence on improvements in any functional outcome (incidence of diarrhea and morbidity, or anthropometry). One review reported a significant weight gain (of 0.4kg), but explicitly stated that this effect could not be directly attributed to zinc [28]. That most zinc fortification studies are conducted in LMICs, and yet there is no evidence of functional benefits, suggests that either there is no risk of zinc deficiency or that zinc fortification is ineffective in improving linear growth.

EVIDENCE FOR ZINC FORTIFICATION IN INDIA

The important question one must ask is what is the desired goal of zinc fortification of foods in India – is it solely to improve SZC or to confer functional benefits such as reduced stunting, reduced diarrhea and other morbidities? As discussed above, SZCs are not the definitive indicators of zinc deficiency, and need to be supported by other indicators. Nevertheless, the SZC cutoffs for zinc deficiency in healthy Indian children are lower than that recommended by IZiNCG, and yield a prevalence of zinc deficiency of ~6%. Thus, in Indian children, it appears that zinc deficiency is not a public health concern. It is then logical to evaluate if target functional outcomes were improved with zinc fortification. Zinc fortification trials have not shown definitive improvements in anthropometric outcomes (like stunting) or reduced diarrheal incidence in children. There is also increasing clinical and basic evidence that the mode of action of zinc supplementation in diarrhea and other morbidities could be pharmacological. Clearly, there is no strong evidence to support zinc fortification of foods yet in India, unless the target is solely to improve the SZCs, or to chase a mirage of functional benefits, which ironically, are not achieved even at therapeutic doses. Further, available estimates of the prevalence of dietary inadequacy data suggest no dietary deficiency, but more detailed data would be helpful, particularly to evaluate risks of exceeding the TUL in the event of fortification or supplementation. For example, an Ethiopian simulation study reported that zinc fortification (providing 4.1 mg zinc/day) significantly reduced dietary inadequacy but increased the risk of exceeding the TUL by 50% among young children [30]. A final important consideration is that once fortification is implemented, it reaches all sections of the population, including men, pregnant women, elderly, and persons with chronic disease. The intended functional outcome in these population sections should be stated, along with risk/benefit analyses, before decisions on universal zinc food fortification are taken.

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Bharati Vidyapeeth Deemed to be University Medical College, Pune, Maharashtra & Rainbow Children's Hospital, Bangalore, Karnataka

Post-Doctoral Fellowship in Pediatric Rheumatology

Greetings! Bharati Vidyapeeth Deemed to be University has been reaccredited "**A" grade by NAAC** and as on today is recognized by the UGC as one of the 20 universities in India for global promotion of education. Bharati Vidyapeeth Deemed to be University Medical College, Pune has an advanced Department of Pediatrics and state-of-the-art infrastructure with multiple well developed Pediatric sub-specialties that offer Fellowship training of a national standing. More than 200 fellows have passed out in last decade form our unit.

Pediatric Rheumatology Clinic offers comprehensive care to children with JIA, SLE, Juvenile Dermatomyositis, Vasculitis, Systemic Sclerosis, Auto-inflammatory diseases etc. The nailfold capillaroscopy, musculoskeletal ultrasound, intra-articular corticosteroid injections and kidney biopsy are commonly performed in the clinic. In-house services of all pediatric sub-specialists including pediatric physiotherapist are available for children with rheumatic diseases.

Rainbow Children's Hospital, Bangalore (RCH) is India's leading multispecialty children's and maternal care chain in the country with 16 hospitals and 1700 beds. The Pediatric Rheumatology department is a growing referral center in the state of Karnataka and neighboring states. The department works closely with acute care services and other specialties to provide optimal care in the field of immunomodulation. The academic environment fosters collaborations with internationally acclaimed centers of repute to stay at the forefront of advancements in the field of Rheumatology and provides an excellent platform for research opportunities. As part of the commitment to academic excellence, the department encourages and supports research work, allowing team members to contribute to the growing body of knowledge in Pediatric Rheumatology.

The fellowship program is of 1 year duration with 6 months rotation at both centers. The fellow will have a 2-mentor advantage along with hands on training of nailfold capillaroscope, MSK ultrasonography, intra-articular injection, ANA reporting etc.

Eligibility: MD / DNB (Pediatrics) **Age** preferably less than **35** years
Course Duration: One year (06 months Rotation policy)

Facilities included at BVUDMC&H: Free shared accommodation, monthly stipend as per University policy
Facilities included at RCH: No accommodation, monthly stipend as per University policy

Fellowship Mentors

Dr. Jitendra S Oswal
Professor of Pediatrics and Rheumatology
Deputy Medical Director
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Eligible and interested candidates may apply with complete biodata and relevant certificates to - **Dr. S. K. Lalwani, Vice Principal, Medical Director, Professor and Head – Pediatrics, 09th floor, New Super Speciality Building, Bharati Hospital, Pune Satara Road, Katraj, Pune – 411 043, MAHARASHTRA. Phone: 020-40 55 55 55 Ex 3931**

OR

E-mail your application with Curriculum vitae to *bvpedfellowship@gmail.com* by **15th September, 2023**

RESEARCH PAPER

Overall and Event Free Survival of Childhood Cancer - Report From a Hospital-Based Cancer Registry in Northern India, 2013-21

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Objectives: Using data from a hospital-based cancer registry (HBCR) in the private sector in Northern India, we provide overall survival (OS) and event-free survival (EFS) for childhood cancer patients.

Methods: All newly diagnosed childhood (age <18 years) cancer patients in our HBCR registered between March 1, 2013 till July 31, 2021 were eligible. 3-year and 5-year OS (death was an event), EFSc (death, progression/relapse was an event), and EFSa (death, progression/relapse, abandonment of treatment was an event) were calculated using the Kaplan-Meier method. Regression analysis was done to see their association with demographic, diagnostic and treatment variables.

Results: 705 newly diagnosed children (36.2% female) with cancer were registered. Common cancers were leukemias (26%), CNS tumors (20%) and bone tumors (16%). 202 (28.6%) had experienced an event at median follow up of 1.95 years (range 0-8.14 years), which included 23 (3.3%) who abandoned treatment. The 3-year OS, EFSc, EFSa were 70.8%, 64.4% and 63.6%, respectively. Correspondingly, 5-year OS, EFSc, EFSa were 66%, 58.6% and 57.5%, respectively. There was no significant difference by age group, gender, nationality, and if cancer directed treatment initiated elsewhere. The OS, EFSa and EFSc by the main and the extended International Childhood Cancer Classification categories varied significantly (P<0.001).

Conclusion: We add more recent registry-based OS data on childhood cancer in India and present the first estimates on EFS.

Keywords: *Management, Outcome, Survival analysis*.

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The measurement of outcome in childhood cancer patients is critical to demonstrate efficacy of treat-ment and gauge progress. Rates of treat ment-related mortality, abandonment and progression/relapse provide a snapshot of events happening during or after treatment. These metrics, while useful, are incomplete, as they do not take into account the length of time it took to achieve (or not achieve) an event. Overall survival (OS), where only death is treated as an event and event-free survival (EFS), where besides death, disease progression/relapse, secondary malignancy and treatment abandonment may also be considered as events, have become the foremost metrics of outcome in childhood cancer [1]. The OS and EFS reported in clinical trials helps us to identify more effective treatments, but does not represent the true outcomes of the population of interest as the studies often exclude the sickest, those with missing data, those who took incomplete treatment, etc. Registry based survival data, which may be population-based cancer registry (PBCR, all patients residing in a defined area diagnosed with disease of interest) or hospital-based cancer registry (HBCR, all patients accessing care in a specific hospital and diagnosed with disease of interest) give a truer estimate of outcomes in that context and population, and is of interest to clinicians, epidemiologists and policy makers [2-4].

Invited Commentary: Pages 517-18.

While there are several published reports from PBCR [5-10] and HBCR [11] in India on childhood cancer, they all look at the incidence and distribution of cancer and only two till date have reported data on OS (they did not report EFS) [5,8]. There is no data from registries (population- or hospital-based) of outcomes of childhood cancer after the year 2000. Using data from a HBCR in the private sector in northern India, we analyzed to provide OS and EFS for a more recent set of childhood cancer patients.

METHODS

Our institution provides care to over 10,000 cancer patients of all ages per year from the local Delhi National Capital Region (NCR), several surrounding and distant states from

northern, Central and eastern India, as well as from other countries [12]. All newly diagnosed pediatric (aged below 18 years) cancer patients in the HBCR who had registered between March 1, 2013 and July 31, 2021, for two of the hospitals, and from January 1, 2016 and July 31, 2021 for one of the hospitals, formed the study group. Patients were registered at these hospitals regardless of whether they took all or some of their treatment there. We did not register those who underwent initial consultation and/or diagnosis with participating but were subsequently transferred to a different facility. However, if they abandoned treatment after initial consultation and/or diagnosis, they were still included in our registry. Abandonment was defined as refusal to initiate treatment or a hiatus of four or more weeks in the scheduled treatment [13].

The patients were primarily identified through the clinical encounters (outpatient and inpatient) in the oncology department. This was supplemented with regular screening of patients in the weekly disease specific tumor boards of neurology, musculoskeletal and hematological cancers; monthly review of all patients with cancer diagnosis in the pathology database; and annual review of patients in the radiation oncology database. This enhanced the completeness of our registration by ensuring that those patients who received only one modality of treatment, and/or may not have come to the oncology department were captured.

Data were entered manually by our social worker, registry staff, and clinicians, and all the data was then cross-checked by another clinician. Data collected included demographic variables and diagnosis (coded as per main and extended International Childhood Cancer Classi-fication) [14], and whether cancer directed treatment was initiated elsewhere. Outcomes of interest were vital status (alive or dead), disease status (progressed/relapsed or not progressed/relapsed), and treatment status (abandoned or not abandoned). Follow-up contact was made through clinics, phone and email every 6-12 months.

Statistical analysis: All variables of interest were cate-gorical and descriptive analysis was done. 3-year and 5-year OS (death was an event), EFSc (death, progression/relapse was an event), and EFSa (death, progression/relapse, abandonment of treatment was an event) were calculated using the Kaplan-Meier method. Regression analysis was done to see the association of the variables with the outcomes. The median follow-up was calculated using the reverse Kaplan-Meier method.

RESULTS

During the study period, 705 children newly diagnosed with cancer were registered, of which 255 (36.2%) were female, 217 (30.8%) were from outside India, and 180 (25.6%) had initiated cancer directed treatment elsewhere. The most common major groups of cancer were leukemias (26%), CNS tumors (20%), bone tumors (16%) and lympho-mas (13%) (**Fig. 1**). Only 0.4% of the cancers were of unspecified histology.

Of these 705 children, 202 (28.6%) had experienced an event at median follow-up of 1.95 years (range 0-8.14 years). In 98 children (13.9%), the first event was relapse or progressive disease (median time to event 393.5 days), in 81 (11.5%) it was death (median time to event 220 days) and in 23 (3.3%) it was abandonment of treatment (median time to event 10 days) (**Fig.2**). Overall, 156 children with cancer died. 63 of the 98 children who had first event as relapse or progressive disease subsequently died, and 35 were alive at last follow-up.

Among the 23 children (47.8% females, 39.1% from outside India) who abandoned treatment, 12 died (death happened at a median of 66.5 days after abandonment of treatment), eight were not contactable immediately after abandoning treatment, and three were alive at last follow- up, which was 58, 160 and 428 days after abandonment. The two patients who abandoned treatment and were still alive after a relatively longer period of follow-up included a 16-year-old child with anaplastic ependymoma (alive at last follow-up of 160 days after diagnosis) who had complete remission after surgery but did not take radiation. The second child was a 16-year-old with supratentorial primitive neuroectodermal tumor (alive at last follow-up of 428 days after diagnosis), who achieved complete remission after surgery and underwent radiation with daily concurrent carboplatin and then abandoned during adjuvant chemotherapy.

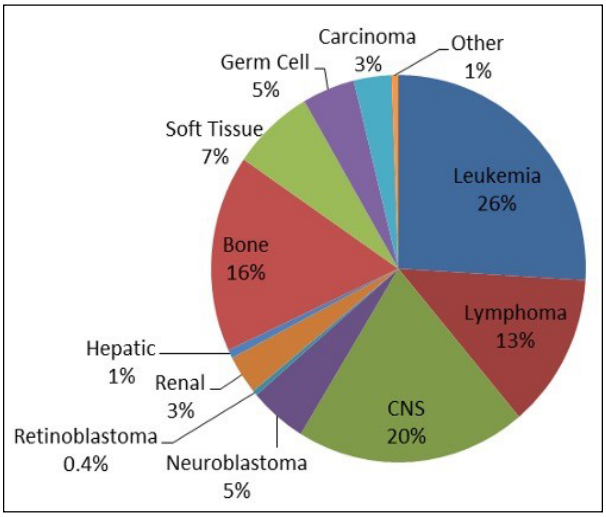

Fig. 1 Distribution of childhood cancers by the main categories of International Childhood Cancer Classification at a hospital-based cancer registry in northern India, 2013-21.

Gender and nationality were not significantly different in those who had abandonment of treatment as a first event in comparison to those who did not abandon. However, the distribution of cancer in those who abandoned treatment (35% CNS tumors, 26% leukemia, 22% neuroblastoma, 17% all other categories) was significantly different (P= 0.004) in comparison to those who did not abandon.

The 3-year OS, EFSc, EFSa were 70.8%, 64.4% and 63.6%, respectively (**Table I**). Correspondingly, 5-year OS, EFSc, EFSa were 66%, 58.6% and 57.5%, respectively. There was no significant difference in the outcome by age group, by gender, by nationality and if cancer directed treatment was initiated elsewhere.

The OS, EFSa and EFSc by the main and the extended International Childhood Cancer Classification categories varied significantly (P<0.001) (**Web Table I**). The highest OS was seen for germ cell tumors, epithelial cancers, lymphomas and liver tumors where more than eight out of 10 children were alive after five years. For certain specific cancers like chronic myeloid leukemia, Hodgkin lymphoma, gonadal germcell tumors, thyroid carcinoma and nasopharyngeal carcinoma, nearly all patients were alive five years after diagnosis.

The 3-year OS approximated the 5-year OS for Burkitt lymphoma, Wilms tumor, and Hodgkin lymphoma. The 5-year OS was lower than the 3-year OS for sarcomas (osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma) as well as hematolymphoid neoplasms (acute myeloid leukemia, acute lymphoblastic leukemia and non-Hodgkin lymphoma excluding Burkitt lymphoma).

DISCUSSION

Through a HBCR in the private sector in northern India, we provide updated survival statistics for children with cancer in India. The estimated 5-year OS of 66% compares favorably (overall and cancer specific survival) with the limited registry data on outcomes published till date in India [5,8]. This information also serves two additional purposes. It allows us to get a sense of the differential in childhood cancer survival outcomes, which exists with Europe (74.3%) and North America (83%) [15]. Data on survival from other HBCRs in low- and middle-income countries is scant and varies between 30-60% [16,17]. There is a possibility to bridge this gap by improving access to all modalities of treatment packaged with service delivery to reduce abandonment and improve quality [15]. Our results are also important in the context of the WHO Global Initiative for Childhood Cancer, which aims for at least 60% survival for childhood cancer globally and save one million additional lives by 2030 [18]. While our results may not be representative of the entire country, it is possible to get a

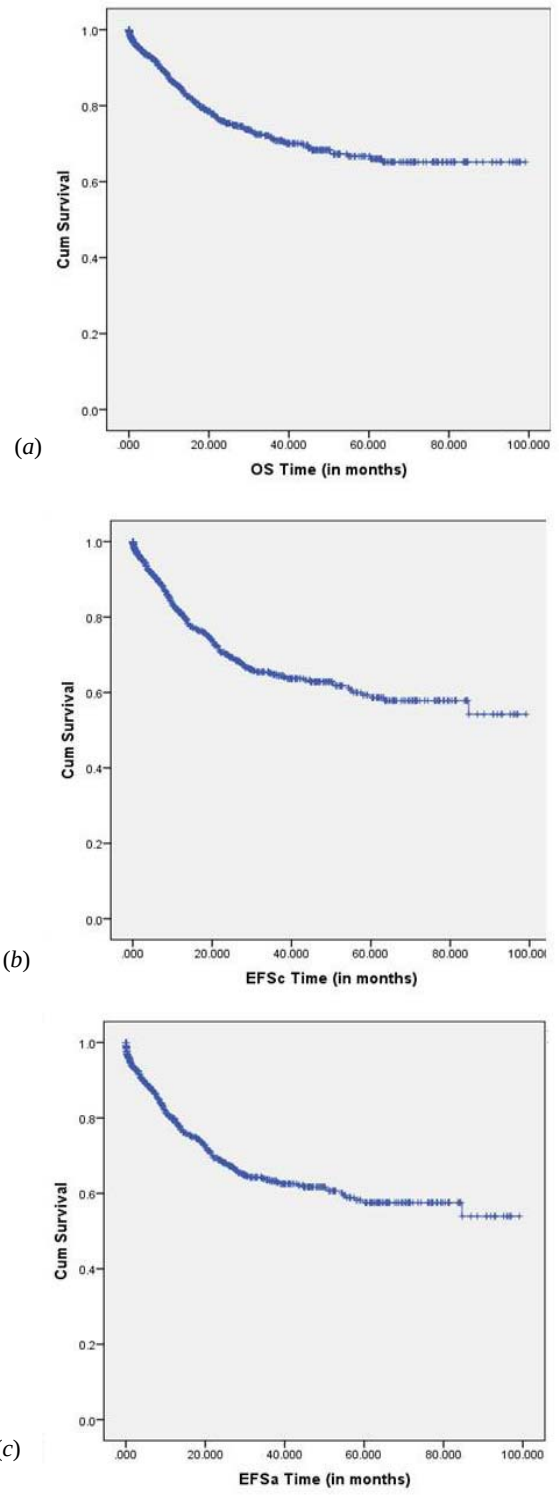

Fig. 2 Kaplan Meier curves for *a*) overall survival (OS), *b*) event free survival with abandonment censored (EFSc), and *c*) event free survival with abandonment included (EFSa) for childhood cancers at a Hospital-based Cancer Registry in Northern India, 2013-21.

nationwide picture by generating similar reports from the multiple other HBCRs (in public, private and charitable trust sectors), which exist. Such information would be critical to the efforts of all stakeholders in India to make progress and achieve the goals of WHO Global Initiative for Childhood Cancer [19].

The distribution of cancer with a relatively lower proportion of leukemias and retinoblastomas and a relatively higher proportion of CNS tumors and bone sarcomas is different from that reported elsewhere in India [20]. It is a reflection of our practice, which is likely affected by socio-economic status of our patients, referral bias, and international medical tourism [12]. A higher male-to-female ratio is not unexpected and has been previously described and thought to be related to a disproportionate degree of under-diagnosis in females [21]. A quarter of patients initiated firstline treatment elsewhere and then moved to our center. While we did not investigate the reasons for this, we postulate that this health-seeking behavior is multifactorial and includes absence of formal referral networks, need for certain specialist services, and patient dissatisfaction in certain settings.

The abandonment rates of 3.3% are among the lowest reported in India [22,23], and would reflect the socioeconomic status of the patients at our centre as well as the robust social support system including assessment by dedicated social workers, access to patient assistance through governmental and non-governmental support, and repeated counselling of patients.

We found no difference in survival by age, gender and nationality. Age and gender were also not found to be significant in previous reports from India [5,8]. OS and EFS varied significantly by the International Childhood Cancer Classification. Some cancers had 5-year OS of less than 50%, which included acute myeloid leukemia, non-Hodgkin lymphoma excluding Burkitt lymphoma, osteosarcoma, Ewing sarcoma and rhabdomyosarcoma. This is similar to data from high income countries where lower survival is observed for some CNS tumors, certain leukemias, and some sarcomas of bone and soft tissues [24].

In our HBCR as well as the pediatric dataset, case ascertainment was through multiple sources, number of cancers with unspecified morphology was 0.4% and the social support team followed-up all registered patients regularly. All data was verified by one of the investigators. Our limitation is that at present we have not collected data on stage and risk groups. Going forward, we plan to use the stage and non-stage prognosticators as recommended by the Toronto Pediatric Cancer Stage Guidelines [25,26]. Another limitation is the relatively short median follow-up of 1.95 years. This is partly because the volume of our work has increased in the latter years and a third center started contributing from 2016, but this is also because 30% of our patients are international and their median follow-up is 0.76

Table I Three-Year and 5-Year OS, EFSc (With Abandonment Censored), EFSa (With Abandonment Included) Categorized by Demographic Variables for Childhood Cancer, 2013-21

	OS		*EFSc*		*EFSa*	
	3-year	*5-year*	*3-year*	*5-year*	*3-year*	*5-year*
All patients (*n*=705)	70.8%	66%	64.4%	58.6%	63.6%	57.5%
Age group (y)						
0-4 (*n*=212)	72.7%	72.7%	65%	62.1%	63.5%	59.6%
5-9 (*n*=205)	70.3%	60.8%	61.5%	53.9%	61.2%	53.6%
10-14 (*n*=173)	67.8%	61.6%	66.8%	59.1%	66.6%	58.9%
>15 (*n*=115)	72.6%	67.8%	65.8%	58.5%	64.4%	57.2%
Gender						
Female (*n*=255)	72%	70.2%	68.1%	63.7%	67.2%	62.7%
Male (*n*=450)	69.9%	63.7%	62.2%	55.8%	60.9%	54.7%
Country of origin						
India (*n*=488)	71.8%	68.3%	65.9%	60.2%	65.1%	59.3%
Outside India (*n*=217)	66.5%	55.7%	59%	52.6%	57.4%	51.1%
Initiation of cancer treatment						
Elsewhere (*n*=180)	72.2%	70.6%	65.5%	64%	65.1%	65.1%
Same center (*n*=522)	70.5%	64.9%	64.2%	57.1%	62.8%	55.8%
Unknown (*n*=3)	33.3%	33.3%	33.3%	33.3%	33.3%	33.3%

OS: overall survival, EFSc: event free survival with abandonment censored, EFSa: event free survival with abandonment included. The OS, EFSa and EFSc each did not vary significantly (P>0.05) for any of the demographic variables.

WHAT IS ALREADY KNOWN?

- There is paucity of childhood cancer survival data from India with no data from registries (population- or hospital-based) on outcomes of childhood cancer after the year 2000.

WHAT THIS STUDY ADDS?

- We provide recent registry-based survival data on childhood cancer from Northern India.

years while those of Indian patients is 2.5 years. We are working on strengthening our follow-up systems, particularly for the international patients. Recognizing this limitation, we have presented our data for 3-year and 5-year survival.

In summary, this study adds recent registry-based OS data on childhood cancer in India and presents the first estimates on EFS. These survival rates are an improvement on previously published data and provide a newer baseline to measure progress and compare with data from other sources. Similar data from other HBCRs in India will aid in providing a nationwide picture.

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Ethics clearance: The hospital-based cancer registry for each of the sites has previously received ethical clearance; No. CT/MSSH/SKT-2/ONCO/12-10 dated July 27, 2012. As this is routinely collected data for clinical care, waiver of consent was approved.
Contributors: RSA: conceived the idea; RK, AA, MS, PJ, RSA: extracted the data; RT, RSA: analyzed the data; RSA: wrote the first draft. All authors reviewed and approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Three-Year and 5-Year OS, EFSc (With Abandonment Censored), EFSa (With Abandonment Included) Categorized by Main and Extended International Childhood Cancer Classification

Main and Extended International Childhood Cancer Classification	*3-year OS*	*5-year OS*	*3-year EFSc*	*5-year EFSc*	*3-year EFSa*	*5-year EFSa*
Leukemias, Myeloproliferative and Myelodysplastic Diseases (n=183)	*69.2%*	*63.3%*	*65.4%*	*55.7%*	*64.7%*	*55.2%*
Lymphoid leukemias (*n*=152)	71.8%	66.1%	67.8%	58.6%	67.8%	58.6%
Acute myeloid leukemias (*n*=22)	51.6%	41.2%	46.5%	23.3%	45.1%	22.5%
Chronic myeloproliferative diseases (*n*=3)	100%	100%	100%	100%	100%	100%
Myelodysplastic syndrome and other myeloproliferative diseases (*n*=3)	50%	50%	50%	50%	33.3%	33.3%
Unspecified and other specified leukemias (*n*=3)	50%	50%	50%	50%	50%	50%
Lymphomas and reticuloendothelial neoplasms (n=91)	87.3%	83.3%	80.3%	76.4%	80.3%	76.4%
Hodgkin lymphomas (*n*=43)	100%	100%	90.6%	90.6%	90.6%	90.6%
Non-Hodgkin lymphomas (except Burkitt lymphoma) (*n*=19)	61.4%	46.1%	62.5%	46.9%	62.5%	46.9%
Burkitt lymphoma (*n*=16)	72.2%	72.2%	72.2%	72.2%	72%	72%
Miscellaneous lymphoreticular neoplasms (*n*=11)	100%	100%	66.7%	66.7%	66.7%	66.7%
Unspecified lymphomas (*n*=2)	100%	100%	100%	100%	100%	100%
CNS and Miscellaneous Intracranial and Intraspinal Neoplasms (n=140)	67%	67%	61%	59.1%	58.5%	56.7%
Ependymomas and choroid plexus tumor (*n*=15)	59.3%	59.3%	63.6%	63.6%	49.5%	49.5%
Astrocytomas (*n*=50)	79.5%	79.5%	67.9%	67.9%	64.8%	64.8%
Intracranial and intraspinal embryonal tumors (*n*=36)	63.2%	63.2%	61.9%	61.9%	60.2%	60.2%
Other gliomas (*n*=16)	20.6%	20.6%	13.8%	13.8%	14.4%	14.4%
Other specified intracranial and intraspinal neoplasms (*n*=21)	88.9%	88.9%	82.5%	66%	82.5%	66%
Unspecified intracranial and intraspinal neoplasms (*n*=1)	100%	100%	100%	100%	100%	100%
Neuroblastoma and Other Peripheral Nervous Cell Tumors (n=35)	64.5%	64.5%	57.3%	57.3%	49.4%	49.4%
Neuroblastoma and ganglioneuroblastoma (*n*=33)	62.9%	62.9%	55%	55%	47.3%	47.3%
Other peripheral nervous cell tumors (*n*=2)	100%	100%	100%	100%	100%	100%
Retinoblastoma (n=3)	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Renal Tumors (n=23)	*73.2%*	*73.2%*	*69%*	*69%*	*69%*	*69%*
Nephroblastoma and other non-epithelial renal tumors (*n*=21)	84.4%	84.4%	76.7%	76.7%	76.7%	76.7%
Renal carcinomas (*n*=1)	0	0	0	0	0	0
Unspecified malignant renal tumors (*n*=1)	0	0	0	0	0	0
Hepatic Tumors (n=5)	80%	80%	80%	80%	80%	80%
Hepatoblastoma and mesenchymal tumors of liver (*n*=5)	80%	80%	80%	80%	80%	80%
Hepatic carcinomas (*n*=0)	-	-	-	-	-	-
Unspecified malignant hepatic tumors (*n*=0)	-	-	-	-	-	-

Malignant Bone Tumors (n=116)	64.1%	47.6%	58.8%	49.8%	58.9%	49.9%
Osteosarcomas (*n*=59)	65.8%	49.3%	59.9%	44.9%	60.3%	45.2%
Chondrosarcomas (*n*=2)	100%	100%	100%	100%	100%	100%
Ewing tumor and related sarcomas of bone (*n*=54)	61.3%	47.3%	56.4%	50.2%	60%	50.2%
Other specified malignant bone tumors (*n*=1)	100%	100%	100%	100%	100%	100%
Unspecified malignant bone tumors (*n*=0)	-	-	-	-	-	-
Soft Tissue and Other Extraosseous Sarcomas (n=50)	56%	52%	30.6%	22.9%	29.9%	22.4%
Rhabdomyosarcomas (*n*=23)	54.9%	47.1%	27.8%	27.8%	26.5%	26.5%
Fibrosarcomas, peripheral nerve sheath tumors and other fibrous neoplasms (*n*=16)	58.8%	58.8%	32.6%	32.6%	32.6%	32.6%
Kaposi sarcoma (*n*=0)	-	-	-	-	-	-
Other specified soft tissue sarcomas (*n*=10)	71.1%	71.1%	37%	37%	37.5%	0.00%
Unspecified soft tissue sarcomas (*n*=1)	0	0	0	0	0	0
Germ Cell Tumors, Trophoblastic Tumors and Neoplasms Of Gonads (n=32)	92.6%	92.6%	92.9%	92.9%	92.9%	92.9%
Intracranial and intraspinal germ cell tumors (*n*=2)	0	0	0	0	0	0
Malignant extracranial and extragonadal germ cell tumors (*n*=6)	83.3%	83.3%	83.3%	83.3%	83.3%	83.3%
Malignant gonadal germ cell tumors (*n*=23)	94.1%	94.1%	94.1%	94.1%	94.1%	94.1%
Gonadal carcinomas (*n*=1)	100%	100%	100%	100%	100%	100%
Other and unspecified malignant gonadal tumors (*n*=1)	100%	100%	100%	100%	100%	100%
Other Malignant Epithelial Neoplasms and Malignant Melanomas (n=23)	95.5%	87.5%	89.5%	81.4%	89.5%	81.4%
Adrenocortical carcinomas (*n*=0)	-	-	-	-	-	-
Thyroid carcinomas (*n*=3)	100%	100%	100%	100%	100%	100%
Nasopharyngeal carcinomas (*n*=8)	100%	100%	100%	100%	100%	100%
Malignant melanomas (*n*=0)	-	-	-	-	-	-
Skin carcinomas (*n*=0)	-	-	-	-	-	-
Other and unspecified carcinomas (*n*=12)	91.7%	78.6%	81.5%	67.9%	81.5%	67.9%
Other and Unspecified Malignant Neoplasms (n=4)	0	0	0	0	0	0
Other specified malignant tumors (*n*=1)	0	0	0	0	0	0
Other unspecified malignant tumors (*n*=3)	0	0	0	0	0	0

* The OS, EFSa and EFSc each varied significantly (P<0.001) by the main and the extended International Childhood Cancer Classification categories; OS Overall Survival, EFSc Event Free Survival with abandonment censored, EFSa Event Free Survival with abandonment included, CNS Central Nervous System

RESEARCH PAPER

Effect of Clinician-directed Technical Specifications on Entrance Skin Doses in Neonates

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Objectives: To compare the entrance skin doses (ESD) before and after implementation of a radiation safety policy in neonates (RSN), which focused on clinician-directed technical specifications on the digital *X*-ray machine. **Methods**: Prospective observations included two sets of *X*-rays: Before (BRSN) and after (ARSN) implementation of RSN (documented indication for *X*-ray/expected posttest findings, settings of 40 kVp, 0.5 mAs, film-focus distance 100 cm, gonadal-shield, optimal collimation, and post-shoot image-enhancement). **Results:** 33 and 32 *X*-rays were analyzed in respective groups. Mean (SD) of calculated and machine-quantified ESD (μGy/m^2) was higher in BRSN group as compared to ARSN group (P <0.001). All ARSN *X*-rays were interpretable for expected post-test findings. **Conclusion:** Clinicians' cognizance of ability to make consequential bedside technical specifications, can reduce ESD without affecting interpretability. These single observations could have a larger impact in sick neonates, where multiple *X*-rays are done.

Keywords: *ALARA, Film-focus distance, Kilovoltage-peak, Radiation safety*.

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Neonatal intensive care involves frequent use of *X*-ray imaging for diagnosis and management of sick infants [1]. Reports confirm that exposures are inversely proportional to gestation age at birth [2]. Radiation sensitivity is highest in the newborn period than at any other point in an individual's lifespan. High mitotic activity and small size make them particularly vulnerable to ionizing radiations that damage biological tissues [1,3]. Considering potential future exposure, neonates are also at the highest risk of cumulative effects [3].

The guiding principle of radiation safety is ALARA, which stands for 'as low as reasonably achievable.' This means that even if it is a small dose, if receiving that dose has no direct benefit, then it is best avoided [4]. The entrance skin dose (ESD) is the simplest method which helps to quantify radiation dose. It measures the radiation incident upon a patient's skin surface during a radiologic examination. ESD does not; however, consider important factors like area of exposure, or radiosensitivity of target tissues [3]. Three protective measures in radiation safety include: *i*) minimization of product of exposure time and current (milliampere-second, mAs) and kilovolt peak (kVp), *ii*) increased distance from source (film-focus distance, FFD), and *iii*) shielding of maximum possible vulnerable tissues [4]. Researchers have previously reported the use of variable kVp, mAs, FFD [5]. This highlights the dearth of uniform recommendations. Moreover, most are retrospective audits [5]. Quality initiatives have concentrated mainly on reducing number of exposures. Bedside practice; however, calls for *X*-rays to be done at some point in a sick neonate's care. There is a role for pushing the limits of technical specifications without affecting *X*-ray picture quality/interpretability [1].

Invited Commentary: Pages 519-20.

We planned this study to analyze the effect of a rigorously designed radiation safety policy in neonates (RSN) on ESD. Our RSN was based on a bundle approach, which included clinician-directed bedside modifications of machine settings to reduce radiation doses, and digital enhancement methods to visualize specific structures in the picture, after exposure.

METHODS

This observational (before-after) analytical study was conducted over two months (September-October, 2022) in a 33-bed Level IIIB (National Neonatology Forum, India) neonatal intensive care unit (NICU), which is part of a referral private sector hospital in Kerala. The radiology

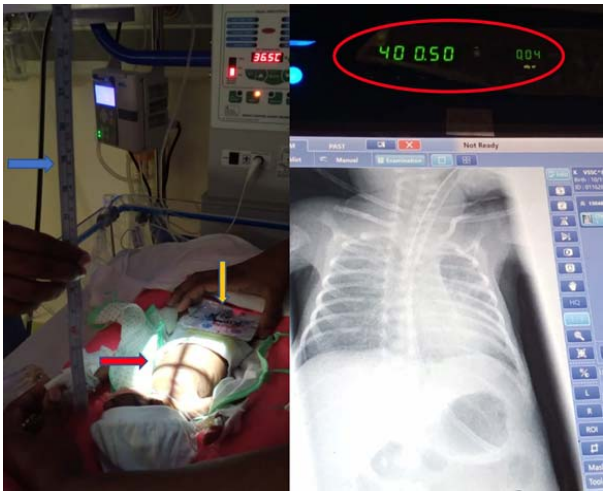

Fig. 1 Clinician-directed radiation safety policy components: Film focus distance increased to 100 cm (white arrow); Gonadal shield (white arrowhead); Collimation for chest and abdomen exposure (black arrow); Machine technical settings reduced to minimum possible (oval) thereby decreasing entrance skin dose. The three values represent kVp, mAs and machine estimated entrance skin dose in µGy.

department is accredited by the National Accreditation Board for Hospitals. Informed consent was taken from parents of infants in the ARSN group to record deidentified data. Approval was obtained from the institute human ethics committee.

Neonates admitted to the NICU during the study period who required at least one portable *X*-ray were enrolled. Those who were receiving care in hybrid incubators were excluded, since FFD could not be maximized to the desired value. In September, during the process of literature review and study design, prospective observations of the neonates were made (Before RSN, BRSN). During this period, the mAS and kVp settings on the machine, FFD, and collimation were being decided by the radiographer. These settings were based the radiology technicians' training, and recommendations by the Radiology department [6,7]. The settings used in BRSN were simply recorded by the bedside team.

Decisions for *X*-rays are usually made jointly by at least two doctors on duty. After several bedside observations of machine settings (made by radiology technicians) during BRSN, and simultaneous discussions on *X*-ray interpretability, incremental changes were made to subsequent *X*-rays taken in the unit to reduce exposure settings to the least possible. The unit finalized a protocol for radiation safety by October, 2022, after which, observations of the neonates were made (After RSN: ARSN). When *X*-rays were deemed unavoidable and could not be replaced by ultrasound examinations, wherever possible, components of RSN included: *i*) documentation of clinical indication and expected findings before the *X*-ray is ordered by the duty team, *ii*) exposure settings ensured by the bedside clinical team to 40 kVp, 0.5 mAs (these are the minimum possible settings on the portable digital machine), *iii*) FFD 100 cm, *iv*) strict collimation to least possible area, *v*) gonadal shield (**Fig. 1**), *vi*) confirmation of baby position by doctor on duty before exposure to reduce chances of rotation and need for reexamination, *vii*) use of enhancement options on the machine display (**Fig. 2**) including focal magnification, noise reduction, brightness and contrast changes, perspective control when necessary (to view certain structures/parts specifically, and *viii*) documentation of whether any modifications were made to clinical management based on findings within next 1 hour. Since the clinical team was

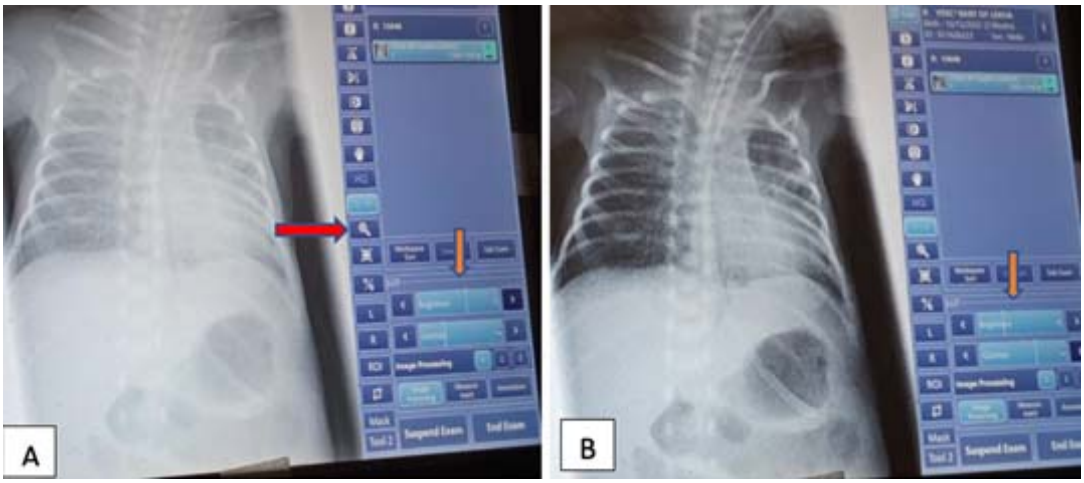

Fig. 2 Post-exposure, digital picture enhancement techniques. (A) Magnification changes are possible (red arrow), *X*-ray is at lesser contrast setting and higher brightness (black arrow), (B) easily visualised endotracheal tube, orogastric tube with less "noise" and sharper picture quality by change in settings (white arrow).

actively involved in the technique itself in ARSN time epoch, the digital picture was seen and interpreted immediately after the exposure.

The primary outcome was comparison of mean ESD calculated for both the groups by the formula ESD (μGray) = c (kVp/FFD)^2 × (mAs/mm.AL) where kVp- kilovolt, FFD – film focus distance in cm, mAs – milliampere-second product, mm. Al – aluminium filter collection factory taken as 1.5 (provided by machine manufacturers) : total filtration correction factor, c- constant (0.277) [8]. Machine-displayed ESD values were also recorded, whenever available. One of the two machines were wheeled into the unit based on immediate availability: one (Shimadazu RM74B6D AA121) displayed the estimated ESD automatically based on settings; the other (DRXR-1) did not have this software installed. Secondary outcomes planned were compliance to specific components of RSN and proportion of *X*-rays that led to active management changes in clinical care.

Assuming a pooled standard deviation of 0.095 units, it was calculated that the study would require a sample size of 23 for each group (i.e., a total sample size of 46, assuming equal group sizes), to achieve a power of 80% and a level of significance of 5% (two sided), for detecting a true difference in means between the test and the reference group of 0.08 units (based on preliminary observations in the unit).

Statistical analysis: This was done with STATA ver 16.0. Student *t* test or Mann Whitney *U* test were used for comparison of means and medians, respectively.

RESULTS

A total of 33 *X*-rays were studied in BRSN group, and 32 in the RSN group. Relevant clinical characteristics of included neonates in each group are given in **Table I**.

Table I Baseline Characteristics of BRSN and ARSN

Characteristic	*BRSN (n=33)*	*ARSN (n=32)*
Birth weight (g)[a]	1660 (1000,2250)	1470 (970,2300)
Gestational age (wk)[a]	30 (30,34)	29 (29,34)
Preterm neonate	24 (72.8)	27 (84.4)
Very low birthweight neonates	16 (48.4)	19 (59.4)
Indications for *X*-ray		
Respiratory distress evaluation	7 (20)	8 (24)
Deterioration on respiratory support	13 (40)	15 (46)
Tubes/lines positions	6 (20)	5 (15)
Abdominal concerns	7 (20)	4 (15)

Values in no. (%) or [a]median (IQR). BRSN: neonates before implementation of radiation safety policy in neonates; ARSN: neonates after implementation of radiation safety policy in neonates.

Median (IQR) calculated ESD was significantly lesser after the RSN was implemented (BRSN: 0.1 (0.065,0.2) vs and ARSN: 0.014 (0.01, 0.016) μGy/ m^2; *P*<0.001) (**Table II**). All *X*-rays were deemed interpretable with respect to clinical information expected from the test. This was augmented by the presence of the clinical team during acquisition itself; followed by post-shoot modifications made to enhance picture quality for specific details when necessary. These enhancement techniques were needed in select situations in ARSN (*n*=9, 28.1%), more so when there was severe subcutaneous edema or severe atelectasis with white-out lungs to ensure catheter/tube positions (where more exposure might otherwise have been required). Proportion of *X*-rays that led to clinical action after *X*-rays were not significantly different between the two groups [OR (95% CI); 1.9 (0.67-5.97); *P*=0.17].

DISCUSSION

The results of this study indicate that ESD can be reduced significantly after implementing clinician-directed changes for each *X*-ray. Over several incremental changes, with due diligence to interpretability, the FFD could be increased, mAs and kVP reduced to limits that are better than previously described in literature. *X*-rays were visualized immediately after, with active involvement of the clinical team in post-shoot picture enhancement techniques. The awareness of the clinician about their ability to direct these changes made a difference to compliance to other components of RSN (like gonadal shield application and collimation).

Quality initiatives have been shown to decrease the median number of *X*-rays from 8 to 2 [1]. This is one

Table II Entrance Skin Doses and Technical Specifications Before (BRSN) and After (ARSN) Implementation of Radiation Safety Policy in Neonates

Parameter	*BRSN (n=33)*	*ARSN (n=32)*	*P value*
ESD (μGy)			
Formula calculated	0.1 (0.065,0.2)	0.014 (0.01,0.016)	<0.001
Machine-quantified	0.43 (0.27,0.6)	0.1 (0.07,0.14)	<0.001
kVp[a]	41.61 (2.57)	40.16 (0.37)	0.002
mAs	2.4 (1.8,2.5)	0.5 (0.5,0.5)	<0.001
FFD (cm)[a]	83.91 (8.59)	98.44 (4.04)	<0.001
Gonadal shield placed[b]	0	23 (71.8)	-
Clinical action taken post *X*-ray within 1 h[b,c]	13 (39.4)	18 (56.2)	0.17

All values in median (IQR), [a]mean (SD) or [b]no. (%). RSN: radiation safety protocol in neonates; BRSN: before RSN; ARSN: after RSN; FFD: film focus distance, ESD: entrance skin dose; mAs: milliampere -second; kvP: kilovolt peak. [c]OR=1.9 (0.67-5.97).

approach to cut down exposures, but a bundled approach towards reduction of any possible parameter related to ALARA would be optimal. It has been shown that ESD was primarily affected by FFD [3]. A retrospective study by non-dosimetric calculation of radiation exposure revealed that median cumulative ESD of preterm infants born at less than 750 g was 4.83 µGy [9]. The authors used FFD at 80-100 cm but higher kVp and mAs than in our RSN. Lau, et al. [7] conducted a retrospective analysis of radiation exposure in preterm neonates using estimation of effective dose using the Monte Carlo simulation software. The authors observed 140 µGy for chest *X*-rays with 50 kVp and 3.2 mAs, 67 cm skin distance [7]. Another method of direct measurement is thermolucent dosimeter, which is costly and not available in most settings. Puch, et al. [10] estimated ESD experimentally by DIADOSE dose meter, wherein the values varied between 11.8 and 15.0 µGy [10].

The RSN was designed pragmatically, considering all parameters and actions that can be altered by the clinician to reduce radiation exposure in neonates. Both cohorts are systematic and prospective observations. However, we must admit that these changes are practicable only if the digital radiography machine, where these changes can be made, are available. We wish to highlight the importance of these technical advancements in NICUs which care for neonates who require multiple *X*-rays.

Significant reduction in ESD was possible after implementation of clinician-directed radiation safety protocol/policy in neonatal intensive care. The neonatologist can take active part in deciding lowest possible exposure settings on the machine, and other measures without affecting quality of the picture. Cognizance of the clinician about radiation safety of the neonate and possible ALARA techniques could result in tangible important benefits in this regard.

Ethics clearance: Human ethics committee No.KIMS/IHEC/APPROVAL/12/2022/05 dated August 8, 2022.

Contributors: FP conceived the study; FP and KNS designed the protocol; KNS collected data (principal investigator); FP and KNS conducted statistical analysis. All authors critically analyzed and approved the protocol, were involved in bedside implementation and approved the final manuscript.

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RESEARCH PAPER

Pediatric Cancer Burden in Different Regions of India: Analysis of Published Data From 33 Population-Based Cancer Registries

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Objective: To provide the regional pediatric cancer (age-group 0-14 years) burden and pattern in India utilizing published data of population-based cancer registries established under the National Cancer Registry Programme and Tata Memorial Centre, Mumbai. **Methods:**Based on the geographic locations, the population-based cancer registries were categorized into six regions. The age-specific incidence rate was calculated using the number of pediatric cancer cases and population in the respective age-group. Age-standardized incidence rate per million and 95% CI were calculated.**Results:** In India, 2% of all cases were pediatric cancer. The age-standardized incidence rate (95% CI) for boys and girls is 95.1 (94.3-95.9) and 65.5 (64.8-66.2) per million population, respectively. Registries from northern India reported the highest rate; while the lowest rate was in northeastern India. **Conclusion:**There is a need to establish pediatric cancer registries in different regions of India to know the accurate pediatric cancer burden.

Keywords: *Incidence, Leukemia, Lymphoma, Surveillance.*

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Pediatric cancer, defined here as cancer among children aged 0-14 years, contributes to approximately 1% of the new cancer cases globally [1]. Although, pediatric cancer only represents a small proportion of all cancers, it is a major cause of death in children across the globe [2], and requires evidence-based public health interventions. Furthermore, almost half of the total 2,06,362 globally registered pediatric cancer cases are from low-income and low- and middle-income countries (LMICs) [1]. High-quality population-based cancer registry (PBCR) data, one of the crucial elements for accurate estimation of childhood cancer burden, are required in LMICs like India for better policymaking and planning decisions [3].

With regards to the Indian PBCRs, which cover less than 15% of urban and 1% of rural population [4], data is scarce on the pediatric cancer burden and patterns, especially from different regions of India. This study summa-rises regionwise incidence of pediatric cancer in India based on the published data of the registries of that region. The study utilized the published data of PBCRs of the National Cancer Registry Programme (NCRP) (period 2012-2016) [5] along with the PBCRs established by Tata Memorial Centre (TMC), Mumbai [6,7] for estimating the burden of pediatric cancer.

METHODS

Based on the geographic position, the PBCRs we recategorized into six regions including central, eastern, northern, northeastern, southern, and western India. Three registries including Bhopal, Nagpur, and Wardha are located in the central area, while in the eastern region,there is only one registry (Kolkata). In northern region seven registries (Chandigarh, Delhi, Mansa, Patiala, Sangrur, SAS Nagar, and Varanasi), northeastern region eleven registries (Ca-char, Dibrugarh, Kamrup urban, Manipur state, Megha-laya, Mizoram state, Nagaland, Pasighat, Sikkim state, Tri-pura state, and West Arunachal), southern region five registries (Bangalore, Chennai, Hyderabad, Kollam, and Thiruvananthapuram) and western region six registries (Ahmedabad urban, Aurangabad, Barshi rural, Mumbai, Osmana-

Invited Commentary: Pages 523-24.

bad-Beed, and Pune) are present. The data reported by NCRP registries are for the year 2012-2016, except Bho-pal, Kolkata, Mumbai, Osmanabad- Beed (2012-2015), Delhi, Bangalore (2012-2014) and Hyderabad registry (2014-2016). The TMC, Mumbai registries include data from Chandigarh and Punjab registries for period 2013-2016, and Varanasi, Uttar Pradesh state for year 2017.

Statistical analysis: To merge region-wise data of pediatric cancer (age-group 0-14 years), cancer cases for each PBCR for each 5-year age-group were taken as a numerator and population of geographic area from each PBCR was taken as the denominator. The age-specific incidence rate was calculated using the number of pediatric cancer cases and population in the respective age-group. Age-standardized incidence rate (ASIR) per million and 95% CI were calculated using world standard population [8].

RESULTS

In India, as per the published data of the registries, a total of 4,30,091 cancer cases (male: 2,15,726, 50.2%; female: 2,14,365,49.8%) were reported. The ASIR for males was 105.5 and for females, it was 104.5 per 100,000 population. Of the total cancer cases, 8,692 (2%) were pediatric cancer (Boys: 5,365 (61.7%); Girls: 3,327 (38.3%)). The ASIR of pediatric cancer is 95.1 (95% CI 94.3-95.9) for boys and 65.5 (95% CI 64.8-66.2) for girls per million population. With regards to the regionwise registry locations, registries from northern India shows the highest cancer incidence rate in boys and girls (156.0 and 97.1 per million) followed by southern India (122.0 and 92.4 per million), while registries from northeastern India showed the lowest incidence rate (47.3 and 33.6 per million). The region-wise Indian pediatric cancer incidence rates, depending on the registry location, are presented as ASIR in **Fig. 1**.

Lymphoid leukemia was the predominant site among boys and girls in all the regions of India. The lymphoid leukemia incidence rate in boys ranged from 10.3 to 50.1 and in girls from 5.9 to 28.7 per million population. Moreover, for both boys and girls, brain and nervous system cancers are among the top three leading cancers in most of the regions of India, with incidence ranges from 4.6 to 16.7 and from 3.0 to 13.7 per million population, respectively. Similarly, myeloid leukemia, with incidence rates ranging from 4.3 to 10.9 in boys and 4.0 to 8.1 in girls per million population, was found to be commonly prevalent cancer both in boys and girls.

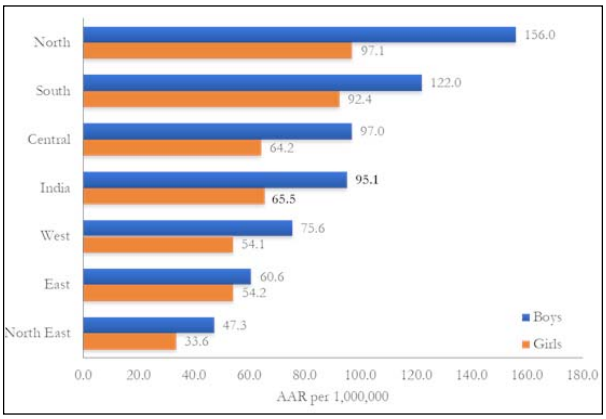


Fig.1 Pediatric cancer burden as per registries from respective regions from India (2012-2016).

The results show that among boys, Hodgkin lymphoma is the third leading cancer in central and eastern region, whereas non-Hodgkin lymphoma is the third leading cancer in northern and western regions of India. It was observed that Hodgkin lymphoma is not among the top ten leading cancer in girls. Among girls, the non-Hodgkin lymphoma ranked seventh with incidence rate ranges from the lowest in northeast region to highest in northern region (1.3 and 5.2 per million population, respectively).

Additionally, malignancies of bone, eye (retinoblastoma) and kidney were the leading cancers both in boys and girls in India; with comparatively higher incidence rate among boys 5.1, 4.7 and 4.5 per million population, respectively. The connective and soft tissue cancers were the ninth leading cancers among boys, with incidence ranging from 1.8-6.8 per million population; whereas, it ranked eighth among girls, incidence ranging from 1.7-4.6 per million population. Leukemia unspecified was the tenth leading cancer in boys, incidence ranging from 1.3-4.9 per million population, while it was the ninth leading cancer in girls, incidence ranging from nil to 3.4 per million population. Furthermore, among girls, ovarian cancer was the tenth leading cancer site with an incidence ranging from 0.8 to 4.1 per million population. The region-wise pediatric cancer burden and the top ten leading cancer sites are presented in **Table I** and **Fig. 2**.

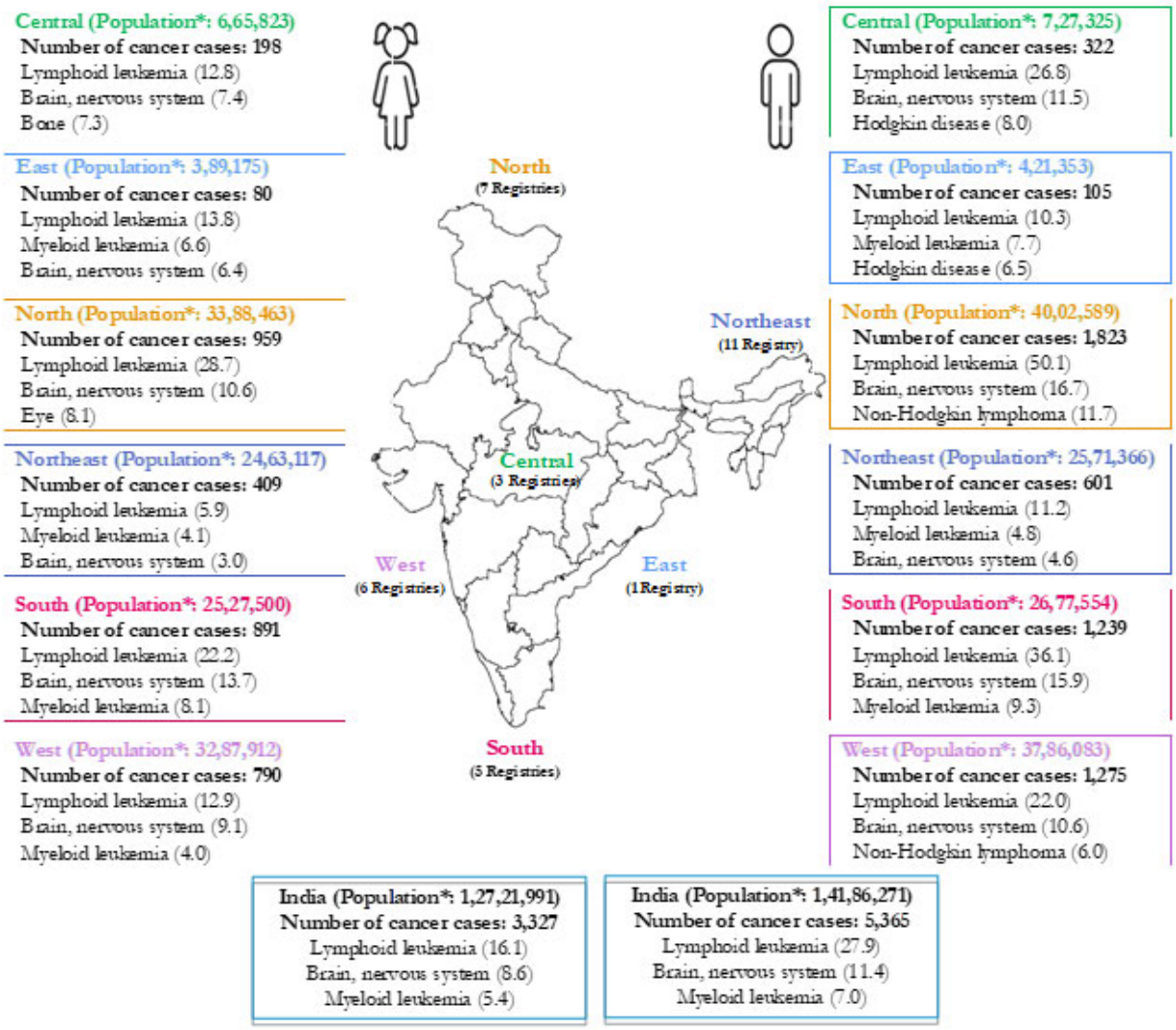
DISCUSSION

We have summarized the pediatric cancer burden in India on the basis of published data on pediatric cancer incidence from33 PBCRs. We observed differences in pediatric cancer incidence region-wise as well as gender-wise. The northern region registries have reported the highest pediatric cancer incidence rate, while the lowest rates are reported by northeastern region registries. Moreover, national and regional data show that boys have a higher pediatric cancer burden than girls. However, it is important to interpret these data cautiously as the regional differences could be due to differences in access to diagnostic and treatment facilities as well as number of PBCRs present in a particular region, the population covered by PBCRs, and cancer registration compliance. It has also been reported that pediatric cancer incidence is lower among girls compared to boys; however, this area requires further research.

Table I Age-Standardized Incidence Rate (per million) for Pediatric Cancer in Different Regions of India; 2012-2016

ICD-10	*Site*	*India*	*Central*	*Eastern*	*Northern*	*Northeastern*	*Southern*	*Western*
Boys								
–	All sites	95.1 (94.3-95.9)	97.0 (93.6-100.4)	60.6 (56.8-64.4)	156.0 (153.7-158.3)	47.3 (46.1-48.5)	122.0 (119.8-124.2)	75.6 (74.3-76.9)
C91	Lymphoid leukemia	27.9 (27.5-28.3)	26.8 (25.0-28.6)	10.3 (8.7-11.9)	50.1 (48.8-51.4)	11.2 (10.6-11.8)	36.1 (34.9-37.3)	22.0 (21.3-22.7)
C70-72	Brain and nervous system	11.4 (11.1-11.7)	11.5 (10.3-12.7)	5.3 (4.2-6.4)	16.7 (16.0-17.4)	4.6 (4.2-5.0)	15.9 (15.1-16.7)	10.6 (10.1-11.1)
C92-94	Myeloid leukemia	7.0 (6.8-7.2)	7.4 (6.5-8.3)	7.7 (6.3-9.1)	10.9 (10.3-11.5)	4.8 (4.4-5.2)	9.3 (8.7-9.9)	4.3 (4.0-4.6)
C82-85, C96	Non-Hodgkin lymphoma	6.7 (6.5-6.9)	5.4 (4.6-6.2)	5.5 (4.4-6.6)	11.7 (11.1-12.3)	2.4 (2.1-2.7)	8.4 (7.8-9.0)	6.0 (5.6-6.4)
C81	Hodgkin lymphoma	5.7 (5.5-5.9)	8.0 (7.1-8.9)	6.5 (5.3-7.7)	10.7 (10.1-11.3)	1.4 (1.2-1.6)	6.8 (6.3-7.3)	4.3 (4.0-4.6)
C40-41	Bone	5.1 (4.9-5.3)	5.6 (4.8-6.4)	4.6 (3.6-5.6)	8.9 (8.4-9.4)	2.8 (2.5-3.1)	6.3 (5.8-6.8)	3.4 (3.1-3.7)
C69	Eye	4.7 (4.5-4.9)	3.2 (2.5-3.9)	3.4 (2.4-4.4)	10.7 (10.1-11.3)	2.8 (2.5-3.1)	5.8 (5.3-6.3)	1.9 (1.7-2.1)
C64	Kidney	4.5 (4.3-4.7)	6.8 (5.8-7.8)	2.0 (1.3-2.7)	7.5 (7.0-8.0)	2.7 (2.4-3.0)	4.9 (4.5-5.3)	3.5 (3.2-3.8)
C47+C49	Connective and soft tissue	3.8 (3.6-4.0)	3.1 (2.5- 3.7)	3.6 (2.7-4.5)	6.8 (6.3-7.3)	1.8 (1.6-2.0)	5.3 (4.8-5.8)	2.3 (2.1-2.5)
C95	Leukemia unspecified	3.7 (3.5-3.9)	4.7 (4.0-5.4)	1.3 (0.8-1.8)	4.9 (4.5-5.3)	1.5 (1.3-1.7)	3.2 (2.8-3.6)	4.9 (4.6-5.2)
Girls								
–	All sites	65.5 (64.8-66.2)	64.2 (61.3-67.1)	54.2 (50.3-58.1)	97.1 (95.1-99.1)	33.6 (32.6-34.6)	92.4 (90.5-94.3)	54.1 (52.9-55.3)
C91	Lymphoid leukemia	16.1 (15.7-16.5)	12.8 (11.5-14.1)	13.8 (11.8-15.8)	28.7 (27.6-29.8)	5.9 (5.5-6.3)	22.2 (21.2-23.2)	12.9 (12.3-13.5)
C70-72	Brain and nervous system	8.6 (8.3-8.9)	7.4 (6.4-8.4)	6.4 (5.2-7.6)	10.6 (10.0-11.2)	3.0 (2.7-3.3)	13.7 (13.0-14.4)	9.1 (8.6-9.6)
C92-94	Myeloid leukemia	5.4 (5.2-5.6)	5.9 (5.1-6.7)	6.6 (5.3-7.9)	6.1 (5.6-6.6)	4.1 (3.7-4.5)	8.1 (7.5-8.7)	4.0 (3.7-4.3)
C40-41	Bone	4.8 (4.6-5.0)	7.3 (6.4- 8.2)	3.2 (2.4- 4.0)	8.0 (7.5- 8.5)	2.9 (2.6-3.2)	6.1 (5.6-6.6)	2.9 (2.6-3.2)
C69	Eye	3.9 (3.7-4.1)	1.1 (0.7-1.5)	4.4 (3.2-5.6)	8.1 (7.5-8.7)	2.6 (2.3-2.9)	4.4 (4.0-4.8)	2.2 (1.9-2.5)
C64	Kidney	3.5 (3.3-3.7)	4.1 (3.3-4.9)	0.6 (0.2-1.0)	5.7 (5.2- 6.2)	2.1 (1.8-2.4)	4.5 (4.1-4.9)	2.5 (2.2-2.8)
C82-85, C96	Non-Hodgkin lymphoma	3.3 (3.1-3.5)	3.7 (3.0-4.4)	2.1 (1.5-2.7)	5.2 (4.7-5.7)	1.3 (1.1-1.5)	4.1 (3.7-4.5)	3.3 (3.0-3.6)
C47+C49	Connective and soft tissue	3.1 (2.9-3.3)	3.8 (3.1-4.5)	3.1 (2.1-4.1)	4.5 (4.1-4.9)	1.7 (1.5-1.9)	4.6 (4.2-5.0)	2.3 (2.0-2.6)
C95	Leukemia unspecified	2.3 (2.2-2.4)	3.4 (2.7-4.1)	0.0 (0.0-0.0)	2.3 (2.0-2.6)	1.2 (1.0-1.4)	2.2 (1.9-2.5)	3.3 (3.0-3.6)
C56	Ovary	2.2 (2.1-2.3)	3.2 (2.6-3.8)	3.8 (2.8-4.8)	4.1 (3.7-4.5)	0.8 (0.6-1.0)	3.0 (2.7-3.3)	1.0 (0.8-1.2)

Note: The figure in parenthesis indicates a 95% confidence interval (95% CI).



**Population of respective region registries for the 0-14 age group.*

Fig. 2 Leading cancer sites in boys and girls as per registries from respective regions in India (2012-2016).

The incidence and mortality of childhood cancer are both inversely correlated with the level of economic development; higher incidence is observed in high-income countries but higher mortality in LMICs. It is evident that in high-income countries, due to easy access to advanced treatment and supportive care, most of the pediatric cancer cases are treated successfully with more than 80% of survival; while in LMICs, the survival rates drop down to 15%-45% as a result of limited accessibility and unaffordable childhood cancer services [9]. The World Health Organization (WHO), along with other collaborators, has launched the Global Initiative for Childhood Cancer (GICC) with the aim of improving outcomes for children with cancer around the world by addressing the gap of non-availability and unaffordable cancer care services in LMICs, and has set the target of achieving at least 60% survival for children with cancer globally [10]. To achieve the target set by GICC-WHO, it is required to utilize accurate population-based estimation of the childhood cancer burden for policy-making and planning and monitoring cancer care services at national and regional levels. In India, considering the vastness of the country, the number of PBCRs are less. Based on the NCRP and TMC registry reports, the PBCRs covers only 13% of the total population [5-7]. Aside from the difficulty of ensuring adequate data collection, PBCRs in India confront a number of challenges, including a lack of cancer awareness among parents, a lack of advanced diagnostic facilities, and non-affordable cancer care, which results in low pediatric cancer case registration [11].

The estimated global and country-specific childhood cancer incidence are not adjusted for under-diagnosis. Under-diagnosis may be due to low coverage, poor access to primary care, lack of awareness, and inadequate or delayed diagnosis [12]. It has been estimated that one-in-two pediatric cancer cases is not diagnosed and treated [13]. As a result, even when registries do exist, the burden of childhood cancer is difficult to measure due to limited access to comprehensive diagnosis, and misinterpretation and under-diagnosis. In India, there is under-reporting/ under-diagnosis of pediatric cancer and the estimated pediatric cancer cases may be almost double [14]. Additionally, one of the reasons for higher proportion of childhood cancer in LMICs compared to the high-income countries is higher population of age-group <15 years in LMICs compared to the developed world. Nonetheless, demographic factors that affect cancer burden are expected to have only a minimal effect on childhood cancer; whereas, industrialization growth may result in greater exposure to risk factors and, as a result, a larger-than-expected increase in childhood cancers [15].

The limitation of our study is that the data on pediatric malignancies are more commonly classified by morphology, while the incidence reported by PBCRs is on a site-based classification. Moreover, the previously reported gender disparities in childhood cancer registration persist in developing nations. Hence, differences in the incidence of childhood cancer should be interpreted cautiously as they may not necessarily reflect only differences in the underlying occurrence of disease. We recommend that pediatric cancer registries should be established for better interpretation of the pediatric cancer burden.

To conclude, region-wise pediatric cancer incidence is variable across India. There is a requirement for high quality data generated through PBCRs. We suggest that pediatric cancer registries be established widely to know the burden of the disease for better policy-making and strategic interventions.

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RESEARCH PAPER

Diagnostic Accuracy of Rapid Antibody Detection Test for Scrub Typhus

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Objectives: To detect the diagnostic accuracy of rapid antibody detection test using IgM immunochromatography for scrub typhus in children. **Methods:** This cross-sectional study enrolled children aged 2 months-18 years hospitalized over a period of 18 months with undifferentiated fever of duration five days or more. The blood samples were subjected to serological tests like Weil-Felix, Scrub IgM ELISA, immunofluroscence assay (IFA) and rapid diagnostic test (IgM Immunochromatography). Diagnostic accuracy was measured against IFA as the gold standard. **Results:** A total of 90 children were included in the study, among which 43 children were positive for gold standard test IFA. Rapid diagnostic test showed sensitivity of 88.3%, specificity of 89.3%, positive predictive value of 88.3% and negative predictive value of 89.3%. The sensitivity, specificity, PPV and NPV of Weil-Felix test was 39.5%, 84.2%, 58.6 and 71.1%, respectively and of IgM ELISA was 93%, 89.3%,88.8% and 93.3%, respectively. **Conclusion:** IgM immunochromatography had good diagnostic accuracy for scrub typhus in children with acute undifferentiated fever.

Keywords: *Immunofluorescence, Rapid diagnostic test, Scrub typhus*.

Scrub typhus is the most common zoonotic disease seen in the tropics of rural Asia, which may be life-threatening [1,2]. The diagnosis of scrub typhus remains difficult with non-specific clinical presentation, low index of suspicion and indeterminate accuracy of available diagnostic test. Immunofluorescence assay (IFA) is the gold standard serological test for the detection of *O. tsutsugamushi* antibodies. The major hindrance to the use of this technique is the non-availability of fluorescent microscopes, and need of expertise in performance and interpretation of the test in endemic areas [3]. An inexpensive, easily available test used routinely is Weil-Felix test that does not require expertise but has low sensitivity and specificity. Scrub IgM ELISA has better diagnostic accuracy, but is costly and is impractical as a point-of-care test in rural areas. With the due consideration of the cost, simpli-city, rapidity and single-test result for diagnosis, immuno-chromatographic test can be used as a point-of care test [4].

The objective of the study was to evaluate the diagnostic accuracy of immunochromatography IgM test for scrub typhus in children (2 months-18 years) presenting with undifferentiated fever of 5 days or more in a tertiary health centre.

METHODS

This cross-sectional study was carried out over a period of 18 months in a tertiary care hospital. Children from 2 months to 18 years with acute undifferentiated febrile illness of 5 days or more with or without eschar, with other presenting features fulfilling the DHR-ICMR case definition [5] were included in the study. Fever with other known etiology at the time of hospitalization and children who were treated on outpatient basis with oral antibiotic (Doxycycline) were excluded from the study. An approval for conducting the study was taken from the institutional ethics committee. Written informed consent was taken from the parents/guardian of the children.

Relevant investigations such as complete hemogram, C-reactive protein, renal and liver function tests, serology for dengue fever, enteric fever, blood and urine culture were done. The epidemiological, clinical and laboratory parameters were recorded on a predesigned proforma. Other investigations like chest *X*-ray, ultrasonography, 2D-echocardiography, cerebrospinal fluid analysis, blood gas analysis and neuroimaging were considered on case-to-case basis.

The blood samples were subjected to serological tests for scrub typhus like Weil-Felix, Scrub IgM ELISA, immunofluroscence assay (IFA) as gold standard, and IgM rapid diagnostic test based (RDT) on Immunochromatography.

IgM immunochromatography test was performed according to the technical brochure provided in the kit (InBios Scrub Typhus Detect IgM Rapid Test). Five microlitre of serum sample was added to the strip, followed by addition of three drops of chase buffer solution provided

with the test into the test tube. Results were read within 15 minutes. A single red line appeared on the control area in normal and a second red line appeared on the test area if the patient had scrub typhus antibody.

The sample size was calculated based on the sensitivity and specificity of ICT and prevalence of scrub typhus reported in the literature [6], using Buderer formula [7]. The reported prevalence of scrub typhus in children of fever more than 5 days with no other etiological diagnosis made with routine diagnostic investigation was 36.4%. With sensitivity of 91%, specificity of 95%, prevalence of 35%, precision of 10% and confidence level of 95%, sample size required was 90.

Statistical Analysis: Data were entered in Microsoft Excel. SPSS version 21 statistical software was used for analysis. Distribution of data was analyzed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated considering IFA as the gold standard. Diagnostic accuracy was calculated as [sensitivity x prevalence + specificity x (1-prevalence)] [8].

RESULTS

During the study period, a total of 90 children with undifferentiated fever were enrolled. Out of these, 43 children tested as positive for scrub typhus IgM IFA. The baseline demographic, clinical and laboratory variables are shown in **Table I**.

The tests of diagnostic accuracy for IgM immunochromatography, Weil-Felix test and scrub IgM ELISA are shown in the **Table II** against IFA as gold standard.

DISCUSSION

The present study showed a comparable diagnostic accuracy of RDT using immunochromatography to IgM ELISA, using IFA as gold standard for scrub typhus in children with undifferentiated fever.

Eschar, considered as pathognomonic of scrub typhus, was present in only one-third of children who were positive on IFA and RDT. The presence of eschar in combination with a positive RDT result has a good positive predictive value [9].

An indirect IFA is a gold standard for scrub typhus with a sensitivity and specificity of 100% and 93.5%, respectively [10]. However, its use is limited by requirement of expensive equipment, a fluorescence microscope, slides with all prevalent serotype specimens time, logistics and expertise [9]. Weil-Felix test is the simplest and easily available test routinely used for the detection of scrub typhus infection. The sensitivity and specificity of Weil-Felix test (compared with IFA test) in this study was similar to earlier studies [11]. The diagnostic performance of IgM ELISA for scrub typhus

TABLE I Baseline Demographic, Clinical and Laboratory Variables of Children With Undifferentiated Fever (*N*=90)

Variables	*No. (%)*
Male	64 (71.1)
Age groups	
2 to 12 mo	3 (3.3)
>12 mo to 5 y	28 (31.1)
>5 to 10 y	28 (31.1)
>10 to 18 y	31 (34.5)
Animal contact	66 (73.3)
Headache	47 (52.2)
Myalgia	37 (41.1)
Arthralgia	18 (20.0)
Generalized lymphadenopathy	72 (80.0)
Rashes	48 (53.3)
Eschar	14 (15.5)
Edema	29 (32.2)
Bleeding manifestations[a]	10 (11.1)
Hepatomegaly	84 (93.3)
Splenomegaly	56 (62.2)
Convulsions and/or altered sensorium	11 (12.2)
Leukocytopenia[b]	29 (32.2)
Thrombocytopenia[c]	47 (52.2)
Deranged LFT[a,d]	34 (37.8)
Deranged coagulation profile[e]	14 (15.5)
Hyponatremia	44 (48.9)

[a]petechiae/purpura/ecchymoses; [b]total leukocyte count <0.4×10^9/L; [c]platelet count <1.5×10^9/L; [d]liver enzymes >1.5 times of normal; [e]PT INR/APTT ratio >1.5 times the normal.

TABLE II Diagnostic Accuracy of Serological Tests for Scrub Typhus in the Study (*N*=90)

Test	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Diagnostic accuracy*
Weil-Felix	39.5 (24.9-55.6)	84.2 (74.04-91.6)	58.6 (42.8-72.8)	71.1 (65.5-76.1)	68.1 (58.9-76.3)
IgM ELISA	93 (80.9-98.5)	89.3 (76.9-96.4)	88.8 (77.7-94.8)	93.3 (82.4-97.7)	91.1 (83.3-96.1)
RDT-ICT	88.3(74.9-96.1)	89.3 (76.9-96.4)	88.3 (76.7-94.6)	89.3 (78.5-95)	88.8 80.5-94.5)

Data presented as % (95% CI). NPV: negative predictive value; PPV: positive predictive value; ICT: immunochromatography; RDT: rapid diagnostic test; Comparison with immunofluorescence assay (gold standard).

WHAT THIS STUDY ADDS?

- Rapid diagnostic test (IgM immunochromatography) as a point-of-care test had good sensitivity and specificity in diagnosing scrub typhus in children with acute undifferentiated fever.

was also in concordance with other studies [12,13]. The point-of-care testing using In bios RDT with IgM immunochromatography showed sensitivity and specificity comparable with other studies [4,14], though lower than another study [15]..

Immunochromatography was performed only for IgM antibodies in this study; IgG and total antibodies were not done as they are not useful in endemic areas and may decrease the specificity with only marginal increase in sensitivity [4,9].

The limitation of the study was that the molecular diagnosis was not performed by polymerase chain reaction in this study as a gold standard.

Our study concludes that IgM immunochromatography RDT has a good sensitivity and specificity in diagnosing scrub typhus in resource poor setting where IFA is not freely available and its cost is high.

Ethical clearance: EIC, JSS Medical College, JSSAHER; No JSS/MC/PG/5189/2019-20 dated Nov 14, 2019.
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RESEARCH PAPER

Advertising of Pre-Packaged Foods in India: A Qualitative Analysis

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Objective: We examined the 'nutrients of concern' in pre-packaged food products that are commonly advertised, as per WHO standards and Nova Classification. **Methods:** This was a qualitative study, using a convenience sampling method, to identify advertisements of pre-packaged food products. We also analyzed their content from information on the packets, and their compliance with applicable Indian laws. **Results:** We found that all the advertisements of the food products in this study did not provide important information about the amount of nutrients of concern i.e., total fat, sodium, and total sugars. These advertisements mostly targeted children, made health claims, and used endorsements of celebrities. All the food products were also found to be ultra-processed in nature and high in one or more nutrients of concern. **Conclusion:** Most of the advertisements are misleading, needing effective monitoring. Health warnings on the front-of- pack label and restrictions on marketing of such food products may go a long way in reducing non-communicable diseases.

Keywords: *Front-of-pack labelling, Junk foods, Marketing, Non-communicable diseases*.

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Marketing and misleading advertisement of unhealthy food products like ultra-processed foods and foods/beverages high in for total fat, sodium and total sugars contributes to poor dietary behaviors in children and diet related non-communicable diseases like obesity, diabetes, and hypertension later in life [1]. Obesity is increasing rapidly in India in children under 5 years, adult men and women, with the consequences of rising burden of non-communicable diseases (NCDs) and deaths in adulthood [2,3]. The World Health Organization has identified food marketing, including advertising for unhealthy items, as detrimental to health and has called upon the governments to improve children's food environment by implementing restrictions on the marketing of 'unhealthy' foods to children [4]. The WHO provides thresholds for nutrients of concern for total fat, sodium and total sugars in food products such as bakery, confectionery, sodas, chocolates and desserts. If the nutrient exceeds a specified limit per 100 g/mL, prohibition of marketing is recommended to curb the consumption [5].

Many advertised food products are seen to be ultra-processed food products (UPFs) defined as industrial formulations of foods made by changing the food matrix, adding chemical additives and substances that are not used in domestic kitchens (like emulsifiers and stabilizers), or food products high in fat, sugar, and salt (HFSS) as defined by Nova Classification [6]. These food products are associated with poor health outcomes independent of nutrient content, mostly through pathways of over-consumption [6-10]. These food products are aggressively marketed by the food corporations as they are ready to consume, affordable and hyperpalatable [11]. Several studies have reported that children exposed to the marketing of such products had a higher risk of selecting the advertised foods or beverages [12]. With continued aggressive marketing, India is also witnessing a rapid increase in the consumption of such foods and beverages [13].

Invited Commentary: Pages 521-22.

In India, the Food Safety and Standards Act (FSS Act) (2006) Section 24(1), provides that "*No advertisement shall be made of any food, which is misleading or deceiving or contravenes the provisions of this Act, the rules and regulations made thereunder*" [14]. The Consumer Protection Act - 2019 (CPA) section 2 (28) defines "misleading advertisement" in relation to any product or service, to mean an advertisement, which – "*i) falsely describes such product or service; or ii) gives a false guarantee to, or is likely to mislead the consumers as to the nature, substance, quantity or quality of such product or service; or iii) conveys an express or implied representation which, if made by the manufacturer or seller or service provider thereof, would constitute an unfair trade practice; or iv) deliberately conceals important information*" [15].

In this context, the current study was conducted to examine the nutrients of concerns as per WHO standards and Nova Classification [6]; and compliance of advertisement content of identified pre-packaged food products with Indian law, respectively.

METHODS

A qualitative study was conducted from 1 February to 31 August, 2022, wherein a total of 48 pre-packaged food products were identified from advertisements aired/printed/ featured on television, YouTube, Instagram, Facebook and select newspapers (viz., *The Times of India*, *Hindustan Times*, *The Hindu*, *Navbharat Times*, *Punjab Kesari* and *Dainik Jagran*) through convenience sampling technique.

For the content analysis of the nutrients of concerns in the advertised products, all 48 products were bought from a supermarket. The content analysis of both the nutritional information available on the labels of the products and their advertisements were undertaken manually by two of the authors. The reference for label analysis of the original samples of all 48 products was based on WHO thresholds for total fat, sodium, and total sugars as per 100 g/mL of foods or beverages. Nova Classification was used to define if these products were ultra-processed or not. According to the Nova Classification of foods [6], ultra-processed foods are defined as a group of foods according to the extent and purpose of industrial processing; including the fractionation of whole foods into substances, chemical modifications of these substances, and frequent use of cosmetic additives in these, such as flavors, flavor enhancers, colors, emulsifiers, emulsifying salts, sweeteners, thickeners, and antifoaming, bulking, carbonating, foaming, gelling and glazing agents.

References for content analysis of the advertisements were provisions of the Consumer Protection Act 2019 for misleading advertisements. Specifically, we used Section 2(28) (iv) deliberate concealment of important information, considering the most important information in a pre-packaged food product is its nutrient content or its status of processing. In addition, we also analyzed other tactics used by the food industry such as endorsement by a celebrity, targeting children and use of health claims. To keep the brand identity confidential, the products were coded as P1-P48.

RESULTS

Based on WHO-SEARO Nutrient Profile Model, all the 48 pre-packaged food products were categorized as confectionery (n=5), fine bakery (n=14), beverages (n=11, juices/milk and dairy based drinks/water based flavored drinks), ready to eat savories (n=7), pasta and noodles like products (n=3), fats and oils (n=1), bread and ordinary bakery wares (n=1), cereals (n=3), sauces/dips and dressings (n=3) **(Web Table I).**

All the advertisements of pre-packaged food products in this study did not provide the most important information about the food product i.e., amount of nutrient of concern. In addition, other tactics used to advertise the pre-packaged food products are also provided in **Table I**.

The list of ingredients and additives were analyzed in these products and all the 48 were found to be UPFs as per Nova Classification [11]. Various additives used in these included emulsifiers, preservatives, thickening agents, anti-caking agents, inverted sugar syrup, raising agent, refined palm oil, natural identical flavoring substances, stabilizers, acidity regulators, artificial flavor and colors, sweeteners, polydextrose and maltodextrin.

Based on the WHO-SEARO Nutrient Profile Model [5], all the 48 products exceeded the cutoff limits of at least one nutrient of concern. It was found that total sugars were high in 34 (70.8 %) products, total fat was high in 32 (66.7%) products and sodium was high in 22 products. Adi-tionally, seven products (14.6%) exceeded the thresholds of all the three nutrients of concern.

DISCUSSION

The objective of the Food Safety and Standards Act, 2006 and the Consumer Protection Act (CPA), 2019, is that there shall be no 'misleading' food advertisement [14,15]. The CPA, 2019 calls the advertisement to be misleading if it does not provide important information. In the present study all the advertisements, did not provide the most important information in a food product i.e., if it is high in total fat, sodium or total sugars (HFSS) or if it is ultra-processed. Other similar reports of aggressive and misleading advertisements of unhealthy food products have been reported from India and other countries [16-20]. A comprehensive content analysis of food advertisements in 2021 revealed aggressive targeting of children through television; 88.6% of the food advertised was unhealthy being high for total fat, sodium, and total sugars (HFSS) and 49% of the advertisements used child actors [16]. In another study, majority of advertisements of confectionary, ice creams, baked products and ready to cook food products were projected to lead to happiness, and displayed adult approval, confirming our findings [21].

Despite well-intended regulations, misleading advertisements of pre-packaged food products continue unabated by the food industry that is able to exploit the lack of specificity in the existing regulations, which defines the misleading advertisement subjectively. Aggressive television marketing of food encourages children to make a choice of unhealthy foods leading to poor dietary habits. Concerns regarding implementation of consumer protection regulations in India have been expressed earlier as well [22].

Table I Type of Advertisements and Other Marketing Tactics for Pre-packaged Foods in Indian Market (*N*=48)

Category, no. of products	*Misleading advertisement*[a]	*Marketing tactics* [b]	*Emotional/ product appeal*
Confectionary, *n*=5	5	Celebrity endorsement, 4; Child actor and pregnant women (family), 2; Incentive, 1	Joy, happiness, love, friendship; Emotional bond, happiness, care, affection; Correlating it with learning, creativity/imagination aspirations of the kid, Kids only; Mood Changer, Happiness and pleasure; Humor, fun.
Fine bakery, *n*=14	14	Child actor, 7; Celebrity endorsement, 2; Health claim, 2; Incentive, 4	Smile, Good day, Happiness, Joy, humor; Love, Warmth, Affordable, Nice Deal; Happiness, Healthy, Joy; Healthy, Decision, Choice; Real; Family bond, Love, Affection, Care, Happiness.
Beverages			Creating fantasies for the buyer; Happiness and friendship; Emotional bond, Affection, Motivation; Fun, playful, joy, bonding; Winning, Victory, Surprise, Challenge; Care, Affection, Sibling love, Bond.
Juices, *n*=5	5	Child actor, 1; Celebrity endorsement, 5; Health claim, 2	Care, Concern, Joy, Love; Humor, Goodness; Very tasty, Love, Happiness; Tasty, Stay Active; Refreshing, Happiness and Humor
Milk and dairy based drinks, *n*=3	3	Celebrity endorsement, 1; Incentive, 1	Refreshing; Mood changer
Water based flavored drinks, *n*=3	3	Celebrity endorsement, 2	Joy, refreshing, happiness, fun; tempting, refreshing; refreshing and energizing.
Ready to eat savories *n*=7	5	Celebrity endorsement, 6; Incentive, 3	Emotion of care, mothers love and affection; Humor, funny and attachment; Humor, fun and happiness; Humor and fun; Emotion of love, happiness and friendship; Crispy, crunchy, delicious, munchy, lip smacking; Humor, fun and laughter.
Pasta and noodles and like products, *n*=3	3	Celebrity endorsement, 1; Child actor, 2; Incentive, 2	Choicest Quality; Emotional bond between mother and child; Goodness of grains; Magic, Happy.
Fats and oils, and fat emulsions, *n*=1	1	Child actor, 1; Health claim, 1	Yummy, Tasty, taste of purity.
Bread and ordinary bakery wares, *n*= 1	1	–	Emotion of happiness.
Cereals, *n*=3	3	Celebrity endorsement, 1; Incentive, 1; Child actor, 1; Health claim, 2	Emotional, Fun and happiness bond with mother and child; Crunchy, Gold.
Sauces, dips and dressings, *n*=3		Child actor, 3	Smile, Happiness and fun, Miracle ingredient.

[a]*Violation of Misleading Advertisement -Section 2(28) (iv) "deliberately conceals important information" of the Consumer Protection Act, 2019.* [b]*health claim, celebrity endorsement, use of child actor, incentives.*

Though, recent guidelines for prevention of misleading advertisements (June, 2022) by the Central Consumer Protection Authority is a welcome step, it has scope for misuse too, due to its provisions [23], providing an easy escape for any food advertiser.

The WHO points out the need for a policy to restrict marketing of such foods that contribute to unhealthy diets, because it targets children and adolescents and remains persuasive and pervasive [24]. Given the findings of this and earlier studies, the government must monitor and act against manufacturers and endorsers of such misleading advertisements. The government may also consider prohibiting advertisements of food products, which exceed WHO limits for total fat, sodium and total sugars, and are UPFs by Nova classification.

Many other factors determine demand and consumption of foods, and this limited study is focused only upon the nutrients of concern and nature of advertisements with

respect to WHO Standards, Nova Classification and provisions of the CPA 2019 for misleading advertisements.

The study provides evidence that advertisements of all pre-packaged food products selected in this study were misleading in nature. The existing regulations are not effective in curbing misleading food advertisements as these do not provide important information on nutrients of concern. Thus, there is a need for vigilant monitoring of advertisements of UPFs or HFSS pre-packaged food products as their increased consumption leads to rising obesity and NCDs. This underlines an urgent consideration for prohibition of advertisements of UPFs and HFSS foods. Health warnings on the front of the pack of labels of such products would be critical. We recommend more formal studies on the influence and prevalence of misleading advertisements. Objectivity in the definition of misleading advertisement may also be helpful.

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Web Table I Category of Pre-packaged Food Product, Analysis of the Content and Nature of Food as Per WHO SEARO Nutrition Profile Model, 2017 [5]

S. No	*Category*	*Product code*	*Nutrient of concern in the pre-packaged food product*			*Ultra-processed food product / UPF (Y/N)*
			Total sugar (g)	*Total fat (g)*	*Sodium (mg)*	
1	Confectionary (5) *(Threshold - Total sugar: 6 g, Total Fat: 8g)*	P1	41	30		Yes
		P2	63.6			Yes
		P3	51	32		Yes
		P4	54.7	32.3		Yes
		P5	44.9	25.4		Yes
2	Fine Bakery (14) *(Threshold* *Total sugar: 6g* *Total Fat; 8g* *Sodium; 250 mg)*	P6	22.7	22.1	938.3	Yes
		P7	24	17	349	Yes
		P8	22	20	551	Yes
		P9	21.5	25		Yes
		P10	13.6	23.4	314	Yes
		P11	29	15.6		Yes
		P12	25.5	13	296	Yes
		P13	35.8	27.2		Yes
		P14	32.2	18	Na	Yes
		P15	38	19.7	420	Yes
		P16	41.1	21.9		Yes
		P17	32.8	27.5	Na	Yes
		P18	21.9	23.4		Yes
		P19	34.2	15.1	300	Yes
3	Beverages -Juices (5) (Threshold Total sugar: 6g)	P20	13.1			Yes
		P21	12			Yes
		P22	15.5			Yes
		P23	13			Yes
		P24	15.5			Yes
	Milk and dairy based drinks (3) (No Threshold provided for Total Sugar, Total Fat 7g)	P25	12.7[a]			Yes
		P26	12 [a]			Yes
		P27	9.5 [a]			Yes
	Water based flavored drinks (3) (Threshold total sugar: 2g)	P28	13.7			Yes
		P29	12			Yes
		P30	10.4			Yes
4	Ready to eat savories (savory snack foods (a)(7) (Threshold Sodium; 250 mg Total Fat 8g)	P31		19.5	Na	Yes
		P32		47.1	835	Yes
		P33		34.6	892	Yes
		P34		34	1146	Yes
		P35		33.6	606	Yes
		P36		21	997	Yes
		P37		32.3	790	Yes
5.	Pasta & noodles and like products (3) (Threshold Sodium:250 mg Total Fat 3g)	P38		13.5	1028	Yes
		P39		9.83	800	Yes
		P40		20.1	1247	Yes
6	Fats and oils, &fat emulsions (1) (Threshold Sodium:100 mg Saturated fat: 35g)	P41		70 (Saturated fat is 48g)	983	Yes
7	Bread & ordinary bakery wares (1) (Threshold Sodium: 250 mg Total Sugar :6 g)	P42	6.24		592	Yes
8	Cereals (3) (Threshold sodium: 350 mg; Total sugar:9g; Total fat: 12 g)	P43	18.4	13.6		Yes
		P44			500	Yes
		P45	13.4		709.7	Yes
9	Sauces, dips, & dressings (3) (Threshold sodium: 300 mg Total fat: 12 g Total sugar: 10g)	P46		35	586	Yes
		P47		42.18		Yes
		P48	22		1806	Yes

[a]In these products total sugar is higher than thresholds of sugar for any category given by WHO, even as threshold is not provided for this specific product.

RESEARCH PAPER

Assessment of QT Interval Abnormalities on Electrocardiogram in Children With Breath-Holding Spells

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Objective: To assess QT interval abnormalities among children with breath-holding spells. **Methods**: This case control study included 204 children (104 cases of breath-holding spells and 100 healthy children) younger than 3 years. Breath-holding spells were evaluated for age of onset, type (pallid/cyanotic), triggering factors, frequency and presence of family history. Twelve- lead surface electrocardiogram (ECG) was analyzed for QT interval (QT), corrected QT interval (QTc), QT dispersion (QTD) and QTc dispersion (QTcD) in milliseconds. **Results**: The mean (SD) QT, QTc, QTD and QTcD interval in milliseconds were 320 (0.05), 420 (0.07), 61.15 (16.20), 102.3 (17.24), respectively for breath-holding spells as compared to control group [300 (0.02), 370 (0.03), 38.6(14.28), 78.6 (14.28), respectively] (P<0.001). Similarly, pallid breath-holding spells had prolonged mean (SD) QT, QTc, QTD and QTcD interval in milliseconds [380 (0.04), 520 (0.08), 78.88 (10.78), 123.33 (10.28), respectively] as compared to cyanotic spells [310 (0.04), 400 (0.04), 57.44 (14.64), 97.90 (15.03), respectively] (P<0.001). The mean QTc interval was 590 (0.03) and 400 (0.04) milliseconds in prolonged and non-prolonged QTc group, respectively (P<0.001). **Conclusion**: Abnormal QT, QTc, QTD and QTcD were observed among children with breath-holding spells. ECG should be strongly considered, especially in pallid, frequent spells occurring at younger age and having positive family history, to identify long QT syndrome.

Keywords: *Evaluation, Long QT syndrome, Management, Outcome.*

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Breath-holding spells are benign, acute paroxysmal, non-seizure episodes that occur during infancy and early childhood and are usually precipitated by emotional stimuli [1,2]. Breath-holding spells often lead to parenteral stress as child appears lifeless and unresponsive during the episode [2,3]. The incidence of breath-holding spells is 0.1-4% [4,5]. The exact etiopathogenesis for these spells is not known but likely due to autonomic dysregulation, delayed myelination of the brainstem, and iron deficiency anemia [6,7]. Rarely congenital long QT syndrome (LQTS) manifest similar to breath-holding spells with prolongation of QT interval on electrocardiogram (ECG), which can lead to ventricular arrhythmias and sudden death due to cardiac arrest [8,9]. Therefore, it is prudent to evaluate QT interval prolongation to recognize LQTS earlier and prevent further complications.

This study was conducted with the aim of to assess QT interval abnormalities on ECG among children with breath-holding spells.

METHODS

This case control study was conducted from 1 October, 2020 to 30 September, 2022 at the pediatric department of a tertiary care medical college hospital after obtaining institutional research committee approval. Two hundred four children (104 cases and 100 controls) presenting to the outpatient department were included in the study after obtaining written informed consent from parents/guardians. Children aged less than three years with typical history of breath-holding spells or those who had typical spell during examination (witnessed) were included as cases. Healthy children younger than three years with no history of cardiac, neurologic, or endocrine disorders coming for routine vaccination and well-baby clinic were included as controls. Children with primary cardiac disease like congenital heart disease or central nervous system disease like seizure disorder, endocrinal disorders, on history and clinical examination and those receiving drugs from macrolide, quinolone groups, ondansetron and frusemide were excluded from this study. Sociodemographic factors like age, gender

and detailed history of the breath-holding spells including age of onset, type (pallid/cyanotic/mixed), triggering factors like anger and/or frustration and pain and/or fear, frequency of spells (minimal: <5/week, average: >5-10/week, high: >10/week) and presence of family history either similar spells in parents or parental consanguinity were noted in a pre-designed form. Details regarding clinical examination including general and systemic examination were carried out and noted.

A 12-lead surface ECG with long lead II was carried out on the same day in children with typical breath-holding spells history while on the next day in those with a witnessed spell. All ECGs were analyzed by a single investigator for both cases and control groups and who was unaware of clinical presentation of breath-holding spells. The ECGs were analyzed for heart rate, rhythm, RR interval, QRS interval, QRS axis and QT interval (QT). The QT was measured from onset of Q wave to the end of T wave and was measured in all leads where Q wave was seen and the longest interval was taken as QT, and a value >440 ms was taken as abnormal. Corrected QT interval (QTc) was defined as QT interval corrected for heart rate and calculated using Bazett formula (QTc=QT/square root of RR interval in seconds) where >470 ms was abnormal [10]. QT dispersion (QTD) and QTc dispersion (QTcD) values were calculated as the difference between the longest and the shortest intervals of QT and QTc, respectively [8]. The minimum sample size calculated was 198, with equal number of cases and controls.

Statistical analysis: The statistical analysis was performed using Microsoft Excel 2016 and Analyse-it version 4.3 for Excel. The frequency distribution concerning demographics, history and clinical data of breath-holding spells and ECG abnormalities were studied. Data was represented as frequency, percentage and mean (SD), where relevant. Unpaired *t* test, *z* test for proportion and chi-square test for association were used. *P* value less than 0.05 was taken as significant.

RESULTS

The total 204 (104 cases of breath-holding spells and 100 controls) children from the age group 2-36 months were enrolled during the study period. The children with typical history of breath-holding spells were 96 (92.3%) while 8 (7.7%) had a witnessed spell. Out of 104 cases (60 males) with mean age of 16.5 (7.22) months, the mean age of onset of spells was 13.9 (6.24) months. The control group had 100 healthy children (42 females) with mean age of 17.37 (7.96) months. The ECG parameters including mean QT, QTc interval and QTD, QTcD values in breath-holding spells group were significantly prolonged as compared to control group (**Table I**).

Table I ECG Parameters in Children With Breath-Holding Spells and Control Group

ECG parameters	*Breath-holding spell group (n=104)*	*Control group (n=100)*
Heart rate (beats/min)	101.92 (14.71)	93.3 (12.85)
RR interval (ms)	590 (0.08)	650 (0.08)
PR interval (ms)[a]	150 (0.02)	140 (0.02)
QRS duration (ms)[a]	70 (0.005)	70 (0.003)
QT interval (ms)	320 (0.05)	300 (0.02)
QTc interval (ms)	420 (0.07)	370 (0.03)
QT dispersion (ms)	61.15 (16.20)	38.6 (14.28)
QTc dispersion (ms)	102.3 (17.24)	78.6 (14.28)

Data expressed as mean (SD). ECG: electrocardiogram, QTc: corrected QT. All P<0.001 except [a]P>0.05.

The children with cyanotic and pallid breath-holding spells were 86 (82.7%) and 18 (17.3%), respectively. The mean age and age of onset of spells for pallid breath-holding spells [12.38 (7.57), 9.83 (5.21)] was significantly lower than cyanotic breath holding spells group [17.40 (6.88), 14.80 (6.11)] (both *P*<0.001). The commonest triggering factors were anger and/or frustration 81 (77.9%) for cyanotic breath-holding spells group. The mean QT, QTc, QTD and QTcD values in milliseconds for pallid and cyanotic were 380 (0.04), 520 (0.08), 78.88 (10.78), 123.33 (10.28) and 310 (0.04), 400 (0.04), 57.44 (14.64), 97.90 (15.03), respectively, which showed statistically significant difference (*P*<0.001).

A prolonged QTc interval (QTc more than 470 ms) was observed in 10 (9.6%) children in breath-holding spells

Table II Clinical Profile and QT Variables on ECG in Prolonged QTc and Non-prolonged QTc Breath-Holding Spells Groups

Characteristics	*Prolonged QTc (n=10)*	*Non-prolonged QTc (n=94)*
Male gender	7 (70)	53 (56.4)
Pallid breath-holding spell	9 (90)	9 (9.6)
Triggering factors		
Anger and/frustration	4 (40)	86 (91.5)
Pain and/fear	6 (60)	8 (8.5)
Family history	9 (90)	4 (4.3)
Age (mo)[a]	8.4 (1.71)	17.40 (7.04)
Age of onset of spells (mo)[a]	6.7 (1.94)	14.71 (6.04)
QTc interval (ms)[a]	590 (0.03)	400 (0.04)
QT dispersion (ms)[a]	84 (8.43)	58.72 (14.89)
QTc dispersion (ms)[a]	128 (10.32)	99.57 (15.51)

Data expressed as no. (%) or [a]mean (SD). ECG:electrocardiogram, QTc:corrected QT. All P<0.001.

WHAT THIS STUDY ADDS?

- Electrocardiogram should be considered in children with pallid and very frequent breath-holding spells at a younger age and with a positive family history, as they may have an underlying long QT syndrome.

group and none in control group; while, non-prolonged QTc interval (QTc <470 ms) in 94 (90.4%) and 100 (100%) children of breath-holding spell and control group. The mean QTc interval in ms was 590 (0.03) and 400 (0.04) in prolonged QTc and non-prolonged QTc group which showed statistically significant difference (P<0.001). The clinical profile of children having prolonged QTc with breath-holding spells showed statistically significant association with male gender, younger age of presentation, pallid spells, high frequency of spells and positive family history (**Table II**).

DISCUSSION

In our study, we included 104 children of breath-holding spells and 100 healthy children to evaluate QT abnormalities on ECG. The prevalence for cyanotic and pallid spells were 82.7% and 17.3%, respectively. We did not find any mixed spells in our study in spite of carefully evaluating the history as type of spell is determined mainly on color change of body during spell.

The QT, QTc, QTD and QTcD intervals in the present study were significantly higher in children with breath-holding spells than healthy children. Movahedian, et al. [8] measured QT parameters in 56 children aged 8.4 (7.03) months with breath-holding spells and compared with normal children. They observed significantly higher values in all four QT parameters in breath-holding spells children and pallid type of breath-holding spells, similar to our study findings. Akalin, et al. [9] observed significant higher values for only QTD and QTcD parameters while not for QT and QTc interval in 43 children aged 22.7 (17.7) months with breath-holding spells. They concluded that their results justify further investigation for rhythm abnormalities. Other authors [11,12] observed significantly increased QTc and QTcD values, respectively in breath-holding spells child-ren. Contrary to our findings, Kolkiran, et al. [13] did not observe higher values for QT variables and no significant difference in pallid and cyanotic spells.

The mechanism for increased QT and QTc dispersion may be underlying autonomic nervous system dysfunction as cyanotic and pallid spells are mediated by hyper-sympathetic and hyper-parasympathetic effects, respectively, which may affect QT interval and QT dispersion [9]. The QT interval represents the time from the start of ventricular depolarization to the end of repolarization, corresponds to the time of mechanical systole and varies with heart rate (HR) [14]. The HR corrected QT interval (QTc) by Bazett formula still remained accurate for diagnosis of LQTS [15]. QT dispersion also assesses ventricular repolarization, which reflects the difference of the durations of action potentials in different localizations within the myocardium [16].

The major limitation of our study was that we could not do genetic testing in prolonged QTc children to confirm LQTS, due to financial constraints.

In conclusion, abnormal QT, QTc, QTD and QTcD were observed among children with breath-holding spells. ECG should be strongly considered among them, especially in pallid, frequent spells occurring at younger age and children with positive family history, to identify LQTS.

Ethical clearance: Institutional Research Committee, DY Patil Education Society, Kolhapur; No. DYPES /DU/2020/67, dated Sep 28, 2020.
Contributors: SOK: conceptualized and planned the study; SOK, RRP, HPB, ABK: collected data; SOK,SSK: analyzed the data and did statistical analysis; SOK,RRP: drafted the manuscript; ABK: supervised the study; SOK,RRP: revised it critically for important intellectual content. RRP: organized the manuscript. All authors read and approved the final manuscript.
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RESEARCH PAPER

Pain and Physiological Stress During Minimally Invasive Surfactant Therapy (MIST) in Very Preterm Infants

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Objectives: To evaluate the pain or physiological stress caused during minimally invasive surfactant therapy (MIST) to very preterm neonates. **Methods**: In this prospective observational study conducted in a tertiary NICU, very preterm neonates were assessed for pain using Premature Infant Pain Profile-Revised (PIPP-R) score before, during and after MIST. Changes in the heart rate and oxygen saturation were also recorded during the procedure. **Results**: 23 neonates who received MIST were assessed for pain using PIPP-R. Mean (SD) PIPP-R score during MIST was 3.87(1.3), before; 12.83 (1.9), during; and 6.26 (1.0), after the procedure, respectively (all *P*<0.001). Heart rate and oxygen saturation were also significantly reduced during MIST (*P*<0.001). **Conclusion**: The high PIPP-R scores during surfactant administration suggest that MIST can cause moderate to severe pain/discomfort and significant physiological stress in very preterm infants.

Keywords: *Adverse effect, Intubation, PIPP-R, Outcome*.

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Neonates admitted to the NICU frequently experience pain as a result of diagnostic or therapeutic interventions or the disease process itself. Chronic exposure to stress and pain may alter short and long term brain development and contribute to developmental impairments found later [1-4]. Neonates admitted to NICU experience a mean of 16 painful procedures a day, with the vast majority of them occurring within the first two weeks of life [5]. Several routine interventions like suctioning, echocardiography, surfactant administration can cause pain and stress in neonates, many are still performed without effective pain control measures [5,6].

Minimally invasive surfactant therapy (MIST) is a less-invasive technique of surfactant delivery with several advantages like decreased need for mechanical ventilation, decreased intraventricular hemorrhage and bronchopulmonary dysplasia [7]. Studies have found that MIST is a less stressful procedure in preterm newborns as compared to INSURE technique of surfactant administration [8]. We planned this study to evaluate if very preterm neonates in our unit experience pain or stress during MIST by evaluating the Premature Infant Pain Profile-Revised (PIPP-R) scores during the procedure.

METHODS

This was a prospective observational study conducted from January, 2021 to June, 2021 in a tertiary care neonatal intensive care unit (NICU), after obtaining approval of the institutional ethics committee. Very preterm infants (28-32 weeks gestational age) receiving MIST within two hours of birth were enrolled after written informed parental consent. Neonates with major congenital malformations, severe perinatal asphyxia, altered sensorium, requiring intubation in labor room, and requiring two or more inotropes were excluded. Any neonate needing a painful procedure during the 15 minutes prior to MIST was excluded from the study.

All preterm infants with respiratory distress syndrome (RDS) with Silverman Andersen Score >3 were provided bubble CPAP with nasal mask. Infants on nasal continuous positive airway pressure (NCPAP) with fraction of inspired oxygen (FiO2) requirement ≥0.30 despite provision of optimum positive end expiratory pressure (PEEP) of ≥6 cm H_2O received surfactant replacement therapy as per unit protocol with 100 mg/kg of beractant (Survanta, Abbott) after written informed consent. Non-pharmacologic pain relieving measures (like swaddling) were provided to the infant. No analgesia or sedation was used as premedication. Beractant was administered as a single bolus by the 'Take-care' technique by a trained post-MD resident doctor using a 5F, sterile nasogastric tube inserted 2 cm beyond the vocal cords and held in position with thumb and index finger at the angle of the mouth, following which the tracheal catheter was removed [9,10]. If visualization of vocal cords and placement of catheter was not possible within 20 to 30

seconds or if heart rate dropped below 100 beats per minute or oxygen saturation (SpO2) dropped below 80%, the infant was stabilized and a second catheterization attempt was made after at least 1 minute post stabilization. Infants who suffered severe apnea and bradycardia (heart rate <100/min), along with desaturation (SpO2 < 80%) lasting longer than 20 seconds, were provided positive pressure ventilation (PPV) by T-piece device. If second attempt at MIST failed, neonate received surfactant by INSURE technique. NCPAP was continued throughout the procedure.

Three videos of 30 seconds duration each were recorded by a nurse using a smart phone camera (12MP+ 64MP+12MP triple camera) to best capture the facial expressions of the infant for assessment of facial profile. Base-line video recording was done 5 minutes before insertion of laryngoscope, during surfactant instillation through catheter and 5 minutes after removal of catheter. PIPP-R score was evaluated at the above-mentioned time-points from the videos by an independent assessor. As face was obscured during laryngoscopy and catheter insertion, PIPP-R score was not evaluated at that time. During the procedure, heart rate (beats per min, bpm) and SpO2 (%) were recorded on Radical-7 pulse co-oximeter (MASIMO Corporation), 5 minutes before insertion of laryngoscope, during laryngoscope insertion, during catheter insertion, during surfactant instillation, and 5 minutes after removal of catheter.

The primary objective was to evaluate PIPP-R score before, during and after MIST. Secondary objective was to evaluate physiological stress defined as change in physiological parameters like heart rate and oxygen saturations before and during laryngoscopy, during catheter insertion, during surfactant instillation and after completion of the procedure.

Statistical analysis: A convenience sample of all eligible very preterm neonates satisfying the inclusion criteria were enrolled during the 6-month study period. Statistical analysis was done using SPSS software (version 25.0). Categorical variables were expressed as frequency and proportion. Continuous variables were expressed as mean and standard deviation or median (IQR). To test association between two independent variables independent sample *t* test was used. To test association between three or more dependent variables repeated measures ANOVA was used.

RESULTS

During the 6-month study period, 42 infants needed respiratory support and surfactant replacement therapy for RDS. Of these, 8 needed intubation in the labor room, one had esophageal atresia, 3 failed MIST and received surfactant by Intubation-Surfactant-Extubation (INSURE) technique, and seven babies required two or more inotropes prior to surfactant replacement and were excluded from this study. Twenty three neonates received surfactant by MIST and were enrolled. The baseline characteristics of these neonates are depicted in **Table I**.

The mean (SD) maximum PIPP-R score during the procedure was 12.83 (1.9) suggestive of moderate to severe pain during MIST. This was significantly higher than the mean (SD) score before [3.87 (1.3)] and 5 minutes after MIST [6.26 (1.0); *P*<0.001] (**Table II**).

The mean (SD) heart rate (HR) was 152.52 (10.84) bpm five minutes before starting the procedure. HR at all three time-points was significantly lower than that before starting MIST (*P*<0.001) (**Table III**). The SpO_2 during the procedure was significantly lower than that before the examination.

DISCUSSION

We found a significant change in physiological parameters – bradycardia and desaturations during MIST, suggestive of physiological stress. Total PIPP-R score increased during the MIST suggesting that infants do experience moderate to severe pain/discomfort during the MIST.

There is no consensus regarding use of analgesia/sedation prior to administration of surfactant with MIST. While use of analgesia/sedation would make the procedure more comfortable for the neonate, there are fears of suppressing the respiratory drive crucial for the success of MIST. Most studies reported in literature have used poractant for MIST. We evaluated pain using the PIPP-R score during MIST with beractant. Beractant is used in a

Table I Baseline Characteristics of Neonates Undergoing Minimally Invasive Surfactant Therapy (*N*=23)

Characteristics	*Value*
Birth weight (g)[a]	1460 (384.6)
Gestational age (wk)[a]	30.62 (1.46)
Male	15 (65.2)
Born to primigravida	12 (52.2)
Antenatal corticosteroids	
Full course, *n* (%)	12 (52.2)
Partial Course, *n* (%)	3 (13)
No steroids, *n* (%)	8 (34.8)
Age at procedure[a]	1.57 (0.59)
APGAR score at 1 minute[b]	7 (7,8)
Apgar score at 5 minutes[b]	8 (8,9)
Need for single inotrope support	16 (69.6)
Failed CPAP within 72 h	5 (21.7)

Values in no. (%) [a]mean (SD) or [b]median (IQR). CPAP: continuous positive airway pressure.

Table II Premature Infant Pain Profile-Revised (PIPP-R) Score Before, During and After Minimally Invasive Surfactant Therapy (*N*=23)

Parameter scored	*Before MIST*	*During MIST*	*After MIST*	*P value*
Physiological parameters (Change from baseline)				
HR score, Mean (SD)	0 (0)	1.91 (0.8)	0.65 (0.7)	<0.001
SpO2 score, Mean (SD)	0.09 (0.3)	1.30 (0.7)	0.09 (0.3)	<0.001
Infant's facial profile				
Brow bulge, Mean (SD)	0.87 (0.3)	2.87 (0.3)	1.0 (0)	<0.001
Eye squeeze, Mean (SD)	0.78 (0.4)	1.96 (0.9)	1.0 (0)	<0.001
Nasolabial furrow, Mean (SD)	0 (0)	2.0 (0.7)	1.0 (0)	<0.001
Subtotal score, Mean (SD)	1.74 (0.8)	10.04 (2.0)	3.74 (0.7)	<0.001
Behavioral state, Mean (SD)	0.48 (0.5)	1.0 (0)	0.74 (0.5)	<0.001
Total PIPP-R score, Mean (SD)	3.87 (1.3)	12.83 (1.9)	6.26 (1.0)	<0.001

Table III Heart Rate and Oxygen Saturation (SpO_2) During Laryngoscope Insertion, Catheter Insertion, Surfactant Instillation and Post-procedure

Parameter	*Before*	*Laryngoscope insertion*	*Catheter insertion*	*Surfactant instillation*	*Post-procedure*
Heart rate (bpm)	152.52 (10.84)	107.48 (14.84)[a]	118.61 (13.98)[a]	138.96 (21.68)[b]	152.74 (12.55)[c]
SpO2 (%)	93.26 (1.711)	83.17 (3.55)[a]	87.78 (2.696)[a]	88.74 (1.42)[a]	93.00 (1.24)[c]

Values in mean (SD). On comparison with base line values: [a]P<0.001; [b]P=0.001; [c]P>0.05.

larger volume compared to same dose of poractant. Okur, et al. [8] also reported a median PIPP-R score of 10 during MIST, suggestive of moderate pain similar to our results.

Physiological responses to acute pain during MIST like bradycardia and desaturation have also been reported by other authors [8,12]. While Dekker, et al. [8] observed heart rate drop of only 2 bpm in the non-sedated group, we found a greater heart rate drop of almost 20 bpm during MIST. This might be related to the greater volume of surfactant (beractant) instilled and greater time required for administration due to higher volume.

Dekker, et al. [8] studied the level of comfort in preterm infants receiving MIST received premedication with low dose of propofol (1 mg/kg). They observed that infants receiving propofol had a higher level of comfort compared to the infants receiving no sedation before MIST. However, infants receiving propofol desaturated for a longer period and needed brief nasal invasive ventilation more frequently during the procedure. They also observed an insignificant increase in the need for intubation and mechanical ventilation during or within 24 hour after MIST [12]. In another recent trial [13], low dose fentanyl (1µg/mL intravenous) vs no fentanyl was administered to very or moderate preterm neonates during less invasive surfactant administration (LISA). They found that a significantly higher proportion of preterm neonates in the fentanyl group had a PIPP-R score ≤12 and were more comfortable than neonates who received no pre-medication. There was no difference in the secondary outcomes [13].

A small sample size and lack of two independent assessors for assigning the pain scores are the main limitations of our study. Significant changes in physiological parameters were found, but certain confounders like ongoing respiratory support, inotropic support and severity of sickness were not considered during analysis.

Considering the findings of these studies, a large randomized controlled trial is warranted to determine whether the benefit of sedation/analgesia to reduce pain scores and reduce fluctuations in intracranial pressure outweighs the risks of complications like respiratory depression and chest wall rigidity leading to escalation of respiratory support during/after MIST. An upcoming multicenter, double blind, randomized, controlled trial is likely to provide more robust data in this regard [14].

To conclude, MIST procedure causes moderate to severe pain/discomfort and significant physiological stress in preterm infants.

Ethics clearance: IEC Human Research, Lokmanya Tilak Municipal Medical College and General Hospital; No. IEC/01/21 dated Jan 1, 2021.
Contributors: SM: conceived the study; TS, SM, PK, TK, SP, JM:

WHAT THIS STUDY ADDS?

- Preterm infants undergoing MIST experience moderate to severe pain/discomfort and significant physiological stress during the procedure.

developed study protocol; TS, PK,TK,SP: implemented the study; SM, JM: supervised implementation; TS, PK, TK, SP: contributed to data collection and analysis; SM, JM: contributed to data interpretation; TS, PK, TK, SP: wrote the initial draft while SM, JM: edited the final manuscript. All authors have reviewed the manuscript and approve the submitted version.

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SYSTEMATIC REVIEW

Pediatrics in Artificial Intelligence Era: A Systematic Review on Challenges, Opportunities, and Explainability

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Background: The emergence of artificial intelligence (AI) tools such as ChatGPT and Bard is disrupting a broad swathe of fields, including medicine. In pediatric medicine, AI is also increasingly being used across multiple subspecialties. However, the practical application of AI still faces a number of key challenges. Consequently, there is a requirement for a concise overview of the roles of AI across the multiple domains of pediatric medicine, which the current study seeks to address.

Aim: To systematically assess the challenges, opportunities, and explainability of AI in pediatric medicine.

Methodology: A systematic search was carried out on peer-reviewed databases, PubMed Central, Europe PubMed Central, and grey literature using search terms related to machine learning (ML) and AI for the years 2016 to 2022 in the English language. A total of 210 articles were retrieved that were screened with PRISMA for abstract, year, language, context, and proximal relevance to research aims. A thematic analysis was carried out to extract findings from the included studies.

Results: Twenty articles were selected for data abstraction and analysis, with three consistent themes emerging from these articles. In particular, eleven articles address the current state-of-the-art application of AI in diagnosing and predicting health conditions such as behavioral and mental health, cancer, syndromic and metabolic diseases. Five articles highlight the specific challenges of AI deployment in pediatric medicines: data security, handling, authentication, and validation. Four articles set out future opportunities for AI to be adapted: the incorporation of Big Data, cloud computing, precision medicine, and clinical decision support systems. These studies collectively critically evaluate the potential of AI in overcoming current barriers to adoption.

Conclusion: AI is proving disruptive within pediatric medicine and is presently associated with challenges, opportunities, and the need for explainability. AI should be viewed as a tool to enhance and support clinical decision-making rather than a substitute for human judgement and expertise. Future research should consequently focus on obtaining comprehensive data to ensure the generalizability of research findings.

Key words: *Artificial intelligence, Data science, Deep learning, Large language model.*

Protocol Registration: International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY): INPLASY202350045.

Science and technology have made significant advancements with the introduction of artificial intelligence (AI), and machine learning (ML) has been a game-changer. ML has enabled computers to learn without explicit programming by combining computer science and statistics [1]. ML has gained momentum in many fields, including healthcare, thanks to emerging tools like ChatGPT, Bard and Glass AI 2.0. These tools are transforming industries by enabling conversations between humans and machines. ChatGPT, a large language model (LLM), has immense potential to assist in healthcare, including helping patients with mental health issues and aiding healthcare providers in decision-making [2,3]. Recently, Glass Health introduced Glass AI 2.0, a similar LLM to ChatGPT, but with a clinical knowledge database created and maintained by clinicians to generate differential diagnoses and clinical plan outputs [4].

The integration and scope of such AI tools in healthcare are growing rapidly. Pediatrics is a field with practical challenges like complex comorbidities, increasing emergency admissions, and a lack of access to pediatric care providers, which could hinder the provision of quality and timely care [5]. ML implementations can streamline the pediatric work-force and assist clinical decision-making by enabling physicians to focus on patient-centered care plans by making better use of their clinical knowledge and time [1]. ML techniques can analyze vast datasets and create predictive models that go beyond human cognitive capabilities.

Even though technological advancements are expanding the integration and scope of ML in pediatrics, there are challenges associated with the implications of AI, such as unintentional bias from data, like racial segregation and

under-performing algorithms, which could jeopardize patient care [6]. To mitigate these issues, it may be better to focus on collective human-support AI systems instead of complete automation. Additionally, ML could facilitate medical training or provide evidence-based care to patients using AI-based web or mobile applications with the help of human-in-the-loop systems. Therefore, it is crucial to evaluate the explainability of AI models, potential opportunities, and challenges when integrating ML in healthcare, especially for the pediatric population.

METHODS

The field of artificial intelligence (AI) is rapidly growing and evolving, with a variety of buzzwords and terms that can be confusing to navigate. In order to clarify these terms and their relationship to one another, this section provides definitions of key buzzwords related to AI in **Box I**. Additionally, a visual representation of the relationship among these buzzwords is presented in **Fig. 1**. By establishing a clear understanding of these terms, the subsequent methodology can be more easily understood and applied.

Since this study focuses on ML in pediatrics; for this purpose, we employ a qualitative approach, expressing research findings and interpretations in terms of non-numeric data. The research thus uses secondary analysis to constitute an evidence-based literature review and associated analysis.

Search Strategy and Keywords

In this review, the focus is on assessing the challenges and opportunities of ML in pediatrics. The search was performed through authentic databases to obtain the relevant information. The search strategy was based on using a set of keywords and Boolean operators.

Keywords that were used during the search for the desired topic that is challenges and opportunities of machine learning in pediatrics are: "machine learning AND pediatrics", "machine learning", "challenges faced during paediatrics care AND technology", and "significance of machine learning AND paediatrics care", "paediatrics AND machine learning history", "machine learning AND future in paediatrics care."

Databases, Data Extraction and Selection Criteria

The databases that were used during the searching process include PubMed Central and Europe PubMed Central [7]. PRISMA guidelines for systematic reviews were used [8] for the data extraction process. The selection criterion defining the inclusion of relevant information is peer-reviewed journals from scholarly databases, the English publication language, the timeline of the last 7 years (2016-2022), and the information relevant to the research objectives. The aforementioned criteria are considered while searching for relevant data.

Data Collection

For data collection, Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA)

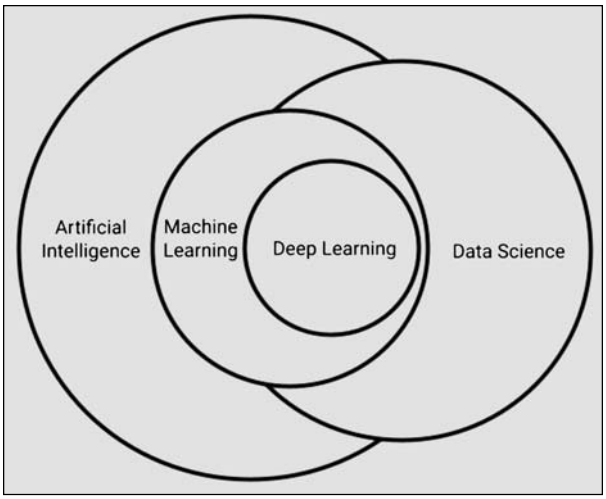

Fig. 1 Relationship between artificial intelligence (AI), machine learning (ML), deep learning and data science. AI is the creation of computer systems that can perform tasks that typically require human intelligence. Machine learning is a branch of AI that enables computers to learn from data without being programmed explicitly. Deep learning is a subset of machine learning that focuses on neural network algorithms. Data science deals with everything related to data, including collecting, cleaning, analyzing and interpreting it.

Box I Simplified Definitions of the Commonly Used Artificial Intelligence Buzzwords

Artificial intelligence (AI): This term refers to the creation of intelligent systems that simulate human thinking and behavior. AI systems can be designed to perform tasks such as speech recognition, decision-making, and problem-solving.

Statistics: Involves making inferences about a population based on a sample of data. It can be used to make predictions and identify patterns within data.

Machine learning: A subset of AI, machine learning involves designing algorithms that can learn from data without being explicitly programmed. It involves finding patterns within data that can be used to make predictions.

Deep learning: A subset of ML, deep learning uses neural network-based methods to generate repeatable predictions by finding patterns within data. It is particularly useful for complex data sets and can be used for tasks such as language, image and speech recognition.

Data science: This is the study of data, which involves data preparation, transformation, and analytics. Data scientists use a variety of techniques and tools to make sense of large data sets and to identify patterns that can be used for decision-making.

guidelines were adopted as shown in **Fig. 2**. The data was collected as per the inclusion and exclusion criteria guidelines in Section 2.2. Initial search results retrieved were *N*=210 searches (this included scholarly articles and, initially, grey literature). Later, primary screening was performed, and duplicated results were removed, leaving 86 articles. These were then passed down to secondary screening, where exclusion based on title/abstracts, language, and timeline was performed, resulting in 39 articles. Finally, the content analysis was performed for quality check, and 20 articles were then selected for the review discussion.

RESULTS

Three themes have been designed based on the achievable results viz., *i*) the current state-of-the-art functioning of ML algorithms in pediatric medicine, *ii*) the challenges of ML algorithm deployment in pediatric medicine, and *iii*) the future outlook of ML in pediatric medicine. The data analysis from this review can be found at: *https://github.com/tsantosh7/supplementary_material/blob/main/review_data_analysis.pdf*

The Current State-of-the-Art

There are many sub-specialty areas in pediatrics, including neonatology, pediatric endocrinology, pediatric emergency, nephrology, neurology, rheumatology, ophthalmology, behavioral medicine, respiratory medicine and many more. ML has integrated into areas where some showed profound outcomes, and others needed improvements. The section will detail the current perspectives on ML application in pediatric medicine.

PTSD diagnosis: Several studies have investigated the use of deep learning models for neuroimaging to classify PTSD in children who have experienced natural disasters [9,10]. Ge and colleagues [9] found that property loss and lifestyle deterioration were the most probable variables for predicting PTSD using ML algorithms. PTSD is a lasting dysfunctional condition in children, and the ability of ML to perform predictive classification has important implications for early intervention and treatment.

Cancer diagnosis: ML has also been applied to cancer diagnosis in pediatric care. Fathi, et al. [11] used the neuro-fuzzy inference system (NFIS) as a deep learning (DL) model for diagnosing pediatric leukemia patients, with the system predicting cases by extracting information from a patient's neutrophil count from blood test records. NFIS has been investigated as a prognostic tool for cancer detection in children, where the prognosis is particularly important, and is therefore highly demanded.

Metabolic condition diagnosis: ML has shown promise in detecting genetic metabolic conditions. Zhu, et al. [12] discussed that even though metabolic data of children are noisy (complex) in a clinical setting, the ML significantly extracts some useful findings from metabolic data to screen phenylketonuria (PKU) in children without a false-positive diagnosis. Moreover, PKU detection in newborns and susceptibility was also reported to be diagnosed with ML models. Rare Disease Auxiliary Diagnosis system (RDAD) is one of the examples of detecting rare phenotype-based metabolic disorders in children [13].

Eye disorder diagnosis: ML has also made contributions to ophthalmic medicine, such as predicting myopia

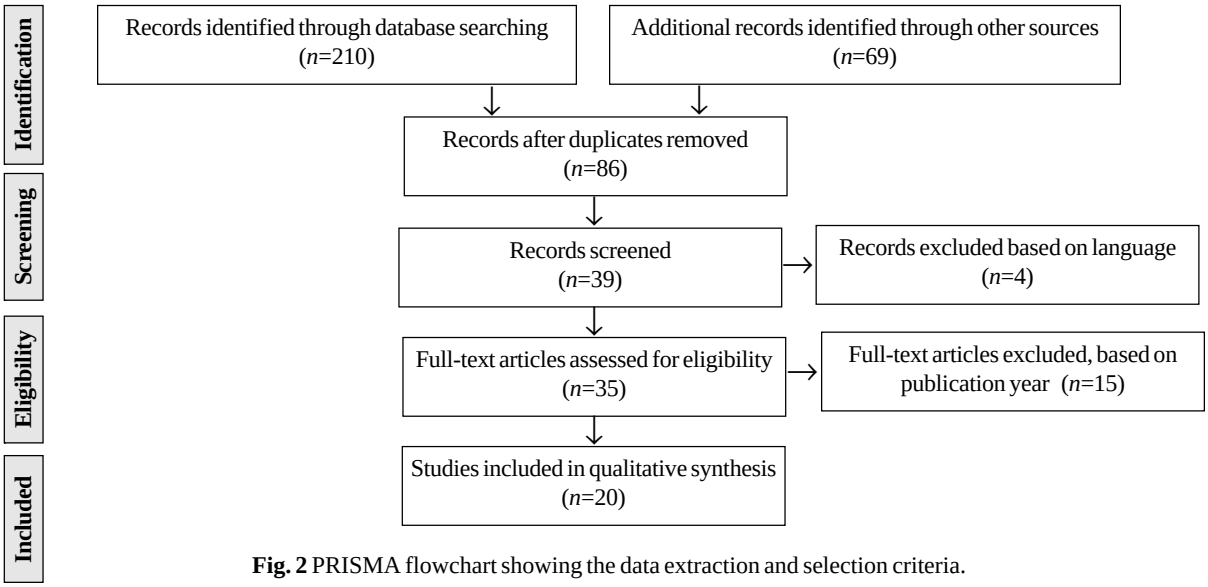

Fig. 2 PRISMA flowchart showing the data extraction and selection criteria.

development in school-aged children [14,15]. Lin and colleagues [14] observed the real-time clinical refraction data by applying ML models to predict myopia development, where acceptable prediction among children was found. Another study [15] used a regression model to predict childhood myopia in Chinese children. At a 95% confidence interval, a suitable diagnostic accuracy was reported. In addition, the study also analyzed the impact of factors on atropine-treated myopia that control intraocular pressure in children [15]. Different AI models have been used to detect factors that can enhance myopia control by optimizing atropine use [16].

Behavioral disorders: AI and ML have the potential to revolutionize analysis of behavioral problems in pediatrics, including autism spectrum disorder (ASD), conduct disorder (CD) and attention deficit hyperactive disorder (ADHD) [17,18]. These conditions lead to disruptive behaviors in children. By analyzing disruptive behaviors, AI and ML can identify patterns and correlations, which can lead to a more accurate diagnosis of behavioral problems and help in the development of more effective treatment plans [18]. Moreover, AI can also analyze speech patterns and behavior in children with ASD and identify specific markers that are indicative of ASD. This information can then be used to develop more personalized treatment plans that are tailored to the individual child's needs [19].

Abuse analysis: Child abuse is an unaddressed public health challenge but causes mental disturbances in children and post-traumatic stress disorder (PTSD) [20]. A study proposed the concept that the development of a convolutional neural network can facilitate the detection of childhood sexual abuse. ML can perform self-figure drawings to be used as a comparative figure with drawings of non-victims to identify cases of maltreatment in children [21].

Amrit, et al. [22] applied ML models to cases of abuse in children in the Netherlands using the data extracted from child specialties. They characteristically converted unstructured clinical notes into structured data and used a classification algorithm to characterize the abuse cases. Literature also studied the effects of ML on child abuse detection. ML has progressed in the predictive analysis of childhood abuse cases.

Improving PICU efficiency: In recent years, the use of AI/ML technologies in pediatric intensive care units (PICU) has greatly advanced patient outcomes for children with severe illnesses. As a result, PICU death rates have significantly decreased, with some studies reporting rates as low as 1-2% [23].

Challenges of ML Deployment in Pediatrics

The key challenges to deploying AI in clinical practice are the barriers preventing AI's clinical translation. The safety and timely transformation into practice, accuracy, algorithmic biases, data biases, brittleness, and irregular interpretability are some barriers that affect the AI-based service delivery in clinical settings [24].

Irregularity in temporality: Clinical patient data are often not recorded at regular intervals causing irregularity. For example, blood pressure measurements are collected only when a patient visits, as and when necessary, or during regular appointments. Irregularities or missing samples are inevitable because a patient can be absent from the appointment, or a clinician may cancel or reschedule the appointment [25]. Xiao, et al. in [26], proposed two important challenges of temporality and irregularity. According to their findings, clinical electronic health records (EHRs) comprise short- and long-term records for patient health trajectories. However, clinical complexity is present in long-term cases, which may interfere with the interpretation and ML-based structuring of clinical data. Furthermore, their analysis showed that the data density of clinical records varies among patients and can produce irregular samples for testing.

Biases in the diagnostic outcomes: The data used to train AI/ML models must be diverse and inclusive of different racial and ethnic groups to avoid biases in the diagnostic outcomes [24]. The limited amount of data available for conditions, such as chromosomal anomalies and genetic malformations, can affect the accuracy of AI/ML models. Approximately 80% of rare diseases (RD) are hereditary in nature, and 75% of them afflict children. Although each case is uncommon, RDs are thought to impact 350 million individuals worldwide cumulatively. Furthermore, the complexity of some syndromic conditions, such as trisomy 21 and Turner syndrome and the variability in their presentations can make it difficult for AI/ML models to diagnose these conditions accurately. So, the lack of standardization in the data collected for diagnosis and the use of different diagnostic tools by different healthcare providers can make it challenging for algorithmic models to diagnose syndromic conditions effectively. Moreover, the interpretation and implementation of AI/ML diagnostic results in the clinical setting require careful consideration of ethical and legal considerations, such as patient privacy and informed consent.

Bias and quality of data: There is also the risk of bias in AI and ML algorithms. If the algorithms are trained on biased data, they can perpetuate that bias in their predictions and decisions. Especially, as PICUs often collect large amounts of patient data, which may be fragmented, inconsistent, or of poor quality, and can impact the accuracy of AI and ML algorithms, which can have serious consequences for critically ill children. Integrating AI and ML into PICUs also

requires collaboration between healthcare providers, AI and ML experts, and patient representatives to ensure that the technology is used ethically and meets the needs of patients and families [6].

Lack of variety in data: Understanding behavioral problems in pediatrics is complex, and AI/machine learning can aid in this process. However, several challenges need to be addressed. Firstly, the data used to train AI models is limited, as it is difficult to collect large amounts of data on children's disruptive behavior, such as ADHD and CD. This can result in models that are not representative of the population and may lead to incorrect predictions. Moreover, children's behavior constantly changes, and AI models must be updated frequently to reflect these changes . Likewise, children's behavior is influenced by many factors, including their environment, genetics, and development stage, making it difficult to predict their behavior accurately. In addition, there is risk of AI models reinforcing existing biases, which can lead to unfair treatment of children [18].

So, there is a need for interdisciplinary collaboration between AI researchers, pediatricians, and child psychologists to ensure that AI models are developed and used to benefit children. This requires a deep understanding of the complexities of child behavior and the development of ethical and transparent AI models. Although AI has the potential to play a significant role in understanding behavioral problems in pediatrics, it is important to address the challenges mentioned above. With the right approach, AI can help pediatricians and child psychologists to better understand and treat children with behavioral problems of ADHD, CD and ASD, leading to improved outcomes for children and their families.

Record duplication: Another significant barrier is record duplication, which limits the use of AI in practice. Vogl [27] discussed this barrier and reported that record duplications are prevalent, especially in children's welfare and protection services, and prevent processing structured data into AI-based DL methods. AI lacks unique identifiers that may differentiate duplicated records. AI itself merges duplicated data across large datasets where challenges for individual-level detection can be incurred. In addition, where records are inaccurately merged, additional challenges arise as a result. The risk of misattributed information is another risk of AI.

Interpretability of the ML models: Another challenge is the lack of interpretability of AI and ML algorithms. These algorithms can make predictions based on vast amounts of data, but it can be difficult to understand how they arrived at a particular conclusion, making it difficult for healthcare providers to trust and use the technology effectively [24]. The interpretability and explainability challenges are discussed further in the Section on explainable AI (XAI).

A recent study by McCartney, et al. [28] commented on the practical challenges associated with AI. The example of the Babylon app was an important predictor of the problems. There are still some challenges in the NHS, which first developed the app for the purpose of a symptoms checker in pediatric patients. The problems are mainly associated with the ineffective evaluation of these clinical apps before commercializing. Babylon was not tested for the safest care and treatment. The Babylon app serves as a notable example illustrating these problems, particularly in the context of the NHS. Originally developed as a symptoms checker for pediatric patients, the app encountered several challenges due to inadequate evaluation before commercialization. Notably, Baby-lon had not undergone sufficient testing to ensure the provision of safe and effective care and treatment. Therefore, it is noticeable that technological advancements, especially AI-based models, should be tested for their proper accuracy before introducing them in clinical practices. The Babylon app, an AI driven diagnostic and triage system, initially claimed 100% accuracy in symptom checking and result evaluation. However, this claim was later proven to be incorrect. Such type of political and legal challenges further complicates the introduction of AI-based technologies into healthcare settings.

Additionally, using AI and ML raise ethical concerns about patient privacy and data security. Healthcare providers must ensure that patient data is protected and used only for the purpose of providing care. Furthermore, Davendralingam, et al. [29] highlighted challenges of data security issues, legal and ethical considerations, and issues with standardizing clinical terms. All these challenges must be addressed to improve AI implications in pediatrics.

Opportunities for ML algorithms in Pediatric Medicine

Clarke, et al. [1] found that AI has improved the precision in diagnosis, with ML models able to identify abnormal findings from normal clinical radiographs of pediatric patients [30]. Pediatric ophthalmology could also benefit from AI in detecting retinopathy of prematurity (ROP) and congenital cataracts, taking into account unique aspects of designing AI applications that differ from adults [31]. Diseases such as asthma require stratification due to heterogeneity in disease severity and response to clinical treatment and trajectories, and ML can improve the classification of such diseases [32]. AI-based algorithms, such as Natural Language Processing (NLP), are also effective in drug development, identifying the most specific druggable targets [33].

One potential application of AI/ML is the prediction of patient deterioration, which can help clinicians respond quickly to this potentially life-threatening condition. AI/ML

can analyze large amounts of patient data, including vital signs, laboratory results, and medical history, and use this information to predict which patients are at risk of worsening [34]. Another opportunity for AI and ML in PICUs is in the personalized treatment of patients by analyzing patients' data, medical history and current condition to develop individualized treatment plans. For example, AI and ML can be used to determine the most appropriate medications and doses based on a child's age, weight, and medical history.

Computational advancement helps track the progress of children with behavioral problems over time. AI can identify changes in behavior and determine the effectiveness of different treatments by analyzing data from multiple sources, such as medical records, behavioral assessments, and patient reports. This information can then be used to make informed decisions about future treatment plans and to adjust them as needed [35]. The sophisticated DL algorithms can analyze data from various sources, including genetic data, family history, and environmental factors; AI can therefore identify children who are at risk of developing behavioral problems of ADHD, CD and ASD. This information can then be used to provide early interventions and support.

AI/ML also has enormous potential in diagnosing syndromic conditions such as Prader-Willi syndrome, Angelman syndrome and Huntington disease in pediatrics. AI can process vast amounts of genetic information about the aforementioned conditions and identify patterns that may not be immediately apparent to the human eye [36]. For example, AI can help identify specific patterns in genetic data that may indicate a particular syndrome, such as Prader-Willi syndrome, allowing for a faster and more accurate diagnosis. This can be particularly useful in diagnosing rare or complex syndromes where traditional methods may be insufficient and give false negative or false positive results. By using AI, pediatricians can make more informed decisions about testing and treatment, leading to improved outcomes for children and their families. Another opportunity is using AI for image analysis, such as in diagnosing craniofacial syndromes such as Goldenhar syndrome, trisomy 21 and DiGeorge syndromes. AI algorithms can analyze facial images and identify specific features that are indicative of a particular syndrome, allowing for a more accurate and objective diagnosis. This can be particularly useful in detecting syndromes early and improving treatment outcomes. In addition, AI can help reduce the time and resources required for diagnosis, allowing pediatricians to focus on providing care to children in need. By automating routine tasks, such as data collection and analysis, pediatricians can spend more time with patients and families, improving the overall quality of care.

Filipow [37] reported that ML can potentially diagnose chronic respiratory conditions such as chronic obstructive pulmonary disease and chronic airway obstruction. Shu, et al. [38] discussed several applications of AI; however, it is crucial to improve the predictive architecture of algorithms to improve diagnostic outcomes and precision. Furthermore, it is widely acknowledged in the literature that the introduction of an AI model into the clinical setting should be based on a thorough assessment of its precision, diagnostic efficacy, and reliability. This evaluation process can serve as a valuable lesson for future iterations of apps such as Babylon, encouraging the implementation of extensive validation practices to enhance their utility and effectiveness.

Explainable AI (XAI)

AI can provide a great benefit to pediatric medicine by assisting in the diagnosis, treatment, and management of diseases. However, it is also essential to explain the decision-making process to both doctors and patients to build trust and provide a better understanding of the reasoning behind a particular diagnosis or treatment recommendation. This need led to the development of explainable artificial intelligence (XAI), which aims to make AI processes more transparent and interpretable. Deep learning algorithms, in particular, can benefit from XAI, as they learn every aspect of the decision-making process on their own, known as "neural weights" [39,40].

There are two main approaches to XAI [40]: model-based and post-hoc explanation-based. Model-based methods make the ML model directly interpretable to medical practitioners, while post-hoc explanation-based methods translate the model into a more understandable format. The counterfactual explanation is an extension of XAI that can help identify and supplement diagnostic indicators. It allows medical professionals to ask, "what if" questions, such as "how would this disease look in an adult?" or "how likely is this diagnosis if the patient were 10 years older?" These methods can be particularly useful in pediatrics, as they can help make connections to general medicine and supplement traditional DL methods.

Limitations

Despite the potential benefits of AI/ML in pediatric medicine and with the recent emergence of AI 2.0 tools such as ChatGPT, Bard, and GLASS A.I 2.0 potentially offering benefits for diagnosing and managing diseases; deploying these tools in practice has several limitations. One significant limitation is the context-specific nature of ML. For example, when developing an ML model to predict hospital mortality in children admitted to the ICU, it is important to ensure that the model performs well on a validation cohort from a different ICU to demonstrate its ability to generalize in different contexts. Similarly, an ML model designed to

analyze as-thma in a specific population e.g., ethnic group, should be able to generalize effectively to other diverse populations as well. These examples highlight the importance of testing and validating ML models across different populations and contexts to ensure their reliability and applicability in diverse settings.

Another limitation in using ML in pediatric medicine is the lack of experiential learning with these models. Experiential learning allows clinicians to learn from their experiences and improve their decision-making over time. However, ML models are pre-determined and do not have the ability to learn from new experiences unless specifically retrained, which can lead to inaccurate predictions or an inability to adapt to changes in the patient's condition over time. Additionally, when there are limited training samples available, statistical noise may arise in the ML predictions. These challenges can be compounded by other biases, such as those related to gender or demographics [41].

To address these limitations, researchers have developed various strategies, including the use of data augmentation to address category imbalance, interpretation and explanation-based ML methods, and monitoring the deployment context [42]. Additionally, collecting demographic data is crucial for mitigating biases in the data, especially given the potential for compounding biases related to gender and demographics in pediatric medicine [41]. Overall, while ML tools offer tremendous potential for improving pediatric medicine, their deployment comes with significant limitations that need to be addressed. Context-specific testing, validation, and monitoring are crucial to ensure that these tools are effective and accurate in different patient populations. Additionally, researchers must find ways to incorporate experiential learning into these models to ensure that they adapt and improve over time (**Fig. 3**). This process starts with defining the problem to be solved using ML, followed by gathering and cleaning relevant data. Exploratory analysis provides a basic understanding of the data and helps identify potential biases in the dataset. The next step is to build a model by training and evaluating the dataset, which is a critical phase in the cycle. As new data becomes available, the model needs to be retrained to ensure its accuracy and effectiveness. Additionally, experiential learning is essential in the healthcare industry, where new medicines and treatments are continually being introduced. As such, ML models need to be continuously trained and adapted to incorporate the latest medical knowledge. Finally, the model is deployed for inference/predictions, and its efficiency is continually monitored and improved by adding more data to mitigate bias. In summary, the ML life cycle is an ongoing process that requires continuous training and adaptation to accommodate changes in data and context and to incorporate the latest medical knowledge.

CONCLUSION

Many healthcare providers depend on clinical decision support tools integrated within the EHRs to enhance patient safety and achieve improved outcomes. With the advancements in AI and ML, these tools have become even more crucial in the practice of medicine. In particular, AI has been integrated into many areas of pediatrics, such as predicting PTSD among children's survivors, early diagnosis of leukemia, and detecting PKU cases with high accuracy. However, AI/ML deployment in pediatrics is still facing several challenges, such as data quality issues, unnoticed, hidden clinical variables, complex clinical data, and lack of clinical labels. To ensure the successful integration of AI/ML into pediatric healthcare, specific or generalized improvements in AI design and validation are necessary.

It is important to acknowledge that AI/ML models are context-specific and need testing in diverse populations to ensure their generalizability and identify any biases within the data. While AI tools could provide valuable virtual support to clinicians and parents by answering questions and providing information about symptoms, treatments, and medications, they are limited by the quality of the data they are trained on and may be biased based on the population they are tested on [1]. Additionally, ML models lack the ability to adapt to new situations, which limits their potential for experiential learning. It is important to recognize these limitations and to highlight the importance of human judgement and expertise in the use of AI/ML in pediatric healthcare.

In conclusion, it is evident that AI/ML has the potential to significantly enhance patient outcomes in pediatric medicine. Although, there are challenges to their deployment, advancements in AI design and validation, and

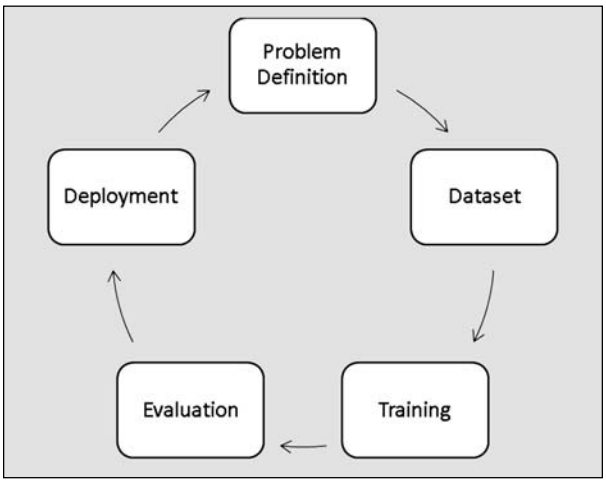

Fig. 3 Machine learning life cycle is a continuous process that requires ongoing training and adaptation of models to accommodate changes in data and context (*see text for description*).

testing in diverse populations can help to overcome these issues. Further research and practical support are recommended to explore areas not yet covered in the current literature. Ultimately, AI should be viewed as a tool to enhance and support clinical decision-making rather than a substitute for human judgement and expertise.

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Methylprednisolone or Intravenous Immunoglobulin in Children with Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS)?

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SUMMARY

Welzel, et al. [1] recently published a randomized controlled trial (RCT) comparing the efficacy of methylprednisolone (MP) with intravenous immunoglobulin (IVIg) for COVID-19 associated pediatric inflammatory multisystem syndrome, also referred to as COVID-19 associated multisystem inflammatory syndrome in children (MIS-C). This study was necessitated by the helplessness associated with the condition, in the face of the COVID pandemic, coupled with the ray of hope offered by these medications, documented through physician experiences and observational studies.

Table I summarizes the salient features of the RCT, and **Box I** presents the main results.

COMMENTARIES

Evidence-based Medicine Viewpoint

Critical Appraisal

The methodological aspects of the RCT conformed to the criteria for low to moderate risk of bias. Random sequence generation, and allocation concealment appeared to be adequate. However, there was no blinding of the outcome assessors and treating physicians. This could directly or indirectly impact the reporting of several outcomes studied in this RCT. Thankfully, there was no attrition or selective outcome reporting. The trial was described as investigator-initiated, hence it is presumed that pharmaceutical companies producing/marketing the study medications had no role in the design, conduct, or analysis stages of the trial.

As expected in a well-designed RCT, there were several methodological refinements. As far as practically feasible, the investigators used clearly defined criteria for situations that are often loosely reported. Thus, there were clearly specified criteria for the condition being studied viz. COVID-19 associated Pediatric Inflammatory Multisystem Syndrome (PIMS). There were also clear definitions for terms such as organ support, PIMS phenotype, cardiac dysfunction, each of the serious adverse events studied, and criteria for defining the duration of the primary outcome. This diminished the subjectivity that could creep in when outcomes were recorded by unblinded observers.

The choice of the primary outcome was rational, considering that duration of hospitalization is a fairly objective parameter, is patient-centric in character, and also considers the need(s) of the healthcare system in general. Surrogate outcomes reflecting the body's response to widespread inflammation (viz. absolute and relative levels of biomarkers, and their changes over time) may be convenient to record, but are less relevant than objective patient-centric outcomes.

The investigators employed robust statistical methods for data analysis. Several subgroup analysis and sensitivity analyses were undertaken to test the robustness of the results. As expected, the trial was properly registered, and the protocol published.

However, there are some issues that merit closer attention. The definition for COVID-associated PIMS was based on the temporal association with microbiologically confirmed SARS-CoV-2 infection or 'putative' contact. However, the definition and implication of the word 'putative' are somewhat unclear. Ordinarily this would not have been important; however in this RCT, the number of children with microbiologically confirmed COVID was not reported. Further, almost two-thirds of the enrolled children had known exposure to COVID, while one-third were previously PCR positive. The duration of 'previous' was also not specified.

The sample size calculation was based on an anticipated effect size of 2.5 days' difference between the duration of hospitalization in the two groups. However, it is unclear on what basis this difference was anticipated; and also whether the investigators *a priori* expected the intervention (methylprednisolone) to be superior, inferior, or equivalent to

Table I Summary of the Trial

PICOTS elements	*Population/Problem*: Children with COVID-19 associated pediatric inflammatory multisystem syndrome (PIMS) *Intervention*: Methylprednisolone (MP); Comparison: Intravenous immunoglobulin (IVIG) *Outcome(s)*: Duration of hospitalization, mortality, clinical parameters, need for supportive therapy. *Timeframe of outcome measurement*: Up to 28 d following hospital admission Setting: Hospital
Clinical question	In children admitted with COVID-19 associated PIMS, what is the efficacy of MP, compared to IVIG, on the duration of hospitalization and mortality within 28 d of admission?
Study design	Multi-centric, open-label, pragmatic randomized controlled trial.
Study setting	Ten hospitals located in Switzerland.
Study duration	Around one year for enrolment (21 May, 2021 – 15 April, 2022), with follow-up for 28 d after admission.
Inclusion criteria	Children (<18y), admitted with COVID-19 associated PIMS. The condition was defined as per the prevalent national and international (consensus) guidelines viz., the presence of fever, elevated inflammatory biomarkers, (one or more) organ dysfunction, confirmed COVID-19 (SARS-CoV-2) infection or contact with a case, after excluding other possible diagnoses.
Exclusion criteria	Undefined medical history deemed to endanger patients in case of study participation, contrain-dication(s) to either of the treatments, unspecified clinical indication necessitating that only one of the treatments could be administered, and newborns with corrected gestational age less than 44 weeks.
Recruitment procedure	Not specified.
Randomization	A computer program was used on an online platform to generate the allocation sequence in blocks of 30, without site-stratification. The allocation ratio was 1:1.
Allocation concealment	Although not described in detail, it appears to have been done by accessing the online platform for enrolment of individual participants.
Blinding	Participants, their families, treating physicians,, and outcome assessors were not blinded to the allocation. However, the statistician analyzing the data was blinded.
Execution of the Intervention (and Comparison)	MP was administered intravenously 10 mg/kg, once daily for three days (maximum dose capped at 1 g/d); IVIG was administered 2 g/kg single dose infused over 8-16 hours (dose capped at 100 g). The medications were administered through central or peripheral intravenous access. Additional treatment options such as fluids, anticoagulant medication, antibiotics, and organ supportive therapies/procedures could be administered at the discretion of the treating physicians. They could also administer additional anti-inflammatory medications based on clinical judgement, which included oral steroids, anakinra, and combinations of these. Treating physicians also had the freedom to use both study medications and switch medications, if they desired, and also to use greater or fewer doses of the allocated study medication.
Outcomes	The primary outcome was the duration of hospitalization (defined as the interval between hospital admission and discharge or death, within 28 d). Secondary outcomes were duration of hospitalization after randomization; all-cause mortality; requirement of organ support and the respective durations (viz., respiratory support categorised as invasive ventilation, non-invasive ventilation with either mode, or supplemental oxygen {high or low flow}, inotrope use, renal replacement therapy, or ECMO); abnormal cardiac evaluation (specifically coronary arterial dilatation, left ventricular ejection fraction <55%, or arrhythmia); and adverse events (major bleeding, thrombotic event, both, and other events that could be attributed to the study medications).
Follow-up protocol	None (outside the timeframe for capturing the primary outcome).
Sample size	The investigators calculated that recruiting 40 participants in each arm would be adequate to detect an effect size of 2.5 days difference in hospitalization between the trial arms, with α=5% and β=20%.
Data analysis	Intention-to-treat analysis was planned and executed, wherein those randomized were analyzed in the trial respective arms, regardless of what they actually received.
Comparison of groups baseline	The participants in the two trials arms appeared to have similar age distribution, gender ratio, body at weight, body mass index, and ethnicity. The baseline vital signs (heart rate, respiratory rate, oxygen saturation, and capillary refill time) were comparable. There were no apparent differences in the clinical features such as fever, cardiovascular instability features, gastrointestinal manifestations, mucocutaneous features, neurologic manifestations, or respiratory symptoms. Key laboratory parameters such as blood cell counts, CRP, D-dimer level, ferritin, troponin, and brain natriuretic peptide, also appeared comparable.

Box I Summary of the Main Results (Intervention vs Comparison)

Primary outcome

- Median (IQR) duration of hospitalization: 6.0 (4.0, 8.0) vs 6.0 (5.0, 8.8) d

Secondary outcomes

- Median (IQR) duration of hospitalization after randomization: 5.0 (4.0, 7.0) vs 5.5 (5.0, 8.0) d
- All-cause mortality: 0/37 vs 0/38
- Proportion requiring respiratory support (at any time): 10/37 vs 21/38 (P<0.05)
- Proportion requiring respiratory support (after randomization): 3/37 vs 11/38 (P<0.05)
- Median (IQR) duration of respiratory support: 2.5 (1.3, 4.8) vs 2.0 (1.0, 4.0) d
- Proportion requiring inotrope medication (at any time): 10/37 vs 15/38
- Median (IQR) duration of inotrope support: 2.0 (1.3, 3.0) vs 2.0 (1.5, 3.0) d
- Proportion requiring renal replacement therapy (at any time): 0/37 vs 0/38
- Proportion requiring ECMO (at any time): 0/37 vs 0/38
- Proportion with coronary arterial dilatation: 2/37 vs 4/38
- Proportion with left ventricular ejection fraction <55%: 5/37 vs 9/38
- Proportion with arrhythmia: 2/37 vs 1/38
- Proportion requiring ICU admission: 15/37 vs 20/38
- Proportion with pre-specified adverse events: 0/37 vs 1/38
- Proportion with adverse events possibly related to the study medications: 2/37 vs 1/38 (P<0.05)

IvIg. The distinctions are important because sample size calculations can vary.

Being a pragmatic RCT conducted during the peak of the COVID-19 pandemic, treating teams had the liberty to use non-study medications without clearly defining their reasons. Although they were advised to desist for at least 24 hours after randomization, the elegant Sankey diagram [1] suggests that this dictum was not strictly adhered to. Further, as many as 41 of the 75 participants (55%) received non study medications. In fact, two-thirds in the methylprednisolone arm received additional medications, about half of whom received IvIg as well. Similarly, among those allocated to receive IvIg, almost half received other medications, one-third of whom received methylprednisolone. Thus, 23 of 75 (31%) participants ultimately received both medications (though not always concomitantly). It would be valuable to study their data separately, since there is evidence suggesting that combined therapy with both medications may be associated with shorter hospitalization in intensive care units [2]. In this RCT [1], it is difficult to determine whether the comparability of the two arms was related to true therapeutic equivalence, or if was artefactual due to participants receiving non-study medications.

How to explain the apparent beneficial impact of methylprednisolone on the requirement for respiratory support? On the one hand, the need for support were lower in those receiving methylprednisolone. On the other hand, the duration of support was not significantly reduced. Although less than 15% children had respiratory distress and/or need for oxygen at baseline, this increased two to three fold during therapy. Further, although the investigators outlined the extent of 'respiratory support' that could be provided, the data on invasive ventilation, non-invasive ventilation, and supplemental oxygen were not shown. The investigators themselves suggested that baseline differences in the trial arms could (at least) partly explain their findings; however the data presented did not reflect such baseline differences. These observations suggest that the data on respiratory support need more careful evaluation before firm conclusions can be drawn.

The investigators highlighted that their Bayesian analysis showed moderate benefit of methylprednisolone over IvIg. This was based on 80% probability of a shorter hospitalization duration. However, careful examination of the data show that the credible interval of the difference in hospitalization duration,crossed the line of no effect (-2.3 days, 1.0 days) confirming a statistically insignificant result. Of course, ideally the investigators should have categorised the levels of benefit, taking into account the credible intervals. In short, moderate benefit should have been defined as an 80% probability that the credible interval would remain on either side of 0.

To be fair, the investigators did highlight some of the other limitations in their RCT [1]. These included narrowly missing the planned sample size, inadequate power to comment on secondary outcomes and/or subgroups, wide latitude to individual clinicians to deviate from the allocated medications, inability to analyse data of eligible but unrandomized children, absence of blinding, minor distinction between duration of hospitalization calculated from the time of admission, vs. time of randomization; and limiting the follow-up duration to 28 days. These self-declared limitations suggest that the investigators held a balanced approach to their findings. The investigators did not disclose the data of individual hospitals, which can be helpful if there are differences amongst trial sites.

The investigators extensively discussed current as well as anticipated studies addressing the research question, comparing and contrasting their data with other data. However, one aspect was not considered, which is the learning curve in physician behavior and responses during

the pandemic. At the onset, when treatment strategies were unclear, most physicians were cautious in prescribing novel medications, This gave way to liberalized prescriptions of (sometimes) multiple anti-inflammatory agents (evidenced by the frequent use of additional therapies in the enrolled participants), followed by a more tempered approach once the desperation associated with managing PIMS abated somewhat. The last phase with greater experience coincided with less lethal variants of the virus also. Therefore, it would be interesting and instructive to review the trial data during quarterly epochs of the study.

CONCLUSION

This well-designed RCT showed that treatment with methylprednisolone in children with COVID-associated PIMS, resulted in a similar duration of hospitalization, compared to those receiving IVIG alone. Barring the need for (unspecified) respiratory support which was less frequent in those randomized to receive methylprednisolone, other clinical and biomarkers of organ dysfunction were comparable between groups. However, the issues highlighted above, and the frequent use of combinations of both medications, necessitates additional data analysis and external validation, before the two medications can be considered equivalent.

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Pediatric Rheumatologist's Viewpoint

The PIMS-TS shares many clinical features with Kawasaki disease. The use of intravenous immunoglobulin (IVIG) as the initial immunomodulatory agent stems from the recommendations for the management of Kawasaki disease [1]. Subsequently, many large observational studies with propensity score matching were conducted to study the best immuno-modulatory treatment for PIMS-TS using IVIG or steroids alone or in combination [2-4]. For pragmatic reasons, conducting a randomized controlled trial comparing the efficacy of IVIG vs steroids to identify the ideal therapeutic option has been a challenge during the ongoing pandemic.

The RCT by Welzel, et al. [5] gives meaningful insight regarding the choice of initial immunomodulatory agent in the management of PIMS-TS. The results of this RCT have shown a comparable efficacy (duration of hospital stay) of intravenous methylprednisolone (MP) and IVIG. Also, fewer subjects in the group receiving intravenous MP required respiratory support compared with those receiving IVIG. These findings are of relevance to LMICs (low middle-income countries) like ours where the approximate cost of treating a 30 kg child with PMIS-TS using IVIG (2 g/kg) would cost INR 1,00,800 vs INR 3600 for intravenous MP (10 mg/kg/day for 3 days). Apart from the approximate 28-fold cost benefit, the use of intravenous MP as a first-line treatment option for PMIS-TS would also help in combatting the shortage of IVIG during these highly demanding times. These results are in sync with the initial BATS (best available treatment study) group, which showed a comparable composite primary outcome (ionotropic support or mechanical ventilation by day 2 or later, or death) in children receiving either IVIG or glucocorticoids alone [3]. Though the present RCT did not permit the combination of IVIG plus glucocorticoids, a recent study from Channon-Wells, et al. [6] has suggested a marginal gain of combination therapy. Moreover, the coronary outcomes were also similar in all treatment arms (IVIG alone, steroids alone and IVIG plus steroids combination). Given the results of this RCT and the existing evidence, it seems that steroids may be used as a first-line option for the management of PIMS-TS in our settings. However, the author cautions against overdiagnosis of PMIS-TS, particularly amid increasing seropositivity for SARS-CoV-2 and the resultant unwarranted use of steroids.

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Pediatrician's Viewpoint

Since MIS-C, a new hyperinflammatory syndrome that emerged post-COVID-19, was first described there was a dilemma about its optimal management. Due to the overlapping clinical and laboratory features, management was extrapolated based on experiences in treating Kawasaki disease, toxic shock syndrome and macrophage activation syndrome. Anti-inflammatory treatment ranged from intravenous immunoglobulin (IVIG), methylprednisolone, combination of both, to biologics (anakinra, tocilizumab, TNF blockers).Though initially IVIG formed the mainstay of therapy, but with time the use of steroids, specially methylprednisolone, either as monotherapy or in combination with IVIG, significantly increased during the second wave. However, there was no head-to-head RCT showing superiority of one form over the other.

The current study is an open label, multi-center two arm RCT, where MIS-C patients requiring anti-inflammatory treatment were randomized to either IVIG or pulse methylprednisolone therapy. Primary outcome was the length of hospital stay, and secondary outcomes were need for organ support. It is important to note that this is the first publication where the two principal drugs for treating MIS-C are compared through RCT.

The study shows that the median length of hospital stay was similar in both the groups and the need for respiratory support was statistically lesser in the methylprednisolone group, without much variation in the need for inotropes, ICU admission, and cardiac events between the two groups. The authors conclude that intravenous methylprednisolone can be an acceptable first line treatment for MIS-C.

There are several limitations to the study, principal being the small sample size and non enrollment of a sizeable number of patients as it was perceived that they will require a combined therapy with IVIG and methylprednisolone. The data pertaining to the initial clinical characteristics between the enrolled and non-enrolled were not analyzed, thereby raising the possibility of a biased sampling. Furthermore, there is no data on the coronary involvement at follow-up between the two groups which has a bearing on the long-term prognosis.

The study is significant considering that it is a RCT whereby methylprednisolone was shown as non-inferior to IVIG, and being significantly cheaper and globally more readily available, would definitely be a more viable treatment option for middle income countries like ours.

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FELLOWSHIP COURSE IN PEDIATRIC INTENSIVE CARE, PEDIATRIC EMERGENCY MEDICINE AND PEDIATRIC PULMONOLOGY 2023-2024 SESSION

The Institute of Child Health and Hospital for Children, Egmore, Chennai is conducting one year post doctoral fellowship courses in **Pediatric Intensive** C**are, Pediatric Emergency Medicine and Pediatric Pulmonology** under The Tamilnadu Dr. MGR Medical University. These courses will impart specialised knowledge in all aspects of pediatric intensive care, emergency medicine and pulmonology. The pediatric intensive care and pediatric emergency medicine training will empower the candidates to independently manage critically ill children and help establish pediatric intensive care and pediatric emergency medicine departments at other medical colleges and in district hospitals. The Pediatric Pulmonology training will empower the candidates to manage Pediatric pulmonology cases and Bronchoscopy.

The eligibility for the course is M.D(Pediatrics)/Diploma in National Board (Pediatrics)

Name of course (Post doctoral fellowship)	*No of seats*	*course duration*
1. Pediatric Intensive Care	2	1 year
2. Pediatric Emergency Medicine	2	1 year
3. Pediatric Pulmonology	2	1 year

Out of the two seats one will be allotted to service candidate and one will be allotted to private candidate in each course. If seat is not filled up in one category the seat will be allotted to eligible candidate from other category.

The course fee is Rs 50,000 [Rupees Fifty Thousand Only] for all candidates. This should be paid at the time of admission, as demand draft favouring "The Director and Superintendent", Institute of Child Health and Hospital for Children. Egmore, Chennai. 600008 .

Selected service candidates will be deputed for the course and they will be eligible for pay and allowances as per GO. MS. No.156 dt 22.6.2011.

The application form can be downloaded from the Tamilnadu Dr MGR medical university website ***www.tnmgrmu.ac.in***.The rules and regulations of the fellowship course and eligibility criteria are clearly given in above mentioned website.

The filled up application along with a DD for Rs 1000 in favour of "The Director and Superintendent, Institute of Child Health and Hospital for Children" should be sent to the following address and superscribed as

'Application for fellowship in pediatric intensive care, pediatric emergency medicine and pediatric pulmonology'

Director & Superintendent, Institute of Child Health &Hospital for Children Halls Road, Egmore, Chennai.

"Service candidates should submit the application through proper channel."

Last date for submission of application: 10.08.2023, 5 PM; date of entrance exam : 24.08.2023, 10 AM.

Venue: Institute of Child Health and Hospital for Children. Egmore, Chennai. 600008.

Course commencement : 8th September, 2023

The qualifying examination will be of 3 hours duration with total 100 MCQ.
Pediatric Intensive care from General Pediatric and Pediatric Intensive care.
Pediatric Emergency Medicine from General Pediatric and Pediatric Emergency Medicine
Pediatric Pulmonology from General Paediatric and Pediatric Pulmonology

For further details please contact

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Educational Research and Scholarship in India: The Way Forward

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Medical education research (MER) aims to improve the practice of medical education by applying the theory of educational research. Internationally, medical education research has grown exponentially and has established itself as a distinct field. In contrast, in India, the medical faculty is either bogged down by clinical responsibilities, or is busy with biomedical research. The recent initiatives such as implementation of competency-based medical education (CBME) for medical undergraduates, and push coming from regulatory agencies besides National Education Policy have become game changers. The emerging concept of scholarship, takes in to account all scholarly activities in a fair manner. The scholarship of teaching and learning (SoTL) is helpful in connecting teaching with better patient care outcomes through evidence based approach. It also promotes a community of practice to boost research and publication activities. Finally, there is a need to enlarge the scope of research from treating sick children to promoting total wellbeing, which requires interdisciplinary and interprofessional approach to research.

Keywords: *Interprofessional education, Medical education research, Mentoring, Salutogenesis, Scholarship.*

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Medical education research (MER) is a relatively new field, which aims to improve the practice of medical education through application of research methods drawn from educational and social sciences [1]. It uses quantitative, qualitative and mixed-methods to solve research questions [2]. However, being an offshoot of medical education, it has been influenced by quantitative approaches. Of late, the untapped potential of MER is being explored, which forms the theme of this paper [3].

India is one of the largest producers of medical manpower, albeit there is shortage of specialists in many areas. Indeed, medical education has grown exponentially during the post-independence era, both in terms of number of medical colleges and student enrolment. However, it is a matter of constant debate for its relevance, access, quality, outcome and impact on health care delivery. Paradoxically, the research in this field (MER) is yet to take off in a big way, in comparison with the international arena. According to a report based on the number of Google citations, only 5003 papers were published from Indian researchers during the last five decades (1971-2020) [9]; whereas, international journals, published more than 100,000 papers during the same period. As per ten Cate [5] "*medical education research today, has grown across the world, and it has been established as an independent discipline - health professions education scholarship.*" The number of international journals in this field has grown from 3 to 35, during the last fifty years, publishing more than 100,000 articles, contributed by a community of more than 20,000 scholars. Mega international conferences are held by organizations such as Association of Medical Education in Europe (AMEE), attracting more than 3800 participants, every year. More than 26 Masters programs and several PhD programs are in place; Maastricht University alone enrolling more than 100 PhD scholars. On top of it, this field has led several epoch-making innovations like problem-based learning (PBL), objective structured clinical examination (OSCE), Simulation pedagogy, Quality assurance, and Workplace based assessment (WPBA) [5].

In contrast, India has very few journals exclusively devoted to medical education, and very few institutes engaged in research. Publication in reputed international journals of medical education is not easy, and article processing charges (APC) are high. Researchers from India and other low- and middle-income countries (LMICs) also face language, geographical and cultural barrier in reaching out to international journals. The developed countries' contexts are different and the editorial boards do not have adequate representation from LMICs. This has been called as 'the leaky pipeline of publications' [9]. However, some specialty associations in India regularly publish papers in medical education, the Indian Academy of Pediatrics (IAP) being a notable example.

NAILING THE PROBLEM

Lack of awareness about the power and utility of MER is a major hurdle. Though faculty development programs (FDP) have become popular, they are focused on pedagogy of instruction and assessment, rather than educational research.

There is no indepth training in the 'what' and 'how' of MER. The courses and fellowship programs in this area are limited. Some of the existing initiatives include courses conducted by National Teacher Training Centre (NTTC) linked with actionable project, Advanced Course in Medical Education (ACME) launched by MCI/NMC, fellowship program run by four Foundation for Advancement of International Medical Education and Research (FAIMER) regional centers located at Ludhiana, Mumbai, Coimbatore and Manipal, certificate programs run by MEU-INDIA, and Diploma, Masters and PhD programs run by a few health sciences universities. For a faculty member, overloaded with teaching or clinical work, MER is not appealing, as there is no incentive, protected time or additional weightage for publication for the purpose of promotion [4]. Even while assessing research contribution, the regulatory bodies are obsessed with easily measurable criteria thus glossing over intangible criteria of validity, quality, outcome and impact of the research study [6]. The gross indicators like number of publications, and funds generated through research are commonly used. Even the criteria of number of citations and impact factor of the journal can be deceptive. What is needed is valid criteria for assessing the overall contribution of a faculty member to the subject area, by using the 360º approach [7].

Poor research design and flawed methodology are other lacunae [1]. Research problems are often repetitive, convenience-based, and frequently not relevant. Too much emphasis is laid on data collection, without attention to the theory (how the intervention works). A systemic analysis of original papers in medical education published from India over a 10-year period (2006-14) reveals that most of the studies (74.6%) are focused on undergraduate education, using quantitative methods. Only 18.3% of studies used mixed methods, and 7% used qualitative methods [8]. Another limitation in the Indian context is the lack of mentoring support from the leaders, and absence of strong network to support capacity building.

In spite of the limitations cited above, MER has its own unique features which are outlined in **Box I**.

Converting Problems in to Opportunities

Since 2019, the implementation of competency-based medical education (CBME) for the MBBS course has raised several issues, which provide a golden opportunity to the teachers to conduct systematic inquiry and research. The research questions that emerge are – how can we organize foundation course, bring curricular integration, use simulation effectively, teach and assess attitude ethics and communication (AETCOM) modules, redefine our assessment, introduce clinical clerkship, and strengthen internship [10]? There is a vast scope for exploring new interventions and to evaluate their efficacy.

The new postgraduate (PG) regulations have mandated the submission of thesis, poster and one original paper as

Box I Unique Features of Medical Education Research

Purpose and scope

MER can address five types of research questions:

- Descriptive (How is smart phone used in community health?)
- Explanatory (Why does the use of smart phones help/hinder the student performance?)
- Exploratory (How can the smart phone be used effectively for enhancing doctor – patient communication?)
- Predictive (Can use of smart phone predict future performance of doctors?)
- Evaluative (What is the impact of a 'smart phone training program' on the performance of final year MBBS exam?)

Methods used

Quantitative methods (focus on numbers), but more often Qualitative methods (focus on words), and mixed methods.

Ethical issues and sampling

Focus on giving benefit to the whole class/cohort, informed consent, and sensitivity of teacher-student relationship while using observation or interview; Universal or purposive sampling.

Research setting and cost

Classroom, laboratory, field or community; no need for sophisticated equipment or resources; hence, cost effective.

Tools, and techniques employed

Experiments are not feasible in MER as many variables cannot be controlled. Descriptive studies, observations, case studies and program evaluation are commonly used.The tools and techniques include, questionnaire, interview, focus group discussion, tests, checklist, rating scales, documents, photography, videography etc., Tools are unlimited, depending upon the purpose

Data collection, analysis

Only quantitative data deploy statistics; qualitative data follows transcription, coding, identification of themes and triangulation to establish authenticity.

Interpretation

Focus on contextualization rather than generalization

requirements for awarding PG degree [11]. This has stimulated a large number of training programs (online and offline) and production of books and resources on research, including MER [12]. Thanks to the emergence of open access journals and online platforms, the problem of shortage of literature is being resolved [13]. However, new applications such as Chat GPT using artificial intelligence, have posed new challenges to circumvent their misuse by unscrupulous elements. This is an area of concern to the researchers.

THE SCHOLARSHIP OF TEACHING AND LEARNING

Scholarship, in common language, means monetary support, a fund or grant for pursuing higher studies. But scholarship in academics means a scholrly activity leading to a valuable contribution to the academic community [13]. To be considered as a scholarly activity, it must satisfy five criteria, called the five Ps: Product of high quality, whose process is explained, peer reviewed, placed under public domain, and which serves as platform for further work. Traditionally, only research satisfied all these criteria and was therefore, considered as gold standard for measuring scholarship [15]. Boyer [16] questioned why research alone is considered as the scholarship, and why not teaching or clinical work, which are on par with research. He, therefore, defined four types of scholarships: scholarship of research, teaching, application and integra-tion [16]. Scholarship of teaching has been later expanded as scholarship of teaching and learning (SoTL) to capture all activities of a teacher that are of high standard, process explained, peer reviewed, and serve as a platform for fur-ther work. SoTL differs from scholarly teaching, in that it assumes high value because of peer review process and wider application for practice [17].

The concept of SoTL is gaining wide acceptance because of its potential to form a network of scholars. This is referred to as community of practice, which can mentor, support, handhold, and empower new researchers [18]. The experience of FAIMER fellowship program is an example of community of practice. The professional associations like IAP already serve as a community of practice.

The assessment of SoTL achieved by a faculty member is a contentious issue. It requires Multiple Source Feed-back (MSF), a 360° approach, which includes a wide variety of evidence such as workshops organized, presentations made at local, national and international conferences, role played as speaker, moderator and chairperson, publication of articles in peer-reviewed journals, member of a crossinstitutional or national committee, reviewer, member of editorial board, editor of journal or book, and role played as expert or consultant at various level [17]. For documenting the achievement on a regular basis, it is necessary to introduce a portfolio. The portfolio helps in self-reflection. It should be reviewed periodically, by a mentor who gives feedback, and motivates the mentee for enhancing the scholarship.

THE WAY FORWARD

Conventionally, research in pediatric education has addressed pedagogical issues related to teaching, curriculum, or assessment of students. It is time for a change. In recent times we hear a lot of behavioral and psychosocial problems of children beyond physical health. Growing examination stress, delinquent behavior, bullying in schools, besides child abuse, child labor and trafficking, early marriage and assaults on girls. There is a need to address mental, emotional, social and moral development of children in a holistic manner. The overall growth and development of children, including cognitive, emotional development combined with human values, is a joint responsibility of pediatricians, parents, schools and civil society.

This implies enlarging the focus of curriculum and research from treating sick children (curative approach or pathogenesis) to promote wellbeing of children (salutogenesis) in a holistic manner. One may argue that this task is 'utopian and beyond the scope of medical education', especially in view of the shortage of pediatric specialists. The present workforce of pediatric faculty and researchers is too little to handle the 444 million child population of India. However, this agenda is futuristic and unescapable in the national interest.

The way out is to collaborate with the schools, colleges, universities and non-governmental organization (NGO) at large, to take up interdisciplinary and interprofessional research to address overall wellbeing of children. This augurs well with the spirit of National Education Policy, 2020 [19]. The welfare programs should be supported by program evaluation for evaluating such programs and determining their impact [15]. It is a robust area of research utilizing both qualitative and quantitative approaches to take decision alternatives.

It is heartening to note that steps are already being taken in this direction. A notable example is Health Promoting Schools [20]. This is a school health program linked with accreditation of schools undertaken jointly by Non Communicable Disease Prevention Academy (NCDPA) and IAP. A statement of 10 commandments was endorsed by the Executive Board of IAP in March, 2022 [21]. Besides physical fitness, the program addresses hygiene, food safety issues and provision for counselling children with learning disorders. Development of human values among children is a matter of universal concern. Pediatricians being the healers are uniquely empowered to chip in this ambitious program, with some orientation programs in ethics and medical humanities.

A large number of NGOs and voluntary organizations are working in India for the welfare of children [21]. For example, Sri Sathya Sai Seva Organization (SSSO), works for the development of five core human values: truth, righteousness, peace, love, and non-violence, and one of their main wings is called Balvikas. The weekly training imparted by their trainers includes story-telling, prayer, group singing, meditation (silent sitting), and service (*seva*) activities [22]. The researchers in pediatrics can establish fruitful collaboration with such organizations, especially in the area of growth and development, program planning and evaluation. This results in a holistic approach, minimizes the cost of research and maximizes the outcome and impact.

In conclusion, there is a need to redefine our research priorities, polish our research methodologies, and reimagine the system of assessing the research. The faculty should be proactive in understanding and applying MER in their diverse settings. The managements and regulatory authorities should go out of the box to look at research contribution from a broader perspective of overall benefit to the society [23]. With concerted efforts from faculty, professional organizations, government and the civil society, India could make a sea change in the content and the contours of future MER. This ascribes a bigger role for researchers to focus on interdisciplinary and interprofessional research. Hopefully, this will help Indian pediatric educators to become game changers, and be on par with international leaders.

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USPSTF and ISPAD Guidelines on Screening for Prediabetes and Type 2 Diabetes in Children and Adolescents

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The rising trends of obesity, metabolic syndrome and diabetes in adults are worrisome globally. The majority of antecedents to adult non-communicable diseases begin in childhood. Type 2 diabetes is recognized as one of the major diseases that contribute to the NCD burden in childhood. Recently, the US Preventive Services Task Force (USPSTF) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) released their guidelines on diagnosis and management of prediabetes and diabetes in children targeted screening for youth-onset type 2 diabetes is suggested in at-risk children (obese, positive family history of type 2 diabetes, etc.), while the role of screening asymptomatic children is not substantiated. Obesity and insulin resistance are important risk factors for type 2 diabetes. The cutoffs of fasting plasma glucose for the diagnosis of prediabetes and diabetes are >100 to 125 and ≥126 mg/dL, respectively. This update briefly summarizes the recommendations on screening for youth-onset prediabetes and type 2 diabetes.

Keywords: *Hyperglycemia, Metabolic syndrome, Obesity, Pediatric, Oral glucose tolerance, T2DM.*

Prevalence of type 2 diabetes (T2D) has been increasing worldwide [1,2], with data from US and other western countries reporting a steep rise in incidence of prediabetes closely matching as of adults [3]. As per Comprehensive National Nutrition Survey (CNNS), 2016-2018, one percent of school-age children and adolescents were diabetic and one in ten school-age children and adolescents were pre-diabetic [4]. Type 2 diabetes in childhood and youth has long term implications on metabolic and cardiovascular risk in adulthood [5,6]. Youth-onset T2D is more common in girls than boys, more severe with faster loss of beta-cell function than adult onset T2D, and shows familial clustering. This makes early identification and prevention of prediabetes and T2D important. Youth with T2D have lower insulin sensitivity, higher insulin resistance (with higher C-peptide and insulin levels) and poorer response to glucose lowering drugs/ insulin than adults [7].

In 2000, the American Diabetes Association (ADA) and American Academy of Pediatrics recommended screening for T2D of asymptomatic overweight [body mass index (BMI) ≥85th percentile for age and sex] youth aged 10 and older (or after onset of puberty) with at least 2 of the following risk factors: non-white race, family history of T2D, maternal gestational diabetes, or signs of insulin resistance [8]. In 2018, the ADA expanded this recommendation to include all overweight youth with one or more of these risk factors [9]. Screening was recommended by using fasting plasma glucose (FPG), 2-hour plasma glucose after 75-g oral glucose tolerance test (OGTT), or HbA1c [10]. A repeat screening is recommended at a minimum interval of every 3 years, if tests are normal. In the presence of pre-diabetes, increasing BMI, worsening cardiometabolic profile and a strong family history of T2D, annual screening may be necessary [9].

In 2021, the US Preventive Services Task Force (USPSTF) recommended screening for prediabetes and T2D in adults aged 35 to 70 years with overweight or obesity but no recommendation was issued for children and adolescents [11]. The task force evaluated the evidence on screening of children and adolescents for prediabetes and T2D for populations and settings relevant to primary care in the US to inform an updated recommendation by the USPSTF [12]. The new USPSTF guideline is focused on the following aspects of screening: the benefits and harms of screening for prediabetes and type 2 diabetes; the benefits and harms of interventions for screen detected prediabetes and type 2 diabetes or recently diagnosed type 2 diabetes; effects of screening and interventions on health outcomes, including mortality, cardiovascular morbidity, chronic kidney disease, amputation, skin ulcers, visual impairment, neuropathy, and quality of life and the evidence on the effectiveness of interventions for prediabetes to delay or prevent progression to T2D.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) also released its consensus guidelines on T2D in children and adolescents in 2022 [13]. These are chiefly based on data from Treatment Options for Type 2

Table I Recommendations on Screening and Diagnosis of Prediabetes and Type 2 Diabetes

USPSTF, 2022 [12]	*ISPAD, 2022 [13]*
Screening of children and adolescents younger than 18 y	
Current evidence is insufficient to assess the balance of benefits and harms of screening for T2D in asymptomatic children	Targeted screening* to identify cases of T2D can be considered after onset of puberty (state of physiological insulin resistance) and adolescents (Grade 1) or after 10 y of age in youth who have BMI ≥85th percentile for age and sex and risk factors for T2D. (Grade A) If tests are normal, repeat screening should occur at a minimum every 3 years. Annual screening may be necessary if BMI is increasing, cardiometabolic risk profile is worsening, there is a strong family history of T2D, or evidence of pre-diabetes. HbA1c and OGTT both can be used to screen high-risk youth; HbA1c suggested by NHANES
Risk factors	
Obesity and excess adipose tissue, especially central obesity, are important risk factors Family history of diabetes (including gestational diabetes) is also a strong risk factor	• Family history of T2D in the first- or second-degree relative. • Race/ethnicity (Black, Native American, African, Latin American, Asian, Middle Eastern, Pacific Islander, Australian Indigenous, Canadian First Nations). • Signs of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS), low birth weight (small for gestational age) or high birth weight • Maternal history of T2D or gestational diabetes during the child's gestation • Current use of weight promoting atypical antipsychotic agents • Occurrence of hypertension, dyslipidemia, NAFLD, PCOS and OSA in childhood
Diagnosis of prediabetes	
A FPG level of ≥100 to 125 mg/dL (5.6-6.9 mmol/L), or an HbA1c level of 5.7% to 6.4%, or a 2-hour plasma glucose level of ≥140 to 199 mg/dL (7.8-11.0 mmol/L) after OGTT	FPG ≥100 to 125 mg/dL (5.6–6.9 mmol/L), or 2-hour plasma glucose is ≥140–199 mg/dl (7.8-11.0 mmol/L) after an OGTT (after 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water), or HbA1c 5.7%-6.4% (39-47 mmol/mol)
Diagnosis of T2DM	
FPG level ≥126 mg/dL (7.0 mmol/L), or an HbA1c level of ≥6.5%, or a 2-hour glucose level ≥200 mg/dL (11.1 mmol/L) on OGTT, or in a patient with classic symptoms of hyperglycemia, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)	FPG ≥126 mg/dL (7.0 mmol/L), or 2-h plasma glucose on an OGTT ≥200 mg/dl (11.1 mmoL/L), or random plasma glucose ≥200 mg/dL (11.1 mmol/L), or HbA1c ≥6.5% (48 mmol/mol)
Management of prediabetes	
Management principles include lifestyle modification, healthy diet and increased physical activity. Inadequate evidence to show improved health outcomes with treatment of prediabetes or screen-detected T2D No studies that evaluated potential harms with screening for prediabetes in asymptomatic children	Testing for islet autoimmunity recommended in youth diagnosed with T2D, or overweight/obese pubertal subjects with T1D

Modified from United State Preventive Services Task Force (USPSTF) Recommendation Statement, 2022 [12] and International Society for Pediatric and Adolescent Diabetes (ISPAD), 2022 [13]. FDA: food and drug administration; FPG:fasting plasma glucose; HbA1c: glycosylated hemoglobin; NAFLD:non-alcoholic fatty liver disease; NHANES:National Health and Nutrition Examination Survey; OGTT:oral glucose tolerance test; OSA:obstructive sleep apnea; PCOS:polycystic ovary syndrome; T1D: type 1 diabetes; T2D: type 2 diabetes.

Diabetes in Adolescents and Youth (TODAY) clinical trial, the SEARCH for Diabetes in Youth (SEARCH) study, and new data from the Restoring Insulin Secretion (RISE) study [13].

This update covers the recommendations from two guidelines (**Table I**) on the risk factors, diagnosis and subsequent management of prediabetes in youth and young adults.

GUIDELINES

The use of a single of the three parameters (FPG, 2h-OGTT, HbA1c) for the diagnosis of prediabetes or diabetes has been questioned. The preanalytical stability of plasma glucose is low requiring immediate sample processing after collection. Performing a HbA1c is simpler as it does not require a fasting state, shows less variations on daily basis and has greater preanalytical stability. However, the process of estimation needs standardization, is costly and levels may be affected by age, ethnicity and haemoglobin variants. The diagnosis based on only testing using HbA1c could correctly detect only 30% of those with diabetes. It is recommended that two abnormal results should be reported in the same sample or two separate samples (using the repeat initial test or an alternate test). Unequivocal high or abnormal single test is confirmatory, while borderline test results should be repeated in 3-6 months using standardized process of measurement [9,10].

The USPSTF guidelines excluded non-English-language articles. The review was limited to asymptomatic children and focused on the screening for prediabetes or type 2 diabetes. It did not cover diagnostic testing of symptomatic children or those with signs of insulin resistance, diagnostic testing of children with conditions associated with insulin resistance, or screening for type 1 diabetes. This review was not applicable to pregnant women and children and adolescents with symptomatic diabetes (eg, weight loss, polyuria, blurred vision, headache). In addition, studies of children and adolescents who had diabetes for more than 1 year or with more advanced diabetes were excluded, aiming to identify the studies with good applicability to a screen-detected population.

ISPAD guidelines were mainly focused on the diagnosis and management of children with T2D. A special emphasis has been made to address the mental health and other socio-demographic and cultural determinants of health that play an important role in determining success of lifestyle interventions. The need for evaluating preventive strategies for T2D in the youth was also highlighted.

INDIAN SCENARIO

At present, there is insufficient data on mass screening for diabetes in children and adolescents. Data from ICMR diabetes registry for young-age-at-onset (YDR) from India during 2000-2011 showed T2D burden as 25.3% among all cases [14]. A comparison of newly diagnosed T2D in YDR between 2006-2012 with SEARCH registry data of United States showed older age at diabetes onset in Indian children (16.1 and 14.7 years), higher HbA1c (9.9 and 7.2%), and higher proportion of high socioeconomic class (88.5 and 23.6%), respectively, than in SEARCH registry. A lower proportion of cases were overweight or obese in YDR than SEARCH (58.2 and 85.4%), as per uniform WHO cutoffs, after accounting for missing data [15]. The definition of elevated BMI for Indian children and adolescents, however, is defined at lower cutoffs as overweight above 71 and 75th centile for Indian boys and girls, and obesity above 90 and 95th centile, respectively. This may be relevant in considering an extrapolation of these guidelines in the Indian context.

The feasibility, cost-effectiveness and validity of testing using a combination of one or more of the three diagnostic criteria of prediabetes/ diabetes for screening in India needs to be further evaluated.

CONCLUSION

With an increase in prevalence of youth-onset T2D, the need for suggesting screening for prediabetes and T2D in children and adolescents has been discussed in the USPSTF guidelines. The USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for T2D in asymptomatic children and adolescents. Screening in at-risk children and adolescents is suggested by the USPSTF and ISPAD guidelines, that may further need to be modified for implementation in the Indian settings.

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Down the Memory Lane of Computers in Medicine

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Computers are now an integral part of our day-to-day life, and this is also true for the healthcare sector. Fortunately, the digital computer which had reduced from the room-sized ENIAC of the 1940s to the refrigerator-sized IBM mainframe of the 1950s to the 'minicomputers' of the 1960s could implement algorithmic search methods at extraordinary speed [1].

"*For man isn't a machine and doesn't like being used as if he were a machine.*"

– correctly written by Laugesen in 1973, in his guest article in *Indian Pediatrics* [2]. In this article, the author appropriately mentioned the role of a doctor, a team leader or coach or manager, who can manage his own and patients' health by training and guiding the ground-level semi-skilled staff. A digital revolution has happened in the health sector during the past half century. Smart use of computers helped us to reduce our burden of structuring the health sector in academic, administrative, security- and service-acquainted patients care, and change the clinic/hospital to the smart clinic/ hospital [3].

Since the digital revolution started in the medical field, there's always a fear that technology may replace the human brain and health professionals and it may become a mechanical industry. Critics expostulated as Zworykin put it, *"to the misconception that we were trying to replace the doctor by a cold, hard, calculating machine,*" [1] fearing distraction of personal bonds between doctors and patients. Some physicians greeted the computer's rote nature as a result of errors arising from being 'too human,'while others raised concerns about the potential for the computer to introduce additional errors, either due to software bugs or the inherent human biases embedded within the code [1]. In contrast to that, digital technology has revolutionized the healthcare industry, furnishing new tools and openings for perfecting patient care and becoming a helping tool rather than throwing out health professionals [4].

THE PAST

Fifty years ago, medical professionals and engineers held a common vision of computers with immense storage capacity and lightning-fast processing capabilities that could assist in making diagnoses, storing medical records, and facilitating the exchange of information. Today, computers are an essential part of modern medicine, and their use will continue to grow as technology advances. The past, present, and future of technology in medicine have been and will continue to be transformative [1].

An overview of how technology has evolved and where it may be headed in the future is provided [4] **(Fig. 1)**. In India, the digital revolution in medicine has been a gradual process over the past few decades, but has gained momentum in recent years due to advancements in technology and increased government support. In the 1990s, telemedicine was introduced in India; EHRs were first implemented in India in the early 2000s. In 2018, the Indian government launched the National Health Stack (NHS) which is a digital infrastructure for healthcare that includes an integrated health information system, telemedicine services, and other digital health solutions. The rapid spread of the COVID-19 pandemic has expedited the integration of digital health solutions within India, such as telemedicine, online pharmacies, and digital health records, as people avoid in-person consultations and hospitals are overloaded. Fundamentals and laws about utilization of digital technology in medicine are now more well defined.

WHAT WE HAVE ACHIEVED TILL NOW

The evolution of technology in the medical field over the last 50 years has been significant and has transformed many aspects of healthcare delivery. Here are some examples of the key technological advancements that have emerged over this time period:

Electronic medical records (EMRs): Back in 1964, inventor Vladimir Zworykin cautioned that the accumulation of medical data was outpacing the cognitive capacity of physicians.[1]. Now, EMRs allow healthcare providers to record, store, and share patient information such as medical history, medications, allergies, and immunizations digitally. EHRs enable providers to access patient information quickly and easily, resulting in more coordinated care which can improve the quality of care. This technology streamlines the record-keeping process and reduces errors. Electronic memories can now be considered as valuable supplements and extensions of a physician's human memory, having replaced paper records in numerous healthcare environments.

Clinical decision support systems (CDSS): CDSS are software programs designed to aid healthcare providers in making clinical decisions. CDSS uses algorithms to analyze patient data and provide recommendations for diagnosis, treatment, and medication. The utilization of CDSS can support healthcare providers in making decisions that are not only more precise and efficient but also contribute to improved patient outcomes.

Medical imaging: The advent of digital technology has brought significant enhancements to medical imaging modalities, including *X*-rays, CT scans, and MRIs. Computers are employed to analyze medical images, and advanced algorithms can help doctors quickly and accurately identify abnormalities and treat a wide range of conditions more accurately and effectively.

Telemedicine: Telemedicine uses video-conferencing and other technologies to connect health professionals and patients remotely. This approach can improve access to healthcare for people in remote areas or with limited mobility, reduce costs, and improve patient outcomes. Telemedi-cine can also be used to monitor patients with chronic conditions, such as diabetes or asthma, from a distance.

Wearable devices: Wearable devices such as fitness trackers and smartwatches can track vital signs and other health metrics, allowing patients to monitor their health and share data with their healthcare providers, which can improve patient engagement and outcomes.

Mobile apps: Mobile apps can provide patients with access to healthcare resources, including educational materials, medication reminders, and communication with their healthcare providers. Online medical calculators help doctors to calculate accurate dosage immediately without any mistakes.

Medical research: Computers are used to analyze large datasets of medical information, including clinical trials and patient records. This helps researchers identify patterns and trends that can lead to new medical discoveries. Data analytics can also help medical professionals to identify areas of inefficiency and opportunities for improvement, enabling them to make data-driven decisions.

Continuing medical education (CME): Computers are used in medical education to provide interactive and engaging learning experiences. Simulation technologies allow medical students to practice procedures in a safe, controlled environment. Online courses offer medical professionals the opportunity to remain abreast of the latest advancements in medicine, enabling them to enhance the quality of care they deliver. It allows medical professionals to take advantage of the knowledge of world-class experts without moving from their place.

Robotics: Robotic technologies have transformed surgical procedures, enabling providers to perform minimally invasive procedures with greater precision and accuracy.

Personalized medicine: Advances in genomics and other areas of medical research have enabled providers to deliver more personalized care that is tailored to each patient's needs and characteristics.

Supply chain management: Technology can help medical professionals to manage their supply chain more efficiently, reducing costs associated with waste, inventory management, and purchasing.

Digital Developments in the Field of Pediatrics

Computers and digital technology have played a significant role in pediatric patient care and also helped pediatricians to improve the quality of care provided to children across the world. Over and above points discussed, leveraging these tools, has been able to provide world-class education and allows pediatricians to connect and collaborate with each other. Online communication platforms support pediatricians in their work, share information, exchange ideas, and work together to improve the quality of care they provide. Telemedicine platforms utilize digital technology to connect pediatricians with patients and other healthcare providers, improving access to healthcare for children in need. Now we cannot think of PICU care without the use of digital technology in record keeping, ventilator care, and remote monitoring. Virtual and augmented reality (VR/AR) technology is being developed and tested for use in pediatrics, offering new ways to engage and educate young patients.

IAP and Digital Technology

The Indian Academy of Pediatrics (IAP) is the premier professional body of pediatricians in India. The central IAP office has the latest computer equipment with excellent NASH storage with data backup. IAP has adopted email as official communication with its 40000 plus members now,

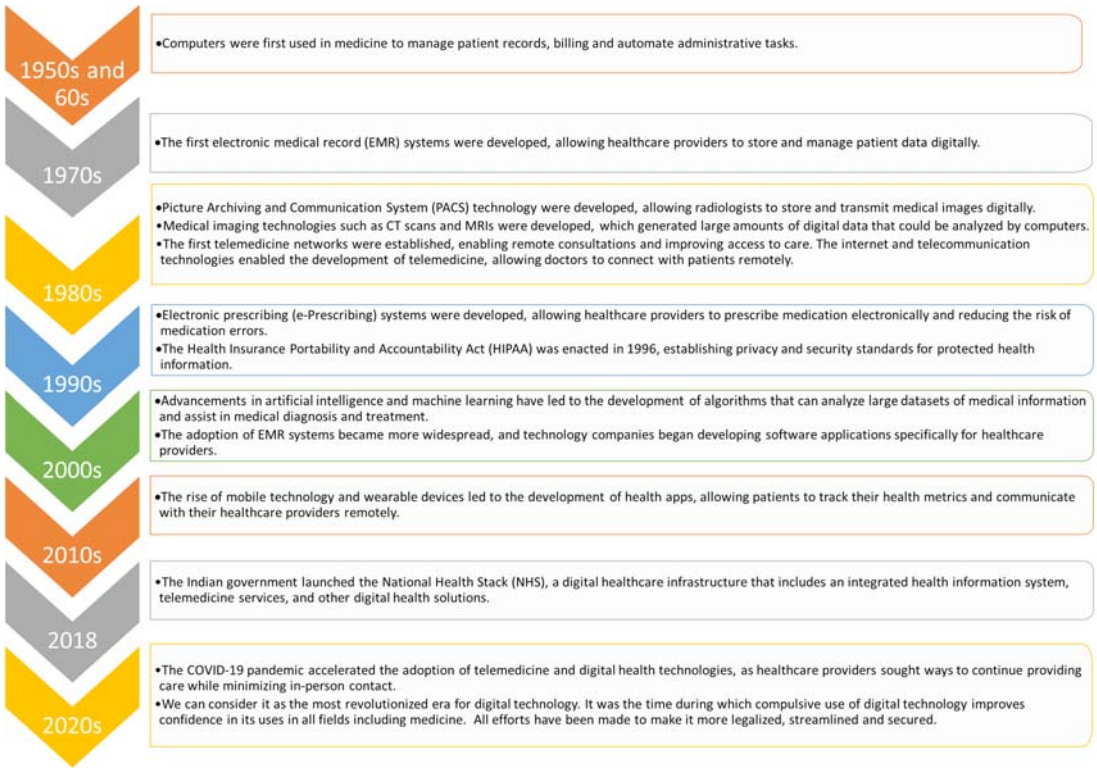

Fig. 1 An overview of how technology has evolved and where it may be headed in the future.

which reduces the printing burden along with real-time dissemination of the messages. It now has a state of the art website providing the best platform to get all details about the IAP functioning along with dissemination of the latest updates in IAP and pediatrics in one place. The computer and Medical Infor-matics Chapter of the IAP had also been started by the techno-savvy members of the IAP in 2002 for sharing knowledge of technology in medicine, which was officially registered in 2012.

During the COVID-19 pandemic, IAP carried out its activities through its digital platform– dIAP. Since then, all scientific online activities have been stored as a digital library on dIAP, which can be accessed by the member at anytime from anywhere. The official journals of the IAP - *Indian Pediatrics* and *Indian Journal of Practical Pediatrics* are available digitally on their international standard websites for easy reference. IAP adopted digital technology for its administrative purpose also, including election – E-voting and E-nomination, new members registration, etc. Pedcard, a digital ID card for the members, has been added recently.

Words of Caution

While the present era of precision medicine, neural networks, and wearable technologies involves distinct objects, networks, and users compared to the earlier era of "mainframe medicine," numerous fundamental issues persist. It is important to note that not all the challenges in digital medicine can be resolved solely through the application of new technologies. Supporters contended that medical computing had the potential to alleviate the escalating shortage of physicians and enable doctors to allocate more attention to human interaction. However, it is crucial to acknowledge that there may also be associated side effects stemming from its utilization. Some potential side effects of digital technology used in medicine are listed:

Information overload: The vast amount of medical information that is available online can be overwhelming for both patients and healthcare professionals. It can be difficult to distinguish between reliable and unreliable sources of information, which can lead to confusion and misinformation.

Technical issues: Digital technology can be prone to technical issues, such as software glitches, internet connectivity problems, and hardware malfunctions. These issues can lead to delays and errors in patient care and can also increase healthcare costs.

Data privacy and security: The use of digital technology in medicine requires the collection and storage of sensitive patient data, which can be vulnerable to cyberattacks and data breaches. These breaches can compromise patient privacy and confidentiality and can also have legal and

financial consequences for healthcare providers.

Digital divide: Not all patients have equal access to digital technology, which can create disparities in healthcare access and outcomes. Patients who lack access to digital technology may miss out on the benefits of telemedicine.

Medical errors: While digital technology can help reduce medical errors, it can also introduce new types of errors, such as incorrect data entry, misinterpretation of test results, and failure to recognize important information due to alert fatigue.

Overall, the side effects of digital technology in medicine can be mitigated through careful implementation, training, and oversight. By addressing these potential issues proactively, healthcare providers can maximize the benefits of digital technology while minimizing its potential harm.

THE FUTURE

In the future, technology in medicine is likely to continue to evolve and advance rapidly. Several emerging technologies, such as artificial intelligence (AI), nanotechnology, virtual and augmented reality, and gene editing, are anticipated to have a substantial impact on the future of medicine. These innovations hold the potential to revolutionize various aspects of healthcare, ranging from diagnosis and treatment to personalized medicine and patient care. AI, as an example, can be utilized to analyze extensive volumes of medical data, thereby identifying patterns and offering personalized treatment recommendations. Nanotechnology holds immense potential to revolutionize drug delivery by enabling doctors to precisely target specific cells or tissues with greater accuracy. Virtual and augmented reality have the potential to be utilized in simulating medical procedures, providing doctors with a safe and controlled environment to practice and enhance their skills.Gene editing technologies may be used to cure genetic diseases or prevent them from developing in the first place.

IAP also stands for interactive application programming, which refers to the process of developing computer programs that interact with users in real time. By developing interactive applications that allow patients to track their symptoms and communicate with their healthcare provider in real-time, provide real-time feedback, healthcare providers can more effectively manage health conditions and provide better care to patients. This would enable providers to monitor patients more closely and adjust treatment plans as needed. IAP could also be used to develop a virtual training program for healthcare providers, allowing them to practice procedures and scenarios in a simulated environment.

CONCLUSION

Overall, computers are a vital tool in modern medicine, and their use will continue to grow as technology advances. The evolution of computers and digital technology in medicine has transformed the healthcare industry, providing new tools and opportunities for improving patient care. Digital technology has transformed the way healthcare is delivered, making it more efficient, accessible, and patient-centered. By leveraging technology to streamline their operations and improve patient outcomes, medical professionals can achieve greater financial success while delivering high-quality care.

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Learning Preference of Medical Undergraduate Students: A Multi-Institutional Survey

This cross-sectional multi-institutional study was conducted to analyze learning preference among medical undergraduate students (*n*=1659) in four colleges in Haryana. VARK questionnaire (v8.01) was administered through designated study leaders of the respective institutes. The most preferred learning modality was kinesthetic (21.7%), which favors experiential form of learning, most suited for teaching-learning of skills in medical curriculum. More information on the learning preference of medical students is needed to optimize learning outcomes.

Keywords: *Kinesthetic, Metacognition, Self-awareness, VARK.*

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Each individual has his/her own way to acquire and process information and this is referred to as 'learning preference/style' [1]. Through the onion ring multilayer framework of learning style construct, it has been accepted that cognitive personality forms the innermost layer while the outermost layer, which is also the least stable, is formed by information processing [2]. This outermost layer is more likely to be influenced by external factors, and learning style frameworks like Kolb's, VARK etc. test this layer by analyzing how individuals use their dominant learning styles to acquire information. The VARK tool is an acronym for visual (V), aural (A), read/write (R) and kinesthetic (K) styles of learning, and defines individual learning styles based on four sensory modalities used by individuals to assimilate new information [3,4]. It has been a preferred tool with researchers since it processes learning preferences, and not personality. It is simple to use, time efficient and has excellent reliability as well as validity. The tool has been validated across a varied spectrum of learners, ranging from undergraduate medical students, students of nursing, physiotherapy to other allied healthcare professionals [5-9].

This cross-sectional, multi-institutional study of VARK learning preference was conducted among Bachelor of Medicine and Surgery (MBBS) students (medical undergraduates) in four different colleges in the state of Haryana, aiming to analyze their learning preference. We also planned to utilize this data to increase self-awareness of our students about learning styles, which we plan to evaluate in the long-term.

The study was done through the designated coordinators of the Medical Education Units of the four institutes (Institute no. 1, 2, 3 and 4, respectively). After taking written informed consent, VARK questionnaire latest version (v8.01) was administered to the students in paper form. It consists of 16 questions with four options each and respondents could select more than one response for each question. Probability sampling technique was used to estimate the representative number of students in total, from each institute and each professional year. Score of each participant was computed based on the recommended scoring system and entered into a spreadsheet provided by VARK officials, which was then mailed to them for analysis. Analysis was undertaken by the VARK producers themselves and the standard VARK algorithm was used for analysis [3]. Unimodal, bimodal and trimodal have been used to represent preferred use of one modality (V,A,R,K) or a combination of two (VA, VR, VK, AK, AR, RK) or three modalities (VAR, ARK, VAK, VRK), respectively. Multi-modals are those who do not have a definite standout mode with one preference scoring over others and; these are further divided into VARK Type-I, Type-II and VARK Transition. Type-I are the ones who have two, three or four almost equal preferences in their VARK scores. They are flexible in their communication prefe-rences and switch from one mode to another depending on what they are working with. VARK Type-II are not satisfied until they have used all of their preferred modes. They take longer to gather information from each mode and, as a result, often have a deeper and broader understanding, owing to which their decision making and learning may be better. The term VARK Transition is used to describe those who fall between type-I and II. At the end, a video was created, summarizing the results of the study and their significance for the students, and was circulated amongst them.

A total of 1659 students were recruited (58.9% males) from four institutes; BPS GMC, Khanpur Kalan; PGIMS Rohtak; KCGMC, Karnal and Adesh MC, Kurukshetra (referred to as institute no. 1,2, 3 and 4, respectively). The largest student participation was from institute no. 2 (697; 42%) while the maximum response rate was from institute no. 4 (388/450; 86.2%). Considering the professional years, maximum representation was from year-1 (571; 34.4%), followed by year-2 (495; 29.8%), and the response rate was also maximum among year-1 students (571/640; 89.2%). The category in the order of preference was unimodal (39.8%), bimodal (24.5%), multimodal (23.2%) and trimodal (12.5%) (**Table I**). On further analysis of

Table I Learning Styles Among Medical Undergraduates (*N*=1659)

Learning styles	*Number*
Unimodal, *n*=661	
V	38 (2.3)
A	246 (14.8)
R	17 (1.0)
K	360 (21.7)
Bimodal, *n*=407	
VA	15 (0.9)
VR	6 (0.4)
VK	35 (2.1)
AR	10 (0.6)
AK	324 (19.6)
RK	17 (1)
Trimodal, *n=207*	
VAR	4 (0.2)
ARK	48 (2.9)
VAK	147 (8.9)
VRK	8 (0.5)
Multimodal, *n*=384	
Type I	115 (6.9)
Type II	193 (11.6)
Transition	76 (4.6)

V: Visual; A: Aural; R: Read/Write; K: Kinesthetic. Type I multimodal: two, three or four almost-equal preferences in their VARK scores; flexible in their communication preferences and switch from mode to mode. Type II multimodal: not satisfied until they have had all of their preferred modes. VARK transition: fall between type I and II.

distribution pattern in each category, the most preferred learning style was K-type, both overall (360/1659; 21.7%) and amongst unimodal (360/661; 54.5%) (**Table I**). A total of 79.4% (1323/1659) had atleast some preference of kinesthetic mode of learning in one or the other forms, either unimodal or in different combinations.

Literature regarding use of learning preference in healthcare has been very controversial. On one hand is the meshing hypothesis, which states that the learning outcomes could be highly achieved, if teaching was matched with predominant learning style of the learner [10]. On the other hand, there is literature which refutes the educational value of accommodating students' learning style preferences to improve learning outcomes [11]. Our study was not intended to compare learning preferences across different groups or to correlate the same to the examination scores, as done in many other studies. Instead we aimed to generate a representative data of learning preference of our undergraduates under the same university curriculum, and utilize it for self-awareness and improvement. Lindsey, et al. [12] have previously noted that none of the published studies have described use of learning style frameworks for increasing self-awareness.

In our study, K-mode of learning was the most preferred type. The K-type learning, by definition, refers to perceptual preference, related to the use of experience and practice (simulated or real). It includes demonstrations, simulations, videos, as well as case studies, practice and applications; key is the reality or concrete nature of the example. People with this preference learn from experience of doing something which in medical curriculum can be referred to as 'experiential learning.' K-type has been reported as the most preferred learning style among healthcare students in few other studies [6,8,9]. There is one Indian multi-institutional study in which VARK was administered on first and second year medical students. Incidentally, in their study too, the most preferred learning styles were the same as ours i.e., K and A [7]. In a study on health professional educators, the authors emphasized that K-mode of teaching can be appropriately matched to the content being taught, such as procedures [13]. Powerpoint, which stimulates only visual learners, is one of the least preferred modality in our study as well as several others [7] but is ironically, still the preferred mode of teaching in many medical institutes.

The concept of metacognition has recently been a topic of discussion among health professional educators (HPE). The theory of Metacognition, as created by John Flavell, refers to 'thinking about thinking.' It is a process of higher-order consciousness that involves active monitoring of one's own learning. With an impending need to engage in self-regulated lifelong learning, it is important that health-care students develop the habit of active monitoring of their own learning [14]. Piza, et al. [13] have suggested that besides teaching of 'content,' HPE need to focus on teaching students 'how to learn' and on facilitating higher order thinking procedures like metacognition. In view of available literature and our own study results, we hypothesize that students, when aware of their learning styles, will be able to enhance learning by utilizing the correct active strategies suited to their learning styles.

There are certain limitations of our study. Although, we intended to increase self-awareness of students, a long term follow-up is needed for evaluating improvement in learning abilities. Addditionally, a need assessment, done at the beginning of the study, would have helped us to identify the proportion of students already aware of their learning styles. Moreover, learning preference of an individual may vary at different points of professional life and a single point of analysis may not be sufficient. Still our study is promising and expected to add to the existing literature on learning style preference amongst medical students.

In healthcare education, where students are expected to retain, recall and apply vast amounts of information disseminated throughout their training period for patient care, the concept of learning preference seems particularly relevant. However, the focus on medical education has always been on the 'content' and not on 'how to learn.' In our study, kinesthetic mode of learning was the most preferred, which is suited for experiential form of learning and ideal for skill development in healthcare education. We hope that our study, by generating a comprehensive and representative data of learning preferences in our students, will help in increasing their self-awareness and in long run, incorporating metacognition as a way of life.

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ERRATUM

Please note following corrections in the article titled "Factors Associated With Hypertension and Cardiovascular Parameters in Children With Infrequently Relapsing Nephrotic Syndrome" published in Indian Pediatr. 2023;60:475-80.

The third sentence of last paragraph, column 2, page 475 should read: "After taking a written informed consent, children aged 1-12 years, diagnosed with IRNS (irrespective of disease duration) and off steroids, not taking antihypertensive medications for minimum of 3 months were included in the study at the time of relapse." instead of "After taking a written informed consent, children aged 1-12 years, diagnosed with IRNS (irrespective of disease duration) and off steroids, taking antihypertensive medications for minimum of 3 months were included in the study at the time of relapse."

Pediatric Acute Cardiac Tamponade: A Conundrum Between Tuberculosis and COVID-19

Cardiovascular manifestations are reported in up to 16% children infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. However, acute effusive pericarditis is rare in coronavirus disease 2019 (COVID-19) children without multisystem inflammatory syndrome (MIS-C). Concomitant tuberculosis further clouds the diagnosis. We describe three children who presented with acute cardiac tamponade, within a single week during the third wave of COVID-19 (Omicron) pandemic.

Case 1: An 8-year-old previously healthy, fully immunized boy presented with 3-day history of difficulty in breathing, right-sided chest pain and cough. He had tachycardia, tachypnea with subcostal retractions, hypoxia and muffled heart sounds. His hemogram and kidney function tests were normal. Liver function tests were normal except for trans-aminitis. Child tested COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) positive. Chest *X*-ray showed cardiomegaly, left upper-middle zone collapse-consolidation, right pleural effusion, and mediastinal and hilar lymphadenopathy. Echocardiography revealed pericardial effusion (PE) 3.6 cm, right ventricular (RV) diastolic collapse suggestive of cardiac tamponade with normal coronaries. Post-pericardiocentesis, echocardio-graphy was normal with minimal pericardial effusion. Possible differentials included severe COVID-19, MIS-C, malignancy, systemic lupus erythematosis (SLE), tuberculosis, human immunodeficiency virus (HIV) infection and COVID-19 associated cardiac tamponade. Child did not fit the criteria of severe COVID-19 and relevant investigations (**Table I**) ruled out the other causes except atypical presentation of COVID-19 and tuberculosis. Child had positive contact with a patient of tuberculosis, Mantoux test of >10 mm reaction, no peripheral lymphadenopathy, normal ultrasound abdomen and no isolation of *Mycobacterium* tuberculosis (MTB) from sputum/pericardial fluid. Child showed significant improvement post-pericardiocentesis; however, on day 3 of hospitalization, he succumbed to sudden cardiac arrest, possibly due to pericardial decompression syndrome/ pulmonary embolism.

Case 2: A 10-year-old previously healthy, fully immunized girl presented with acute onset respiratory distress and cough for 2-3 days. She had tachycardia, tachypnea, chest retractions, hypoxia and muffled heart sounds. Her baseline hematological biochemical workup was within normal range. Child tested COVID-19 RT-PCR positive. Chest *X*-ray showed cardiomegaly, left upper zone infiltrates with left pleural effusion. Echocardiography showed 2.2 cm PE, RV collapse suggestive of cardiac tamponade with normal coronaries. Post-pericardiocentesis echocardiography was normal. Possible differentials included MIS-C, severe COVID-19 disease, tuberculosis, malignancy and SLE. On further probing, mother gave history of on-and-off low grade undocumented fever and cough for 1-2 months. Mantoux test was positive (18 mm at 72 hours) and ultrasound abdomen was normal. Contrast-enhanced computed tomography (CECT) of chest showed bilateral pleural effusion, left upper lobe consolidation, and necrotic mediastinal lymphadenopathy; although, MTB was not isolated from sputum or pericardial fluid. Child was started on antitubercular therapy and showed gradual improvement.

Case 3: A 4-year-old previously healthy, fully immunized boy presented with history of on-and-off undocumented fever and cough for 1-2 months with acute onset respiratory distress and worsening of cough for 2-3 days. Child had tachycardia, tachypnea, subcostal retractions, hypoxia and muffled heart sounds. His hemogram showed raised total leukocyte counts with neutrophilia. Blood biochemical work up was normal except for presence of transaminitis (alanine transaminase 125, aspartate aminotransferase 249). Child tested COVID-19 RT-PCR positive. Chest *X*-ray showed cardiomegaly, left lower zone consolidation, and left pleural effusion. Echocardiography showed 3.1 cm PE, RV diastolic collapse suggestive of cardiac tamponade, and normal coronaries. Post-pericardiocentesis echocardio-graphy was normal. Mantoux test was positive (14 mm at 72 hours), but child had no peripheral lymphadenopathy, no MTB isolation from gastric aspirate or pericardial fluid with normal ultrasound abdomen. CECT chest showed left lower lobe consolidation, ground glass opacities and fibrotic opacities in left lung, with PE and mediastinal lymphadenopathy. Child showed gradual improvement after institution of anti-tubercular therapy.

Cardiac manifestations are seen in 80-100% of children with MIS-C as pericarditis (23.4-32%), myocarditis and myocardial dysfunction (17.3-59%), coronary dilation or aneurysm (up to 25%) and arrhythmias (7-60%) [1,2]. Cardiac manifestations in SARS-CoV-2 positive children

Table I Clinical Profile, Investigations, Treatment and Response of Children With COVID-19 and Cardiac Tamponade

Parameter (normal value)	*Case 1*	*Case 2*	*Case 3*
Pericardial fluid	Hemorrhagic, 650 mL, 800 cells/mm^3; L=87%, *P*=13% S=67 mg/dL, *P*=3050 mg/dLCulture - sterile, cytology-RBCs with numerous lymphocytes and neutrophils. No malignant cells. AFB negative	Serous, 850 mL,1600 cells/mm^3, L=65%, *P*=35%S=96 mg/dL, *P*=5090 mg/dLCulture-Sterile, Cytology-histiocytes, lymphocytes. No malignant cells. ADA-50.19U/L. AFB negative	Serous, 650 mL,3200 cells/mm^3, L=85%, *P*=15%, S=73 mg/dL, *P*=5029 mg/dL Culture-sterile, cytology-RBCs, numerous histiocytes, lymphocytes and neutrophils. AFB negative
CPK-MB (5-25 IU/L)	35	15	27
PT (s)/aPTT (s)/INR	20.1/32.6/1.48	13.1/32.4/1.1	18/27.6/1.32
D-Dimer (mg/L)	536	152	2099
ESR (<10 mm/1st hour)	34	23	15
CRP (<5 mg/dL)	22.3	72.7	4.06
PCT (<0.5 ng/mL)	0.4	0.13	0.3
Total proteins/albumin	6.8/3.7	7.5/3.8	5.6/3.3
Ferritin (6.24-137 ng/mL)	156	141	17.6
Interleukin-6 (<7pg/mL)	50.8	26	166
Blood culture	Sterile	Sterile	Sterile
HIV	Non-reactive	Non-reactive	Non-reactive
ANA/Anti-ds DNA	Negative	Negative	Negative
Treatment	Pericardiocentesis, ceftriaxone, high flow nasal oxygen (HFNO)	Pericardiocentesis, ATT with steroids (TB pericarditis), by venturi mask	Pericardiocentesis, ATT with steroids (TB pericarditis), HFNO
Duration of hospital stay	60 h	16 d	17 d
Time to COVID RT-PCR negative	Not applicable	23 d	10 d
Outcome	Death	Discharged	Discharged

L: lymphocytes, P: polymorph, S; sugars, P: proteins, RBC: red blood cells, AFB: acid fast bacilli, ADA: adenosine deaminase, CPK: creatine phosphokinase-MB, PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio, ESR: erythrocyte segmentation rate, CRP:C-reactive protein, Procalcitonin, HIV: human immunodeficiency virus, ANA: anti-nuclear antibody, ATT: anti-tubercular therapy.

without MIS-C are scarce [1]. PE is reported in less than 4% COVID-19-positive children without MIS-C [1]. Cardiac tamponade has thus far been reported only in a single SARS-CoV-2 infected child without MIS-C [3]. Another case of cardiac tamponade [2] had been described prior to the recognition of MIS-C and would fit criteria for MIS-C if re-assessed as per current WHO definition [4]. All three children in our series did not match the case definition of MIS-C yet developed cardiac tamponade. In a systematic review of SARS-CoV-2 positive cases (29 adults, 1 child) with cardiac tamponade [5]; in majority, pericardial fluid was exudative with serous or serosanguinous pattern while hemorrhagic appearance was reported in only two patients [5]. Pericardial fluid examination in our series was hemorrhagic in one case, and serous in other two cases. All three were biochemically exudative. Interestingly, in all of our cases, work- up for tuberculosis (initiated due to rarity of severe PE in non-MIS-C SARS-CoV-2 positive children, suggestive history, and high tuberculosis incidence in India) came positive. However, the point of note was the peculiar presentation as acute cardiac tamponade with minimal respiratory manifestations and no systemic involvement.

Tuberculous pericarditis occurs in 1-2% of adult patients with pulmonary disease. Amongst children, tuberculous pericardial effusion is rarer still, and mostly occurs as a part of disseminated disease [6]. Less than 7% children with tuberculosis pericardial effusion develop tamponade [6]. It is possible that in all three of our cases, the tamponade was a manifestation of tuberculous pericardial effusion. However, the clustering of such a rare presentation over a 3-month period, with all three testing SARS-CoV-2 RTPCR positive during the third wave of COVID-19 suggests otherwise. While in case 2, the pericardial fluid had raised adenosine deaminase levels, this was not so in the other two children. In all three cases the diagnosis of pulmonary tuberculosis was made clinico-radiologically with positive Mantoux test, thus establishing co-infection

with SARS-CoV-2 and *M. tuberculosis*. Till date, only a single case of tuberculous pericarditis with SARS-CoV-2 co-infection has been reported. This was a 47- year-old man who presented with cardiac tamponade with minimal respiratory involvement [7]. A systematic review of 146 patients of tuberculosis with SARS-CoV-2 co-infection (22 extra-pulmonary or disseminated tuberculosis cases; no case of tuberculous pericarditis) established worsening of underlying tuberculosis in the presence of COVID-19 infection with higher mortality [8].

These cases raise some important issues. With the ever evolving newer variants of SAR-CoV-2, it is possible that newer manifestations of pediatric COVID-19 are coming to fore like cardiac tamponade as predominant manifestation of acute infection. Secondly, severe PE and cardiac tamponade may manifest in children without MIS-C, especially when associated with an underlying infection. Therefore, a suspicion of cardiac tamponade should be kept in suggestive cases, especially if the child presents with refractory shock, and not just attribute it to MIS-C shock. Co-infection of SARS-CoV-2 and tuberculosis may unmask rarer and more serious presentations of either disease [8]. It is possible that SARS-CoV-2 induced inflammatory response acted as the catalyst for rapid progression of tuberculous pericardial tamponade in our patients. Alternately, the underlying tubercular infection may have amplified the pathogenicity of SARS-CoV-2 infection and lead to its unusual presentation as cardiac tamponade. It is postulated that as tubercular lung infection predisposes to other airborne infections, similarly it enhances susceptibility to and severity of SARS-CoV-2 infection [8]. Moreover, impairment of the immune mechanisms and cytokine overexpression in COVID-19 infection play a vital role in reactivation of latent tuberculosis and progression of existing infection.

To conclude, large pericardial effusion without concomitant myocardial injury or severe respiratory tract involvement or MIS-C, might be seen in SARS-CoV-2 infected children, with tipping over to cardiac tamponade in the presence of a co-infection like tuberculosis. Timely search for possible co-infections in atypical presentations can be life-saving.

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Refractory Status Epilepticus and Leukoencephalopathy in an Infant With SARS-CoV-2 Infection

Approximately 2-5% of cases of coronavirus disease 2019 (COVID-19) involve children, the symptoms are generally mild [1]. However, there is scarcity of data regarding neurological symptoms in pediatric population, especially in neonates. Herein, we describe the clinical and imaging features of a neonate with COVID-19 infection, who presented with status epilepticus and encephalopathy.

A 35-days-old, male baby, born late preterm, second twin, with uneventful antenatal, natal and postnatal period, was admitted to intensive care unit with four episodes of short lasting multifocal clonic seizures followed by status epilepticus. The baby was irritable and was crying excessively since the previous day. There was no history of fever or any respiratory symptoms. The random blood sugar (RBS) was 86 mg/dL. He was intubated, and received injection phenobarbitone (20 mg/kg) intravenously. Seizures subsided, but recurred after 12 hours, for which loading dose of intravenous levetiracetam (40 mg/kg) was given. Even after the control of seizures, the baby had poor activity, and ventilatory support was continued. Empirical treatment with antibiotics and acyclovir were also started.

Sepsis workup was negative. Hemoglobin, leukocyte counts, liver enzymes, urea and creatinine were within normal range. C-reactive protein was 0.6 mg/L. Cerebrospinal fluid (CSF) study showed clear fluid, with 14 red blood cells/cu mm, no leukocytes, glucose was 59 mg/dL and protein was 49 mg/dL. Serum HSV1 and 2 antibody (IgM) was negative. Arterial blood gas (pH 7.38, HCO3 22 meq/L), arterial lactate (1.5 mmol/L), and ammonia (39 µg/dL) were within normal limits. Tandem mass spectrometry was negative for amino acid, organic acid and fatty acid oxidation disorders. Baby's nasopharyngeal swab sample for severe acute respiratory syndrome coronavirus (SARS-CoV-2) reverse transcriptase-polymerase chain reaction (RT-PCR) came as positive. The D-dimer (1129 ng/mL) and ferritin (875 mcg/L) were elevated, but C-reactive protein (CRP) was within normal range. Electroencephalogram (EEG) done on the second day showed low amplitude waves (<20 µv) without any epileptiform discharges, suggestive of moderate degree of diffuse electrophysiologic dysfunction. Magnetic resonance imaging of the brain (**Fig. 1**) showed multifocal area of diffusion restriction involving supratentorial white matter, corpus callosum and corticospinal tract, with no area of infarction or hemorrhage. A repeat lumbar puncture was attempted for testing SARS-CoV-2 RT-PCR in the cerebrospinal fluid, but it happened to be a dry tap.

Rapid antigen test for SARS-CoV-2 was positive for the mother and grandmother, who were asymptomatic. The other twin had mild nasal discharge and nasal block, and was also found to be positive for SARS-CoV-2.

The baby was treated with intravenous methyl prednisolone (30 mg/kg) with a presumed diagnosis of COVID-19 related encephalopathy/encephalitis. Baby improved rapidly, and was extubated after 48 hours of admission. At the time of discharge, after 8 days of hospitalization, the baby was alert and active, feeding well and was seizure free. Oral levetiracetam (20 mg/kg) was continued till 3 months of age, and then tapered and stopped. The baby had normal development, and had no neurological deficits, at 6 months follow-up.

Neurological manifestation of COVID-19 in adults are relatively common ranging from headache, arterial/venous infarcts as well as encephalopathy. There are only isolated case reports of COVID-related encephalopathy in newborns [2,3]. Raised inflammatory markers like D-dimer and ferritin with marked response to steroids in our case, and in literature [3], points to the role of neuroinflammation in COVID-related neurological problems.

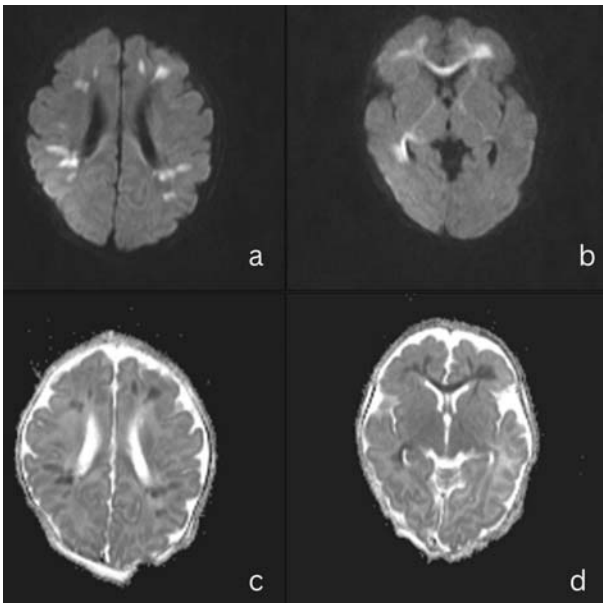

Fig. 1 Magnetic resonance imaging of brain, axial sections showing hyperintensity over the subcortical white matter and the genu of corpus callosum (a and b) in diffusion weighted imaging (DWI) and hypointensity over the corresponding areas in ADC map (c and d) suggestive of diffusion restriction indicating cytotoxic brain edema.

The imaging finding of restricted diffusion involving the supratentorial white matter, and corpus callosum has also been described in influenza (H1N1), rota virus, enteroviruses and parchovirus infections in infants [4]. Similar findings were observed following prolonged status epilepticus as a peri-ictal change. However, there may be additional involvement of mesial temporal lobe, hippocampus and other neocortical structures, and splenium of corpus callosum, which are absent in our case [5]. The throat swab could not be sent for the presence of viruses due to technical constraints. There were no gastrointestinal symptoms, which is commonly associated with rota virus infection. H1N1 characteristically involve the splenium of corpus callosum. Parechovirus infection, produces exactly similar clinical and imaging features. Enteroviral infection is often associated with involvement of brain stem in addition to the subcortical white matter involvement. However, presence of COVID-19 infection in the other twin and all the family members is a pointer that it may be a causal association. There are many reports of similar imaging findings in adults with COVID-19 associated leukoencephalopathy [6]. Fragoso, et al. [3] reported a 4-day-old neonate with positive SARS-CoV-2 antigen (mother was positive for SARS-CoV-2 the time of delivery) with similar imaging findings [3]. Baby's CSF was unremarkable and RT-PCR for SARS-CoV-2 in CSF was negative, suggesting that it is encephalopathy and not actual infection by the virus.

Even though, SARS-CoV-2 can be transmitted through the placenta from the infected mother to the newborn, the disease is relatively mild in babies. In most of the case reports of COVID-related encephalopathy in neonates, the transmission is horizontal, from the mother or other family members through contact, postnatally.

In conclusion, possibility of encephalopathy associated with SARS-CoV-2 infection should be considered in the differential diagnosis, in neonates presenting with encephalopathy and/or seizures with negative septic screen, CSF study, and normal metabolic work-up, especially in presence of multifocal areas of diffusion restriction involving the supratentorial deep white matter, corpus callosum and corticospinal tract.

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Educational Research and Scholarship in India: The Way Forward

The Perspective by Adkoli [1] on medical education research (MER) rightly highlights the importance, techniques, utility, and other issues related to MER, and compares what is required from MER in India *vis-à-vis* the international scenario. His call to reset the agenda of the future pediatric education and research i.e., moving the focus from only treating sick children to striving towards overall well-being and health, is welcome. Some issues, however, like differences between clinical research and MER, need more elaboration.

The practice and delivery of medical education is not standardized. Thus, it is not possible to compare say 5g of a lecture with 4g of a flipped classroom. In addition, a lecture can have many different ways of conceptualization and delivery, and therefore it may be difficult to interpret or generalize results of such a research study to improve educational practices. Cook [2] rightly comments that none of the practices in education are inherently superior or inferior; they are mostly complimentary to each other and importantly, the effectiveness of a practice depends on the way it is used. Usually, it is the element of novelty and subsequent attention being paid by the research team to the new method, which makes it 'interesting' and appear more promising, probably due to Hawthorne effect. Although, the language used for clinical and educational research may sound similar, there are important differences in the two paradigms. Mis-application of clinical research skills in MER can result in studies that are poorly conceived, interventions that are ineffective, and projects that waste resources [3].

Using the analogy of drug comparison, it can be said that molecules being compared, before becoming clinically available, have already been extensively studied. We know their structure, mechanism of action, drug interactions, contraindications, and toxicity fairly well. However, the same may not be true for educational innovations. Most of the time, educational innovations are conceived and tested at the same time. Additionally, in clinical or scientific research, the end point is generally easily measurable outcome (e.g., temperature, pulse rate or blood sugar); but in MER, the end point is usually a construct, which cannot be seen or measured easily but only interpreted from surrogate measures. In clinical research, one can get the body rid of one drug before administering the second; making it possible to attribute the effects to the first or the second drug. This 'washout' may not be possible with two different teaching methods. What the student has learned with one method stays in her cognition, and therefore, an increase in examination scores alone cannot be used as an outcome measure. Additionally, after taking one test, the student may have read more about the topic, discussed with someone, or even reflected upon it, all of which have a bearing on the second test. It is also extremely difficult to prevent mixing up of students if they have been randomized.

A good number of studies use a "pre-test - post-test" model to evaluate the effectiveness of an intervention. The construct is not clear in these situations. What we are looking for is the superiority of the new method in effecting learning or ability of the participants to use new methods in their teaching, but we end up testing short term memory. It is interesting to note here that there are hardly any studies where post test scores were lower than the pre-test one, or where a new intervention has been rated low at the reactions level.

I feel that the Likert scale remains one of the most inappropriately used instrument in MER. The researchers write some statements, claim them to be validated by "experts" (without specifying the expertise) and put 5 points to be used by the respondents for responding. A tool is never valid or invalid – it is the inference that we draw from the tool that is valid or otherwise [4]. It has a further problem as many others down the line continue to use the same published "validated scale" without making any effort to modify or contextualize it.

Many a times, simple research like utility of internal assessment for learning keeps on getting neglected because one cannot demonstrate in the conventional way that this resulted in better learning. However, the justification frequently lies in educational theory, logic and common sense.

Clinical research is non-contextual and any factor confounding the results is considered a nuisance. Educational research, on the other hand, cannot afford to ignore context. Sometimes, these contextual factors make the difference between effective and ineffective intervention. It would be futile to attribute the effects of a lecture to just the slides while ignoring the role of the person delivering it, characteristics of the student, and the nature of the topic [5]. One of the methods very commonly used in such situations is qualitative research, which is in a better position to tell us why things work (or do not work). Qualitative research; how-

ever, has not got its due in Indian scenario, as already mentioned in the perspective [1].

These observations are not to suggest that MER should not use the same rigor that is used for clinical research, but I want to reiterate that though clinical and educational research might draw on similar skills, they require different expertise [3]. MER is needed, but so is training to plan and execute good educational research. Training in clinical research alone may not be able to fill that void.

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Consideration of Regional Differences While using Kangaroo Mother Care During Neonatal Transport

We read with interest the article by Nimbalkar, et al. [1]. We compliment the authors for this relevant study on kangaroo mother care (KMC) during neonatal transport. We agree with the conclusions made by authors that neonatal transport has to be tailor-made for a specific region depending on the climate, geographic condition, available mode of transport, and cultural differences. We would like to highlight certain aspects in the study, and request clarifications from the authors.

National health mission operating guidelines on KMC during neonatal transport in absence of incubator already exist [2]. A recent meta-analysis in the NICU setting concluded that KMC is safe with positive impact on certain physiological markers (heart rate, respiratory rate, temperature, oxygen saturation etc.) in preterm infants [3]. Index study looked into a single physiological parameter (hypothermia).

Thermoregulation is a complex process, especially in low birth weight and premature neonates, and depends on ambient temperature. The index study was conducted over a period of 18 months in Western India with temperature fluctuating from 15ºC in winters to 45 ºC in summers. With the use of non-thermal controlled ambulance it becomes even more difficult to control ambient temperatures. The clothing used in the study and control groups was also mentioned as uniform across all seasons. Though randomization nullifies the differences, discussion on these aspects would have made the outcome of the study more concrete. Also, it may not be prudent to compare studies from developed world with meticulously controlled conditions of transport, as defined in the Swedish study [4].

The authors concluded that the mean temperature in the KMC group was higher compared to controls, and a mean temperature rise of .01 ºC in study group within 5 minutes of transit. These minor differences of two decimal places in mean temperatures in study are reported using a brand of thermometer that reflects temperature to single decimal point, thereby diluting the conclusions. Moreover, exposing the neonate every 5 minutes for 1 minute to record axillary temperature in control group also exposes the control group neonates to a greater risk of hypothermia.

The mentioned discharge criteria for neonates is weight >1700 g, while the neonates enrolled were as less as 1000 g. This anomaly also needs to be explained.

The authors also concluded that the differences in mean temperature were significant till 15 minutes and after reaching home, and not at 20 or 25 minutes. The reason for the same is not clear. There is also a lack of subgroup analysis, which may have given us some clues about the gestational age and weights of children who experienced hypothermia.

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AUTHORS' REPLY

We thank the authors for their interest in our article [1], and bringing out important issues for discussion. The KMC guidelines have been in place since 2014 [2], but it has only a single line on KMC transport, which does not do justice to newborns, service providers, and health systems. The National Neonatology Forum's clinical practice guidelines are based on robust methodologies for developing guidelines, as laid out by World Health Organization [3]. However, most of the guidelines on the Ministry of Health and Family Welfare website, including the KMC guidelines, are based on consensus of experts rather than good evidence [2]. Since 1992, neonatal resuscitation guidelines have been published every five years through the efforts of the International Liaison Committee on Resuscitation [4]. Yet, the guidelines keep changing as more evidence comes to light. Hence the need to develop local evidence for our country becomes necessary.

As the authors mention themselves, randomization does nullify the differences. Hence, it would not add much to the scientific field. However, it is important to note that few northern Indian states would have similar weather as Europe, so we ensured we could address them in the discussion.

While the thermometer did measure temperature to a single decimal point, we reported means, which can have more decimal points even if individual readings have a single decimal point.

Authors point out that taking the temperature every five minutes exposes the child to hypothermia, and we were mindful of this. As responsible researchers, we have taken great care to ensure minimal exposure for this process.

We recruited newborns with a birth weight of more than 1000 g, who were discharged once their weight was more than 1700 g, which is also described in the methods.

We want to draw the author's attention to Table 2, as well as the results section of the article [1], where we clearly stated that *"During the transport, from 10 minutes until the baby arrived home, the mean temperature in the study group was significantly higher than in the control group."*

We attempted subgroup analysis for the preterm babies and reported that in the result section, similar findings were found. However, due to inadequate power, journals and reviewers often do not recommend reporting details.

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Do Non-Invasive Parameters Correlate With Invasive Blood Pressure in Late Preterm and Term Infants With Shock?

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We compliment Natarajan, et al. [1] for their study, and would like to seek clarifications on certain aspects of the study.

The details of plethysmography variability index (PVI) are not clear from the reference provided, and more details are requested. Moreover, the sample size calculation should take into consideration estimates from previous studies or experience from the same unit as a pilot project. Based on the assumed estimates provided in the study (r=0.9, CI=95%, power=90%) for calculating sample size, using STATA 14.2 (Stata Corp LP) we got the total needed sample size of 8 [2].

We are also interested in knowing whether recording of parameters from the pulse oximeter was done manually or from the system i.e., electronically transcribed using the software (Massimo @ Trace) [3]. The mean of all the observed parameters would better reflect the near-correct value rather than the mean of just high and low values. This might lead to erroneous results because extreme values may be due to movement of the right upper limb while measuring SpO2. Cutoff values for perfusion index, PVI, and serum lactate were derived from the receiver operating curve (ROC) for measuring sensitivity, specificity, positive predictive value, and negative predictive value, but there is no mention of the time point (0, 12, 24 or 72 hours) it was constructed. To derive the cutoff values from the ROC curve, whether a logistic regression analysis was done and, if it was done, what variables were used. At the same time, invasive blood pressure is a gestational age-dependent parameter, and Fig. 2 [1] provides a general correlation of the three parameters with invasive blood pressure irrespective of gestational age. Ideally, the correlation should be provided for each gestational age or postmenstrual age.

In the results and discussion part, it is mentioned that there is a weak to moderate correlation, but this quantification is not clear to us. A correlation coefficient value of 0.9 was used, and the results show extreme values (mostly negative values), so it would be imperative that this was deliberated upon in the discussion section. The parameters used in this study depend on the newborn's physiological status, so how would it not apply to intramural units?

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AUTHORS' REPLY

We thank the readers for their interest. The relevant reference for details of plethysmography variability index (PVI) is provided [1].

For the sample size calculation- as there were no previous studies using all three surrogate markers of shock (PI, PVI and SL), hence we calculated the sample size using single marker (SL), which yielded maximum sample size using SPSS 22.0 software [2]. The reader has apparently calculated the sample size assuming a hypothesized correlation of 0 (null hypothesis or r0 being 0) and reached figure of 8. We used an r0 (null hypothesis) value of 0.8. With that assumption, the estimated sample size by Stata (Stata Corp LP) is 79.

We did not extract mean values by using software due to logistic issues, and it was done manually. We agree that using the software to derive mean for the PI and PVI would have been more accurate; however, we retrieved the data manually as it was pragmatic, and has also been done previously [3].

ROC curve was constructed at 0 hour for deriving cutoffs for PI, PVI and serum lactate. We did not do logistic regression as we did not intend to derive a prediction score including these variables.

We agree to the comment that blood pressure is gestational age dependent and hence invasive hypotension was defined as invasive blood pressure <5th centile for the gestational age and not based on any absolute number. To account for gestation related variations in the blood pressure values, we had chosen a reasonably homogeneous population of late preterm and term infants, as generating

correlation of the variables with blood pressure at various gestational age is not feasible and would rather need a mammoth sample size.

We observed a weak to moderate correlation between PI, PVI and SL and invasive blood pressure. The correlation coefficient is *a statistical measure of the strength of a linear relationship between two variables*. Its value can range from -1 (perfect negative or inverse correlation) to 1 positive correlation [4]. Strength of correlation is defined arbitrarily on the clinical context and is not based on any absolute numbers.

We did not qualify our neonatal intensive care unit (NICU) as exclusively 'extramural' in the methodology section, and it was unintentional. However, we have reasoned it as one of the limitations of the study in the discussion section [5]. We do believe that being an extramural unit itself could have had some confounders affecting the outcome assessment. In an extramural NICU, babies at admission itself could have already received fluid boluses or some type of inotropic support for which data were not available. Hence, we believe the results may not be applicable in an intramural unit and the results might be different and must be studied.

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Dengue Severity Score for Predicting Severe Dengue in Children: Need to Validate in Different Settings

Gayathri, et al. [1] have recently reported on development and validation of a bedside dengue severity score to predict severe dengue. The proposed score had good validity in the selected population [1]. However, they also pointed out that it is advised to validate the score in various situations and patient demographics [1].

We feel that the suggested scoring system may or may not be effective in diverse settings, as its performance will depend on the population studied. The grading method refers to the clinical presentation as a fundamental component [1]. Children with underlying morbidity may have atypical presentation.

Dengue is highly prevalent in our region of Indo- China, and some of the clinical indicators, like a low platelet count, are helpful. While the others may be of limited utility due to locally prevalent endemic genetic diseases. Children with underlying thalassemia typically have a low hemoglobin level and an enlarged liver. Thus hemoconcentration, or high hematocrit, becomes a low sensitive parameter for determining dengue severity [2]. Other conditions like B12 deficiency causing both anemia and thrombocytopenia [3] may additionally hinder the use of this score.

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Framework for Prevention of Obesity

Non-communicable diseases (NCDs) are responsible for approximately for 74% of all deaths worldwide and majority of these are occurring in low- and middle-income countries. Obesity is a major risk factor for non-communicable diseases, and its onset during early years of life is associated with cardiovascular diseases, poor productivity and premature death. The sustainable development goals (SDG) target 3.4, aims to achieve one-third reduction in premature deaths due to NCDs. WHO has recently released the "Health service delivery framework for prevention and management of obesity." This document focuses on the expansion of the health services for prevention and management of obesity in all age groups by integrating these into existing health care system. Further, it highlights the need of patient-centric approach with active coordination among the different levels of health care and community with special focus on the high-risk groups. They have suggested primary health centre as the entry point into the system, and referral and back referral system for continuity of care of these cases.

As India has become the most populated country in the world, this is high-time to take active steps for curb obesity and overweight in our population. (*who.int May 17, 2023*)

Treatment for Progressive Pediatric Myopia

Refractive errors are the most common cause of visual impairment in childhood. Studies have documented its prevalence varying from as low as 8-10% to as high as 75% among the children from European and Asian countries, respectively, with an average global prevalence of 30-35% which is predicted to increase to approximately 50% by 2050. Both genetic and environmental factors play role in the development and progression of myopia. The usual age of onset is during 6-12 years, which may progress during adolescent years and then stabilise in majority of children. Onset of myopia at a younger age is associated with the risk of development of high myopia i.e., > –6D and complications like glaucoma, cataracts, retinal detachment, and macular degeneration. Though refraction correction by glasses/lens is the simplest way to manage myopia but it does not stop the progression of myopia and needs frequent correction.

Promising results of a recently published CHAMP (Childhood Atropine for Myopia Progression) trial - a multi-centric double-masked, placebo-controlled, parallel-group, randomized phase 3 clinical trial conducted over a period of three years at 31 sites in Northern America and Europe indicates that pharmacological agents may be helpful in halting the progression of childhood myopia. In this trial, the safety and efficacy of a preservative free, low dose atropine (0.01% and 0.02%) was tested with placebo as the control. Five hundred seventy-six children aged between 3-16 years with 0.50 diopter (D) to 6.00 D spherical equivalent refractive error (SER) and no worse than 1.50 D astigmatism were randomized into three groups in 2:2:3 ratio and prescribed once daily dosing of placebo, low dose atropine (0.01%) and low dose atropine (0.02%), respectively. At the end of trial, findings suggest a significant slowing of spherical equivalent refractive error and axial elongation of the globe, without any serious ocular or systemic effects.

Encouraging results of this trial gives hope against the imminent pandemic of pediatric myopia. (*JAMA Ophthalmol. June 1, 2023*)

Chemo Assist mHealth App for Children

In today's world, apart from a rapid mode of communication, mobiles are also a source of knowledge and learning. mHealth applications provide an effective mode of patient monitoring and record keeping. A team of researchers from Indonesia developed and evaluated a mHealth app – "Chemo Assist for children (CAC)" to monitor and manage chemotherapy related symptoms in children with acute lymphoblastic leukaemia (ALL). In initial phase, individual or group interviews were conducted using semi-structured guide on 31 parents of children with ALL to understand the context and need of the end users. Subsequently after the development of app, 10 parents were enrolled to check its usability. Actions, behaviors, and commentary (ABCs) observation sheets and a satisfaction questionnaire were used for this. Results of the study showed that CAC is easy to use and is able to help the parents in the management of the symptoms arising due to chemotherapy. Such development helps the clinicians by providing data about the status of patients when they are outside the hospital settings, as well as makes the parents more independent and empowered to the care of their children. (*BMC Pediatrics May 30, 2023*)

Glue for Umbilical Catheter

Placement of umbilical catheters is a life-saving procedure in neonates, especially in premature babies. Umbilical catheterisation is associated with complications, among which, malposition and catheter-related bloodstream infection are most common. Securing a catheter is foremost important step to avoid its displacement, but use of adhesive tapes or sutures breaks the continuity of thin fragile skin of preterm neonates and predisposes them for infection. 2-octyl cyanoacrylate are biological adhesives and sealants which have been approved by USFDA for closure of incised skin, and as a barrier against common bacterial agents. Its use has been associated with more rapid wound closure with better cosmetic results. In a recent non-blinded, randomized control trail researchers have evaluated the role of cyanoacrylate glue in reducing the dislodgement of umbilical venous catheters (UVC). The enrolled neonates were divided into two groups according to the method used for securing the UVC– cyanoacrylate glue plus cord-anchored suture (group one) vs securement by suture alone (group two). Primary outcome measured was the safety and efficacy securement between two groups measured by reduction in dislodgment of the external tract of the catheter. Results showed a significant lower rates of catheter dislodgement in the cyanoacrylate glue plus cord-anchored suture compared to suture alone group. This suggests that cyanoacrylate glue is safe and effective for securing the UVC. (*J of Pediatr May 25, 2023*)

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Dermatitis Neglecta

A 7-year-old boy with Duchenne muscular dystrophy presented with blackish discoloration of penis, scrotum and groin for 3 months. Examination revealed multiple scaly hyperpigmented macules, papules, and plaques over shaft of penis, penoscrotal junction, upper part of scrotum and inguinal folds (**Fig. 1**). On rubbing with alcohol swab the dirt lesions were partially scrubbed off. The condition was diagnosed as dermatitis neglecta, and parents were advised to repeat the procedure daily and maintain skin hygiene.

Dermatitis neglecta (dermatitis passivata or dirty dermatoses) is a disease of self-neglect and poor hygine, occurring in elderly, and physically or mentally challenged individuals. It is due to the collection of dirt, sebum, sweat and keratinous crusts. It presents as asymptomatic hyperpig-mented macules, papules, cornflake-like scales and some-times verrucous plaques. Lesions are seen in groin, chest, and previous surgical sites. Differential diagnosis includes conditions causing scaling or hyperpigmentation e.g., dermatitis artefata (a factitious reaction of a skin lesion), several forms of icthyosis, and acanthosis nigricans. Treatment includes cleansing with isopropyl alcohol and washing/scrubbing with soap. Moisturizers, urea, and lactic acid can also be used.

Fig. 1 *a*) Dirt and keratinous debris appearing as multiple hyperpigmented papules and plaques in shaft of penis and groin; *b*) Dirty lesions appearing as hyperpigmented macules and papules in scrotum.

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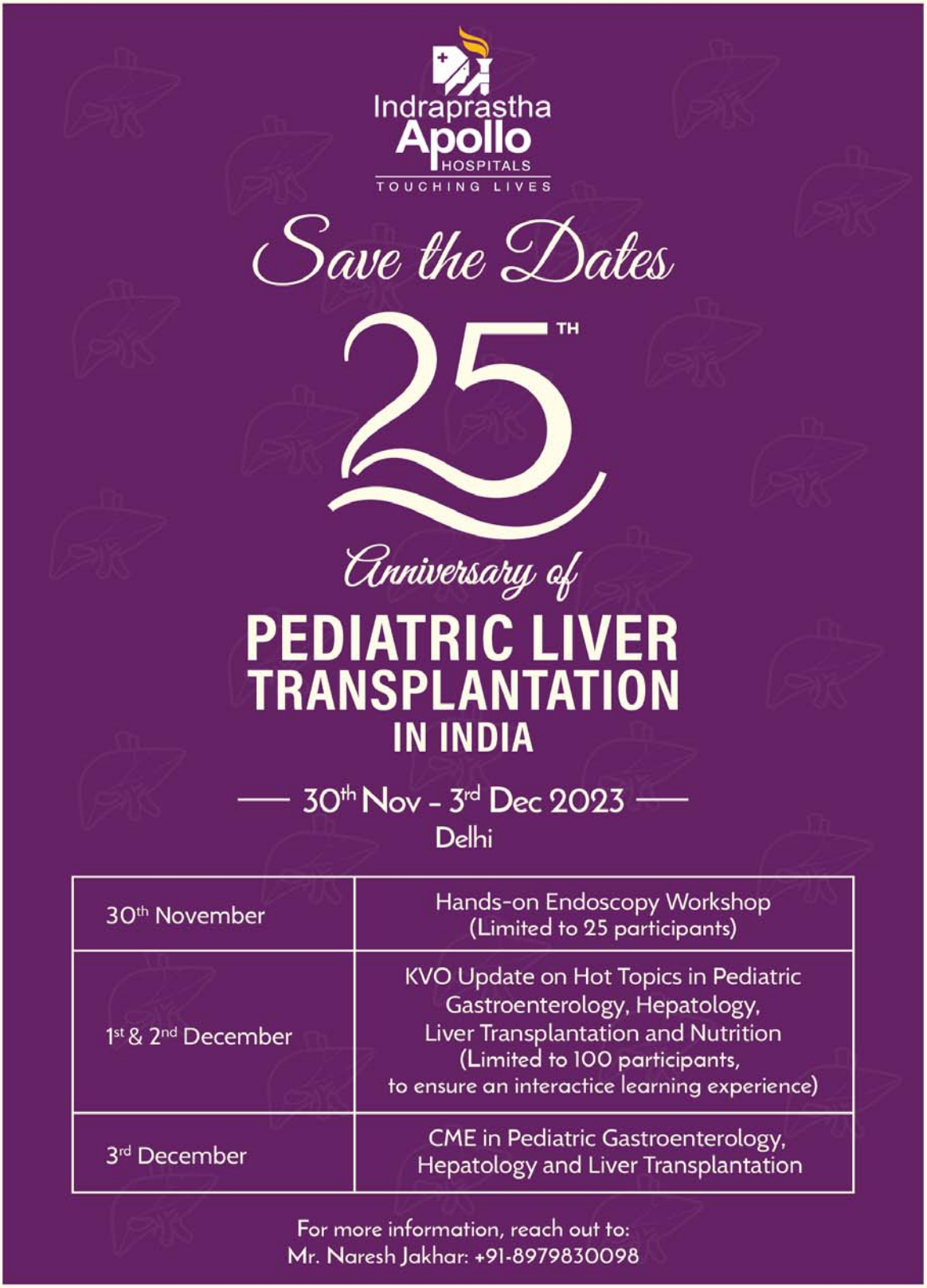
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