

Diagnostic Accuracy of Modified Kenneth Jones Scoring Criteria as Screening Tool to Diagnose New Cases of Pulmonary Tuberculosis in Children

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Abstract

Objective: To evaluate the effectiveness of the Modified Kenneth Jones Scoring System as a screening tool for diagnosing pulmonary tuberculosis in children.

Methodology: A cross sectional study was conducted to assess the symptoms of tuberculosis among 100 pediatric patients with male to female ratio was 67:33. through Modified Kenneth Jones Scoring System (MKJSC) at Gulab Devi Tertiary Care Hospital, Lahore from June-December, 2022. The study included symptoms based on gender, drug usage and microbial load. Patients diagnosed with TB were included in this study to assess the system's effectiveness in identifying specific symptoms and clinical manifestations of TB. This inclusion allowed for a comprehensive evaluation of the MKJSC's diagnostic accuracy and its potential utility in early detection and intervention in pediatric TB cases. The Data was analyzed using SPSS to identify specific symptoms.

Results: The Modified Kenneth Jones Criteria diagnosed 65 patients out of 100 with one false positive. The sensitivity for TB detection was 84.2% (95% CI: 73.6% - 91.2%), specificity was 95.8% (95% CI: 76.8% - 99.7%), positive predictive value was 98.4% (95% CI: 90.5% - 99.9%), and negative predictive value was 65.7% (95% CI: 47.7% - 80.3%). Statistical analysis with 5% confidence interval revealed a medium of age of 73 months and a mode of 120 months among patients. While cough prevalence varied, all patients had a history of prolonged fever. Meningeal irritation was observed in 52% of participants and 77% had contact with TB patients. Other findings included malnutrition 50%, pneumonia 48% and BCG screening 24%.
Conclusion: The Modified Kenneth Jones Scoring System demonstrated high sensitivity and specificity in detecting tuberculosis, outperforming previous methods. It proves to be an effective tool in resource-limited healthcare settings for diagnosing TB in children.

Keywords: Tuberculosis, Bacterial load, Modified Kenneth Jones Scoring System.

Introduction

Tuberculosis (TB) remains a major global health concern, causing significant morbidity and mortality worldwide.¹ To effectively combat this infectious disease, it is essential to comprehend the clinical and diagnostic manifestations of tuberculosis patients, particularly with respect to their physical aspects and related signs and symptoms. Early detection and precise diagnosis are critical for ensuring prompt treatment initiation and decreasing the spread of TB in the community.¹

The majority of pediatric populations who are infected with Mycobacterium tuberculosis exhibit a lack of clinical symptoms.^{1,2} On the other

hand, the likelihood of disease progression and extrapulmonary manifestations is greater within the first two years of life, with a progression risk of 40-50%.³ Of all cases of TB disease in children, pulmonary TB accounts for approximately 60-80%, with most cases developing within 2-12 months of initial infection.⁴ The most prevalent extrapulmonary manifestation is lymphadenopathy, followed by central nervous system involvement.⁴ The classification system utilized here distinguishes between thoracic and extra thoracic disease, recognizing that hilar or mediastinal adenopathy, often viewed as extrapulmonary disease, is a defining characteristic of pulmonary disease in children. Separating pulmonary foci from regional adenopathy is not biologically significant.⁵

The primary source of infection for most children who have contracted the disease share close living quarters, often within the same household. This course of action facilitates the identification of children who are at risk of developing TB disease because of recent infection within the household and enables the early detection of eligible children who can benefit from isoniazid preventive therapy (IPT).⁶ By implementing contact screening, vulnerable children can be recognized, and appropriate measures may be taken to prevent the progression of the disease.⁷ In the Kenneth Jones scoring system, various clinical and radiological factors are assessed to determine the likelihood of TB in a child. These factors include symptoms like persistent cough, fever, weight loss, and radiological abnormalities like chest X-ray findings.⁸ However, the presence and severity of these symptoms and abnormalities may vary depending on the type of TB manifestation in the child.

In this study, Kenneth Jones scoring system was used as screening tool for TB diagnosis in children, where sputum contained a high bacterial load.⁹ Despite recent advancement and improvements in bacteriological test, their performance in diagnosing childhood TB does not meet the expectations outline in the world health organization, endorsed target products profile for TB diagnoseis.¹⁰ The study aimed to assess the diagnostic accuracy of MKJSC as screening tool

for diagnosing pulmonary tuberculosis in children. In involved evaluating TB symptoms among pediatric patients and analyzing data to determine the sensitivity, specificity and predictive values of the MKJSC in detecting TB cases. The objective was to provide insights into the performance of the MKJSC and its potential utility in resources limited healthcare setting for early TB diagnosis in children. By examine the diverse physical aspects such as specific sign and symptoms, we aimed to acquire insights into the presentations of TB in this population.

Methodology

The present research employed a cross-sectional study design to investigate TB patients' clinical and diagnostically manifested symptoms with implementation of MKJSC. A study was conducted at Gulab Devi Tertiary Care Hospital in Lahore, Pakistan, serving as a representative sample of the region. A detailed methodology was employed to compile and analyze the data. The data was collected and underwent analysis utilizing the SPSS statistical tools to ensure the statistical validity of the finding. The research study focused on evaluating the diagnostic accuracy of the modified Kenneth Jones scoring system as a screening tool for the identification of new cases of tuberculosis. The ethical letter was obtained from ERB with tracing ID: AAMC/IRB/EA-28.2022.

The study sample comprised of 100 children of both gender, who were diagnosed with TB based on clinical and laboratory criteria. A convenience sampling approach was implemented, wherein qualified participants who satisfied the inclusion criteria were consecutively enrolled until the desired sample size was attained. The patients were recruited from outpatient department of the participating hospital after obtaining consent from the legal guardians of the children. Sputum culture was used as a scoring standard to determine the diagnostic accuracy of MKJSC, and the scoring system was determined by calculating measures such as sensitivity, specificity, positive predictive values, negative predictive values and the area under the receiver operating characteristic curve. These measures offer an assessment of the system's ability to accurately identify individuals with and without tuberculosis. The trained personnel involved in the research project employed standardized data collection forms, which included clinical symptoms, medical history, and participant demographics such as age and gender. Diagnostic procedures and bacterial detection techniques were performed to ascertain the level of microbial burden and establish the presence of TB infection. SPSS version 21 was used to analyze the data. Descriptive statistics, such as frequencies and percentages, were utilized to compile the research participants' demographic details and clinical symptoms. In instances where it was appropriate, as per the collected data and information, the chi-square test or Fisher's exact test was employed to examine the relationship between variables. The statistical significance was defined as a p-value of 0.05.

Results

The system exhibited a high degree of sensitivity, specificity, and an overall accuracy in differentiating between individuals with

tuberculosis and those without the disease. Table 1 shows the distribution of ages within the study population. The median age was 73 months (average 67.01 months), while the mode was 120 months. Although only 69% of participants reported having a cough that lasted longer than two weeks, all patients had a history of fever that lasted longer than two weeks. In the oldest and youngest age groups, coughing was more prevalent.

The 52% of the patients surveyed showed signs of meningeal irritation, including symptoms of fits; 77% of respondents said they interacted with somebody who had previously been diagnosed with tuberculosis; 4% of interviewees said they had never had whooping cough, whereas 15% confessed they had measles in the past. Only 24% of the patients showed evidence of the BCG vaccine scarring, and 52% of the patients showed signs of malnutrition. Physical tests of the patients indicated pleural effusion in 8%, gibbus deformity of the thoracic spine in 2%, and pneumonia in 48% of the patients. In 49% of the research sample, radiological data showed significant opacity and different bronchovesicular patterns. Additionally, 14% of the people showed signs of miliary mottling. In 57% of the individuals, a BCG response higher than 10mm indicated a satisfactory diagnostic result. 52% of those polled had CSF fluid that may have been connected to tuberculous meningitis. Compared to 29% of the patients who had positive results for acid-fast bacilli, only 11% had cultures that tested positive for *Mycobacterium tuberculosis*.

The Modified Kenneth Jones criteria were found to be satisfied by 65 patients, and there was only one incidence of a false positive diagnosis. It's important to note that, according to the Kenneth Jones criteria, only 12 out of the total study participants received a negative score (below 7). However, the results of subsequent tests revealed that these patients did in fact have tuberculosis. The computed sensitivity for tuberculosis detection using the Kenneth Jones criteria was 84.2%, with a 95% confidence interval (CI) ranging from 73.6% to 91.2%. A specificity of 95.8% (95% CI: 76.8% to 99.7%) was found. Additionally, it was found that the positive predictive value was 98.4% (95% CI: 90.5% to 99.9%) and the negative predictive value was 65.7% (95% CI: 47.7% to 80.3%).

The quantification of the bacterial load, which represents the concentration of *Mycobacterium tuberculosis* in a patient's system, was assessed and categorized into three levels: low, medium, and high. By quantifying the bacterial load, medical practitioners can employ the most optimal means MKJSC of infection control to curb the spread of tuberculosis and make informed decisions about the selection and duration of antibiotic therapy.

The outcomes of the study propose that the modified Kenneth Jones scoring system can be a valuable tool in the primary screening and diagnosis of tuberculosis cases. Its high diagnostic accuracy makes it a potentially useful approach in resource-limited settings where access to advanced diagnostic techniques may be limited. The sign and symptoms with bacterial load over age are mentioned in Table 2 within gender base.

Table 1: Data of some patients from this cross sectional study

Age (months)	Gender	Symptoms	Bacteria Load Detection	Other Evidence	MKJSC
14-15	Male	Cough, Weight Loss	Low	Mantoux Positive, Hemoptysis	3-4
13-14	Female	Fever, Cough	Low	Mantoux Positive, Sputum ATB Positive,	≥5
12-13	Male	Fever, Cough, Weight Loss	Medium	Sputum ATB	3-4
11-12	Female	Fever, Cough, Weight Loss	Medium	Sputum ATB	3-4
8-10	Male	Fever, Cough	High	Mantoux Positive, Sputum ATB Positive,	≥5
5-8	Female	Fever, Cough, Weight Loss	High	Mantoux Positive, Sputum ATB, Sputum	≥5
3-5	Male	Fever, Cough, Weight Loss	High	Sputum ATB	3-4
1-2	Female	Fever, Cough, Weight Loss	High	Sputum ATB	3-4
<1	Male	Fever, Cough, Weight Loss	High	Sputum ATB	3-4

Table 2: KJ Scoring and Gene Expert Comparison

KJ Score	Inference	Gene Expert*	KJ score Efficiency (Total)	Std. Dev.
3-4	Negative	Negative	100%	3.808
≥5	Positive	Negative	MTB Detected	
3-4	Negative	Negative	100%	
3-4	Negative	Negative	100%	
≥5	Positive	Positive	100%	
≥5	Positive	Positive	100%	
3-4	Negative	Negative	100%	
3-4	Negative	Positive	MTB Not Detected	
3-4	Negative	Negative	100%	

*Gene Expert is a rapid molecular diagnostic test for tuberculosis and rifampicin resistance. It detects Mycobacterium tuberculosis DNA and rifampicin

resistance mutations using PCR technology, providing results within two hours.

Discussion

A comprehensive research investigation was carried out on patients with TB based on the provided data, which focused on both male and female individuals across different age groups and examined clinical manifestation, symptoms and detection of bacterial load in order to gain insights into the progression and transmission of the disease.¹¹ The study reveals that TB patients exhibit similar signs and symptoms across age groups, but the severity of bacterial burden varies, suggesting different stages of the disease. Bacterial load was categorized into low, medium, and high levels, providing insights into microorganism proliferation and potential implications.¹² Some patients show early-stage disease with lower bacterial loads, indicating early infection or less active disease, while a considerable proportion display medium or high bacterial loads, signifying advanced disease stages and increased transmission risk.¹⁴

Screening new cases of pulmonary tuberculosis in children is a critical task that requires an accurate diagnostic tool. The modified Kenneth Jones scoring system has been evaluated for its efficacy as a screening tool.¹³ It integrates multiple clinical and laboratory parameters to assign a scoring the indicate the likelihood of tuberculosis. These parameters may encompass symptoms, radiographic findings and laboratory test results.⁵ Understanding the bacterial burden in TB patients is essential for disease management including treatment decision infection control and assessing transmission risk.¹⁵ Quantifying bacterial load helps healthcare provides choose antibiotics, monitor treatment response and implement infections control measure to contain TB spread. Early detection and intervention are emphasized to prevent transmission and reduce diagnostics and treatment options, considering the challenges posed by varying bacterial loads and clinical manifestations in TB.^{16,17}

Further analysis of symptoms presentation between male and female TB patients reveals both similarities and differences. Both genders commonly experience symptoms such as fever and cough while females may also present with chest pain, weight loss vomiting abdominal pain.¹⁸ The findings underscore the importance of early detection, tailored treatment approaches and effective infections control measure to mitigate the impact of TB on individuals and communities. The data also highlights the ongoing need for further research and advancement in diagnostic and treatment options to address the challenges associated with varying bacterial loads and the divers' clinical manifestations of TB.¹⁹ This study describes a cross sectional study that aims to evaluate the clinical and diagnostically manifestation symptoms of TB patients in relations to their physical response. The following sections offers compressive description of the study methods data analysis and results followed by discussion other implications and potential applications of the findings. The study extensively highlights its methodology, including aspects such as age, distribution, symptoms, bacterial load detection, and the MKJSC utilization. For instance, the findings reveal a median age of 73 months and a mode of 120 months among the participants. Furthermore, all patients exhibited a

history of prolonged fever, with the prevalence of cough varying across different age groups. The sample size is determined using sample size determination for estimation of a single population proportion formula and the following assumptions are considered 95% confidence interval. The determination of the sample size was conducted through the utilization of appropriate statistical methods to guarantee ample representation of the intended population.

The total number of cases detected through specific testing strategies defines the diagnostic yield. In the case of intrathoracic tuberculosis in children by following Kenneth Jones scoring system as a screening tool, various factors affected the diagnostic yield, which included Persistent cough (>2-3 weeks), persistent fever (>1 week), unexplained weight loss, close contact with a TB case, presence of night sweats, enlarged lymph nodes, BCG vaccination status, chest X-ray abnormalities (hilar lymphadenopathy, lung infiltrates, cavitations), and detailed CT scan findings. The factors mentioned, including the inherent diagnostic accuracy of laboratory tests, specimen quality and quantity, transport efficiency, and laboratory system quality, directly influence the diagnostic yield of the Kenneth Jones scoring system. For example, if laboratory tests used to confirm TB are not accurate or if specimen collection is inadequate, the diagnostic yield may be compromised.^{5,8}

Moreover, the drivers' manifestations of intrathoracic TB in children such as cavity disease or primary lymph node disease, affected bacilli recovery from secretions. Cavity disease often yield higher concentrations of bacilli compared to primary lymph node disease where bacilli level might be lowered. This variations in bacilli recovery can impact the sensitivity of diagnostic test and consequently the diagnostic yield of the Kenneth Jones scoring system.

Therefore, these factors collectively influence the sensitivity and specificity of the Kenneth Jones Scoring Criteria, impacting its ability to accurately diagnose intrathoracic TB in children. These include the inherent diagnostic accuracy of laboratory tests, the quality and quantity of collected specimens, the efficacy and promptness of specimen's transport and the availability of high-quality laboratory system which rely on skilled personnel. It is noteworthy that intrathoracic TB in children has a broad secretion,⁸ for example, cavitary disease such as Ghon focus lesion, the most common form of intrathoracic TB in children, may exhibit very low levels of bacilli, MKJSC might be utilized as a screening tool for its diagnosis. By illuminating the diverse manifestations of tuberculosis, this study aims to contribute to the ongoing efforts in tuberculosis research and enhance the understanding of this global health challenge.²⁰ This study's primary goal was to evaluate the diagnostic accuracy of the modified Kenneth Jones scoring system, which was used as a screening tool to find new cases of pediatric pulmonary TB. The study identified diverse symptoms and bacterial burden levels in tuberculosis patients. Accurate quantification of bacterial load is vital for disease management and control. Early detection and intervention are crucial to reduce transmission and disease burden. Further research is needed for improved diagnostics and treatments for varying bacterial loads in tuberculosis patients.²¹

The findings exhibited a moderate degree of diagnostic accuracy, characterized by excellent sensitivity and positive predictive value (Table-2). The results of study identified the ability to identify the specific physical characteristic linked to tuberculosis, as well as their correlation with patients' attributes, providing healthcare professional with valuable insights for timely identification and intervention.^{22,23} These discoveries bear substantial consequences for the management, treatment, and formulation of preventive approaches for tuberculosis globally. The study places its findings within the wider framework of tuberculosis research, addressing the challenges posed by diverse bacterial loads and clinical presentations. It also delves into the potential utility of the Modified Kenneth Jones scoring system in settings with limited resources, emphasizing its effectiveness as a screening tool for diagnosing tuberculosis in children.

Limitations

The relatively small sample size may affect the generalizability of the results. Secondly, the research was conducted at a single hospital in Lahore, which may limit the applicability of findings to other regions. Thirdly, the study relied on the Modified Kenneth Jones Scoring System without comparing it to other advanced diagnostic tools, potentially limiting its comprehensiveness. Additionally, there may be selection bias as patients were recruited from outpatient departments, possibly excluding more severe cases not attending the clinic. Lastly, the cross-sectional design captures data at a single point in time, which may not reflect long-term outcomes or variations in symptoms over time. However, these tests have limited sensitivity in detecting paucibacillary TB in diagnosing testing, which refers to cases with low levels of bacilli, due to inherent technologies limitations.

Future Perspective

By examining TB clinical manifestations and laboratory parameters, we assessed the system's sensitivity, specificity and predictive values in detecting TB cases. Understanding the performance of the MKJSC in diverse patients' populations in different areas under disease conditions is essential for its effective implementations in clinical practice. Moreover, insights gained from this study may inform strategies for early detection and intervention, particularly in resource limited setting where access to advanced diagnostic techniques may be limited. To minimize cost in implementing the modified Kenneth Jones scoring system for pediatric TB screening, leverage existing infrastructure train healthcare staff prioritize cost effective diagnostic test, and integrate screening into community health program.

The manuscript puts forward the need for additional investigation and advancement in area of diagnostic and therapeutic options to address the challenges associate with fluctuating bacterial and diverse clinical manifestation of TB. The modified scoring system created by Kenneth Jones holds promise as a valuable tool in the initial screening and identified of TB cases, particularly in setting with limited availability of state of art diagnostic techniques.

Conclusion

The finding of our research pertaining to the scoring chart de-

veloped by Kenneth Jones have demonstrated higher level of sensitivity and specificity in comparison to previous investigation conducted in the field.

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Authors' contribution: SS conceptualization, data collection, analysis, drafting, and revising; MN supervision, review, and approval of the final manuscript; AS departmental oversight, clinical expertise, and manuscript review. MS data contribution, clinical insights, and manuscript review; BUH data contribution, methodology feedback, and manuscript assistance; SR data collection, clinical insights, and manuscript review.

References

- 1) Visca D, Ong CW, Tiberi S, Centis R, D'Ambrosio L, Chen B, et al. Tuberculosis and COVID-19 interaction: a review of biological, clinical and public health effects. *Pulmonology*.2021;27(2):151-165. doi: 10.1016/j.pulmoe.2020.12.012. Epub 2021 Jan 22. DOI: 10.1016/j.pulmoe.2020.12.012
- 2) Dartois V, Dick T. Therapeutic developments for tuberculosis and nontuberculous mycobacterial lung disease. *Nature Reviews Drug Discovery*. 2024;28(1):1-23. doi: 10.1038/s41573-024-00897-5.
- 3) Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. *Paediatric Respiratory Reviews*. 2007;8(2):107-117. DOI: 10.1016/j.prrv.2007.04.008
- 4) Byashalira K, Mbelele P, Semvua H, Chilongola J, Semvua S, Liyoyo A, et al. Clinical outcomes of new algorithm for diagnosis and treatment of tuberculosis sepsis in HIV patients. *The International Journal of Mycobacteriology*. 2019;8(4):313-9. doi: 10.1056/NEJMra1405427.
- 5) Rajvanshi N, Goyal JP. Combating Tuberculosis in Malnourished Children. Addressing a Silent Epidemic. *Indian Journal of Pediatrics*. 2024 Apr 26:1-2. <https://doi.org/10.1007/s12098-024-05136-8>
- 6) Long M, Kar P, Forkert ND, Landman BA, Gibbard WB, Tortorelli C, et al. Sex and age effects on gray matter volume trajectories in young children with prenatal alcohol exposure. *Frontiers in Human Neuroscience*. 2024 Apr 10;18:1379959. <https://doi.org/10.3389/fnhum.2024.1379959>
- 7) Sajid A, Riaz S. Role of Gene Expert /MTB Test in Childhood Tuberculosis. *Journal of University Medical & Dental College*. 2018;9(3):1-5. doi: 10.1371/journal.pmed.0040238.
- 8) Morgan V, Casso-Hartmann L, Bahamon-Pinzon D, McCourt K, Hjort RG, Bahramzadeh S, et al. Sensor-as-a-service: convergence of sensor analytic point solutions (SNAPS) and pay-a-penny-per-use (PAPPU) paradigm as a catalyst for democratization of healthcare in underserved communities. *Diagnostics*. 2020;10(1):22. doi: 10.1099/jmm.0.000171. Epub 2015 Jan 11.
- 9) Mir F, Mahmood F, Siddiqui AR, Baqi S, Abidi SH, Kazi AM, Nathwani AA, Ladhani A, Qamar FN, Soofi SB, Memon SA. HIV infection predominantly affecting children in Sindh, Pakistan, 2019: a cross-sectional study of an outbreak. *The Lancet Infectious Diseases*. 2020;20(3):362-370. doi: 10.1183/09031936.00120908.
- 10) Wobudeya E, Bonnet M, Walters EG, Nabeta P, Song R, Murithi W, Mchembere W, Dim B, Taguebue JV, Orne-Gliemann J, Nicol MP. Diagnostic advances in childhood tuberculosis—Improving specimen collection and yield of microbiological diagnosis for intrathoracic tuberculosis. *Pathogens*. 2022;11(4):389. doi: 10.3390/pathogens11040389.
- 11) Goletti D, Lee MR, Wang JY, Walter N, Ottenhoff TH. Update on tuberculosis biomarkers: from correlates of risk, to correlates of active disease and of cure from disease. *Respirology*. 2018;23(5):455-66. doi: 10.1111/resp.13272. Epub 2018 Feb 18.
- 12) Chakaya J, Petersen E, Nantanda R, Mungai BN, Migliori GB, Amanullah F, et al. The WHO Global Tuberculosis 2021 Report—not so good news and turning the tide back to End TB. *International Journal of Infectious Diseases*. 2022;124(1):26-29. doi: 10.1016/j.ijid.2022.03.011. Epub 2022 Mar 20.
- 13) Jonas DE, Riley SR, Lee LC, Coffey CP, Wang SH, Asher GN, et al. Screening for latent tuberculosis infection in children: updated evidence report and systematic review for the US Preventive Services Task Force. *Jama*. 2023;329(17):1495-1509.
- 14) Khademi F, Derakhshan M, Yousefi-Avarvand A, Tafaghodi M, Soleimanpour S. Multi-stage subunit vaccines against *Mycobacterium tuberculosis*: an alternative to the BCG vaccine or a BCG-prime boost?. *Expert Review of Vaccines*. 2018;17(1):31-44. doi: 10.1080/14760584.2018.1406309. Epub 2017 Nov 22.
- 15) Singh M, Dhingra B, Bishnu B, Pandey D, Anand PK, Gupta S, et al. Pulmonary Tuberculosis in Severely Malnourished Children Admitted to Nutrition Rehabilitation Centers: A Multicenter Study. *Indian Journal of Pediatrics*. 2023;20(1):1-8. doi: 10.1093/cid/ciw376. Epub 2016 Aug 10.
- 16) Iqbal NT, Ahmed K, Qamar FN, Shaheen F, Mehnaz A, Arif F, Saeed AA, et al. Antibody-secreting cells to diagnose *Mycobacterium tuberculosis* infection in children in Pakistan. *Mosphere*. 2020;5(1):10-128. doi: 10.1016/j.fjma.2016.07.001. Epub 2016 Aug 10.
- 17) Ainan S, Furia FF, Mhimbira F, Mnyambwa NP, Mgina N, Zumla A, et al. Xpert® MTB/RIF assay testing on stool for the diagnosis of paediatric pulmonary TB in Tanzania. *Public Health Action*. 2021;11(2):75-9. doi: 10.4103/0971-5916.159566.
- 18) Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries; a systematic review and meta-analysis. *PLoS medicine*. 2016;13(9):e1002119. DOI: 10.1371/journal.pmed.1002119
- 19) Gill CM, Dolan L, Piggott LM, McLaughlin AM. New developments in tuberculosis diagnosis and treatment. *Breathe*. 2022;18(1). doi: 10.1183/20734735.0149-2021. Epub 2021 Mar 8.
- 20) De Martino M, Lodi L, Galli L, Chiappini E. Immune response to *Mycobacterium tuberculosis*: a narrative review. *Frontiers in pediatrics*. 2019;27(7):350. doi: 10.3389/fped.2019.00350. eCollection 2019.
- 21) Singh M, Dhingra B, Bishnu B, Pandey D, Anand PK, Gupta S, Das VR, Dhochak N, Kabra SK. Pulmonary Tuberculosis in Severely Malnourished Children Admitted to Nutrition Rehabilitation Centers: A Multicenter Study. *Indian Journal of Pediatrics*. 2023 Jul 20(1):1-8.
- 22) Shakoor S, Mir F. Updates in pediatric tuberculosis in international settings. *Pediatric Clinics*. 2022;69(1):19-45. doi: 10.1016/j.vaccine.2006.03.017.
- 23) Saleem S, Shaheen A, Naeem M, Sahi SM, Rubab S. Prevalence Of Rifampicin Resistance in New Cases Of Pulmonary Tuberculosis In Children. *Journal of Rawalpindi Medical College*. 2024;28(1).1-10 doi: 10.1056/NEJMra1405427.