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Cycle Threshold (CT) and Neutrophil-To-Lymphocyte (NLR) Values as Predictors of Clinical Symptoms in Pediatric Covid-19 Cases: A Systematic Literature Review

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ABSTRACT

Background: The COVID-19 epidemic has impacted persons across all age demographics, including children. An opposing viewpoint is that despite the extensive discussion surrounding the neutrophil-to-lymphocyte ratio as a potential indicator of clinical symptoms in pediatric COVID-19 cases. This systematic literature review aims to explores the correlation between CT readings, neutrophil-to-lymphocyte ratio, and clinical symptoms in pediatric cases with COVID-19. **Method:** This systematic review examined the existing research on Cycle Treshold (CT) and Neutrophil-To-Lymphocyte Ratio (NLR) values as indicators of the clinical progression in children with COVID-19. An extensive search of databases Scopus revealed studies that satisfied our inclusion criteria. They utilized CT valuess and the neutrophil-to-lymphocyte ratio as indicators for predicting clinical symptoms. The inclusion criteria for this study were specifically centered around juvenile patients with COVID-19 from scopus databased. The chosen studies underwent a thorough evaluation to determine their quality and relevance. Various nations, including Korea, China, Italy, the United States, Egypt, South Africa, India, Japan, Brazil, and others. **Result:** The papers included in the analysis demonstrate a noteworthy correlation between CT readings and clinical symptoms in children with COVID-19 Pediatric COVID-19 cases with elevated CT values demonstrated a greater propensity for severe clinical manifestations, including respiratory distress and pneumonia. Upon reviewing the available research, it is evident that hematological parameters, specifically the neutrophil-to-lymphocyte ratio, significantly impact forecasting the severity and clinical prognosis of juvenile COVID-19 cases. **Conclusion:** The neutrophil-to-lymphocyte ratio and CT values were identified as dependable indicators of illness severity in pediatric patients. The results emphasize the significance of hematologic measures, specifically the neutrophil-to-lymphocyte ratio, as helpful markers for evaluating the clinical symptoms and outcomes of juvenile COVID-19 patients.

Keywords:
Cycle Threshold, Neutrophil-To-Lymphocyte, Clinical Symptoms, Pediatric, Covid-19

1. INTRODUCTION

Pediatric COVID-19 cases pertain to persons under 18 diagnosed with COVID-19, a respiratory ailment caused by the new coronavirus SARS-CoV-2. Children diagnosed with COVID-19 display distinct clinical characteristics compared to adults, with the majority exhibiting modest symptoms [23]. Prior research has examined the clinical manifestations, diagnostic test results, and treatment modalities administered in verified cases of COVID-19 among children. [4] Prior research has additionally demonstrated that children with COVID-19 typically experience moderate symptoms similar to those of other viral infections in the upper respiratory tract. Consequently, this similarity presents difficulties in accurately diagnosing the condition (A. Chen et al., 2020).

A comprehensive analysis and synthesis of existing studies on children with COVID-19 yielded data supported by scientific evidence, specifically regarding the clinical symptoms observed in pediatric patients affected by COVID-19 (Cui et al., 2021) (Duan et al., 2020). The CT scans of pediatric patients with COVID-19 exhibit a wide range of characteristics and do not display distinct patterns, indicating the challenging Nature of diagnosing this disease in children. Furthermore, a study was conducted to evaluate the long-term consequences in children previously hospitalized due to COVID-19 and the associated factors that increase the risk (Osmanov et al., 2022). This study emphasizes the significance of comprehending the condition's progression in pediatric patients. CT values, or cycle threshold values, quantify the quantity of target nucleic acid in a specific sample. Regarding COVID-19, CT values derived from real-time reverse transcription polymerase chain reaction testing can provide insights into the presence and quantity of SARS-CoV-2 virus in a patient's respiratory sample (int, 2022). Higher CT readings in juvenile COVID-19 cases have been linked to asymptomatic infection and less severe illness [4].

CT values, also known as cycle threshold values, acquired from real-time reverse transcription polymerae chain reaction (RT-PCR) assays indicate the sample's quantity of target nucleic acid. The values exhibit an inverse relationship with the quantity of target nucleic acid (Üstündağ et al., 2022). They can be employed to group viral genes and variations, offering an understanding of the existence and quantity of the SARS-CoV-2 virus in a patient's respiratory sample (Accorsi et al., 2022). Furthermore, a comparison has been made between the CT values of symptomatic and asymptomatic cases, revealing their efficacy in comprehending the clinical presentations of the illness (Schwierzeck et al., 2021). The characteristics of pediatric COVID-19 cases have been studied by collecting and analyzing clinical and epidemiological symptoms and RT-PCR cycle threshold (Ct) data (Schwierzeck et al., 2021) [4]. Furthermore, comprehensive evaluations and statistical studies have demonstrated that most COVID-19 cases in children exhibit no symptoms, underscoring the need to comprehend CT data when evaluating the seriousness of the condition (Cui et al., 2021). A study examining the epidemiological and clinical characteristics of SARS-CoV-2 infection in children emphasized the significance of understanding virus transmission dynamics through epidemiological exposure (Wang et al., 2022).

The neutrophil-to-lymphocyte ratio (NLR) is calculated by dividing the number of neutrophils by the number of lymphocytes acquired from a complete blood count test. Multiple studies have demonstrated that the Neutrophil-to-Lymphocyte Ratio (NLR) may accurately forecast the severity of disease and the clinical progression in children with COVID-19 (Dao Thi et al., 2020). The neutrophil-to-lymphocyte ratio (NLR) strongly indicates the severity of the disease and the progression of clinical symptoms in children with COVID-19 (Ji et al., 2020). Elevated levels of neutrophil-to-lymphocyte ratio (NLR) have been linked to a heightened risk of blood clot formation, abnormal small blood vessel function, and inflammation. This suggests that NLR could be a useful indicator for predicting the severity of disease and persisting symptoms in children with COVID-19. The most pertinent reference supports the importance of the neutrophil-to-lymphocyte ratio (NLR) in pediatric COVID-19 cases. A logistic regression analysis demonstrates that an NLR value of 5.03 or higher increases the risk of MIS-C by a factor of 19.3 (Radhakrishnan et al., 2022).

Additionally, a proBNP value of 329.5 ng/L or higher increases the risk by a factor of 238, while a troponin-I value of 0.03 μg/L or higher increases the risk by a factor of 60 (Güllü et al., 2022). Significant disparities were observed in several laboratory measurements, such as NLR and CT values when comparing patients admitted to the ward with those admitted to the critical care unit. The NLR was elevated in kids who were admitted to the ICU, suggesting a possible correlation between NLR and the severity of the disease in pediatric COVID-19 cases.

The study compared patients admitted to the ward and those admitted to the intensive care unit (ICU). It revealed notable disparities in laboratory measurements, such as the Neutrophil-to-lymphocyte Ratio (NLR) and cycle threshold (CT) values (Otto et al., 2020). The NLR was elevated in kids who were admitted to the ICU, suggesting a possible correlation between NLR and the severity of disease in pediatric COVID-19 cases. [4] Furthermore, CT values derived from real-time reverse transcription polymerase chain reaction (RT-PCR) analysis can offer valuable information regarding the existence and quantity of the SARS-CoV-2 virus in a patient's respiratory specimen (Cui et al., 2021).

Forecasting the trajectory of pediatric COVID-19 cases is difficult because of the heterogeneous manifestation and fluctuating intensity of the illness and the developing comprehension of the virus within this demographic. Multiple investigations have emphasized the clinical symptoms and results in pediatric patients with COVID-19 [4]. Children infected with COVID-19 may have a less severe form of the disease, characterized by unusual clinical symptoms and a rare condition called lymphopenia (Cui et al., 2021) Furthermore, it has been shown that the clinical characteristics of COVID-19 in children are identical to those of other viral infections affecting the upper respiratory tract, which presents difficulties in diagnosing (A. Chen et al., 2020). COVID-19 functions as a systemic ailment that can range in severity from asymptomatic clinical manifestations to respiratory failure and heightened mortality (Gisi et al., 2022).

Potential predictors of unfavorable outcomes in pediatric COVID-19 cases have been discovered as laboratory markers. Children who needed care in the ICU had considerably higher levels of CRP, procalcitonin, and lower platelet counts compared to those treated in a standard hospital(Henderson et al., 2022). Hematological

inflammatory markers have been proposed as useful diagnostics for detecting COVID-19 infections in pediatric clinics (Üstündağ et al., 2022). Furthermore, it is crucial to acknowledge that our understanding of the frequency and symptoms of COVID-19 in children is currently limited, and more information from cases involving children must be gathered better to comprehend the clinical characteristics of COVID-19 in this population (Ji et al., 2020). Gaining insight into the determinants of regular vaccine reluctance in children is crucial for sustaining pediatric immunization rates and fostering vaccine confidence throughout and following the COVID-19 pandemic (Martin et al., 2022) (He et al., 2022).

It is imperative to consider the counterarguments that emphasize the necessity of thorough and precise data regarding the clinical symptoms of COVID-19 in youngsters to have a complete understanding of the virus's effects on this demographic. While it is true that certain studies indicate that children with COVID-19 tend to experience less severe symptoms and have better outcomes than adults, there is evidence of situations where children and teenagers have developed serious illnesses and need to be hospitalized and treated in intensive care units (Yilmaz Ciftdogan et al., 2022). This undermines the widely held belief that COVID-19 in children is always moderate and raises worries over the possible long-term consequences of the virus in pediatric patients, such as the possibility of multisystem inflammatory syndrome in children and other issues that may arise after COVID-19 infection. Furthermore, the dynamic Nature of the virus presents difficulties in properly forecasting the clinical progression of juvenile COVID-19 infections (Parsons et al., 2021). Due to the diverse range of appearances and varied severity of the disease, it is important to approach each case of pediatric COVID-19 with caution and continuously monitor the patient. This is because pediatric COVID-19 might exhibit unusual clinical symptoms, which can complicate the process of diagnosis and timely intervention (Ma et al., 2020).

While laboratory indicators such as increased CRP levels, increased procalcitonin levels, and reduced platelet counts have been linked to unfavorable outcomes in pediatric COVID-19 cases, it is crucial to acknowledge that the clinical characteristics and progression of the disease in children with COVID-19 are still inadequately comprehended (J. Chen et al., 2020). Hence, it is imperative to conduct thorough longitudinal studies in order to gain a deeper understanding of the clinical symptoms, predictors of severe disease, and long-term consequences of COVID-19 in pediatric patients. Utilizing CT and NLR values as prognostic indicators in juvenile COVID-19 patients can offer useful insights into the progression, severity, and prognosis of the disease in this specific population (Mark et al., 2021). These factors aid in identifying high-risk patients who necessitate enhanced surveillance and more rigorous therapies.

This work is significant as it emphasizes the necessity for meticulous assessment and surveillance of pediatric COVID-19 cases, as children may exhibit unusual symptoms and experience different levels of disease severity that may not align with the typical pattern reported in adult cases (S. Lee et al., 2020). Moreover, applying CT and NLR values in forecasting clinical results can assist in detecting and promptly addressing high-risk pediatric individuals, including those with preexisting medical disorders or weakened immune systems. The primary inquiry of this investigation is " Can Cycle Threshold (Ct) And Neutrophil-To-Lymphocyte (Nlr) Values As Predictors Of Clinical Symptoms In Pediatric Covid-19 Cases?"

This study aims to assess the predictive value of CT and NLR values in pediatric COVID-19 cases, specifically concerning disease severity, comorbidities, and outcomes. Furthermore, this analysis will examine the practical consequences of CT and NLR values in the management of pediatric COVID-19. Finally, examine the future research recommendations regarding predictors of pediatric COVID-19 and their potential implications for clinical practice and research. The results of this study could help create guidelines and protocols based on solid data for managing pediatric COVID-19 cases.

2. METHOD

This systematic review examined the existing research on Cycle Treshold (CT) and Neutrophil-To-Lymphocyte Ratio (NLR) values as indicators of the clinical progression in children with COVID-19. A search was conducted in the Scopus database using the keywords "cycle," "threshold," "covid," and "neutrophil." This search yielded 204 current documents from the past five years. Subsequently, the scope of the articles was restricted from Scopus databased, resulting in the acquisition of 196 articles. Only publications written in English were considered, resulting in a total of 188 articles. Additionally, only articles from journals with open access were included, resulting in 173 articles. Out of the 173 articles, a subset of 9 article were chosen for study. The inclusion criteria for this study were specifically centered around juvenile patients with COVID-19. The study sought to examine the relationship between CT and NLR values and the clinical progression of the disease. The chosen studies underwent a thorough evaluation to determine their quality and relevance. Various nations, including Korea, China, Italy, the United States, Egypt, South Africa, India, Japan, Brazil, and others, have provided useful insights on utilizing CT and NLR values as indicators of the clinical progression in pediatric COVID-19 patients.

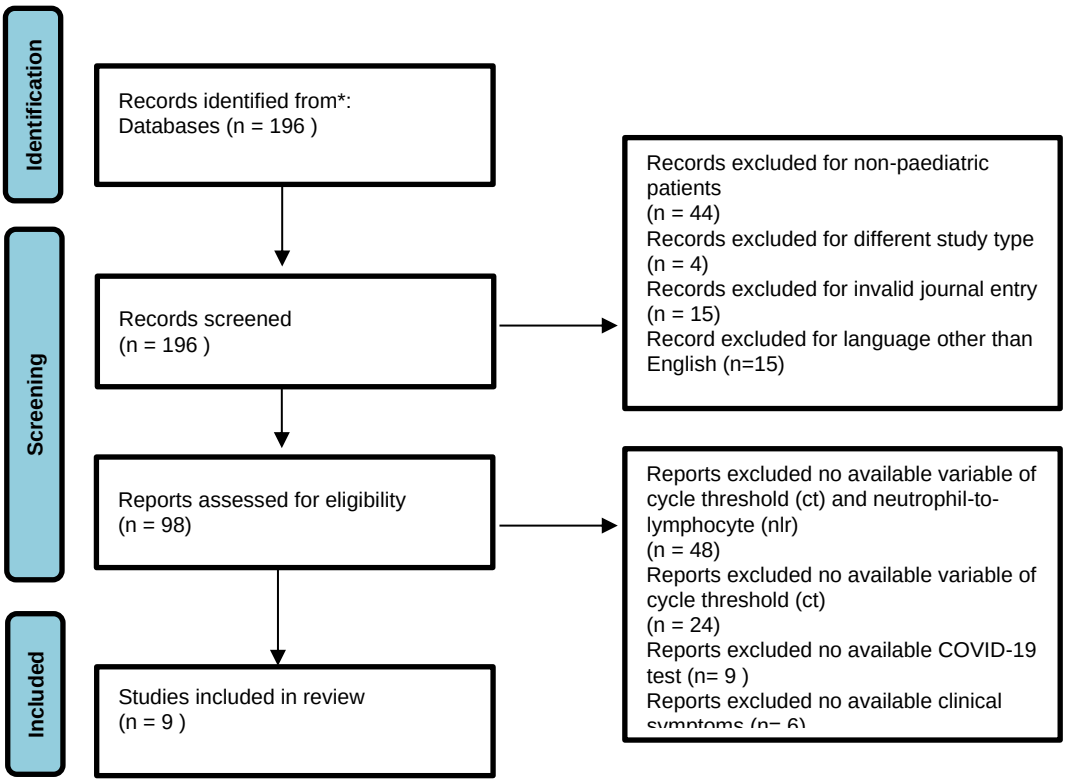

Figure 1: The PRISMA flowchart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta Analyses

The data extraction process for the selected studies on pediatric COVID-19 cases followed the PRISMA 2020 statement guidelines (Page et al., 2021) flow chart guideline, template was used to extract relevant information from the selected studies, including study characteristics (author, year of publication, location), study design, sample size, age range of participants, CT values and NLR measurement methods, clinical outcomes assessed, and key findings related to the association between CT values/NLR and the clinical course of pediatric COVID-19 cases. The extracted data was conducted by two researcher. first author performed the initial extraction, and the second author independently reviewed the extracted data for accuracy and completeness.

3. RESULTS AND DISCUSSION

Result for analyzing the selected studies by table 1, with mind finding, study design, study objective, methodology, independent variable, dependen variable, clinical manifestation and region show that there is significant variability in the methodologies used to measure CT values and NLR in pediatric COVID-19 cases. critical finding from the literature synthesis revealed that both CT values and NLR can serve as predictors of the clinical course in pediatric COVID-19 cases.

Paper	Main Finding	Study objectives	Methodology	Independent Variable	Dependent Variable	Clinical Manifestation	Region
Could an Increased Percentage of Immature Granulocytes Accompanying Dyspepsia Predict COVID-19? Kadir Gisi et al 2022	The main findings of the study are that dyspepsia may be a symptom of SARS-CoV-2 infection, immature granulocyte percentage (IG%) values were significantly higher in SARS-CoV-2-positive patients, and an optimal cut-off value for IG% (≥0.650) showed promising sensitivity and specificity for predicting COVID-19 infection in patients with dyspepsia.	The study objectives are to determine the presence of SARS-CoV-2 in patients presenting with dyspepsia but not the typical symptoms of COVID-19 and to investigate the role of immature granulocytes in the early diagnosis of these patients.	The methodology involved the inclusion of patients with dyspepsia, division into positive and negative groups based on SARS-CoV-2 PCR test results, recording of hematological parameters, use of automated hematological analyzer and real-time PCR detection system, and various statistical analyses.	The independent variables in the study are the patients' SARS-CoV-2 status, demographic data (age and sex), laboratory data (complete blood count results, WBC counts, neutrophil counts, lymphocyte counts, IG counts, and IG% values), and the cut-off points of hematological parameters for the diagnosis of SARS-CoV-2 infection.	Dependent variables: Results of SARS-CoV-2 PCR tests, complete blood counts, white blood cell counts (WBCs), neutrophil counts, lymphocyte counts, hemoglobin levels, immature granulocyte counts, immature granulocyte percentages, and C-reactive protein (CRP) tests	**Dyspepsia**	**Turkey**
Clinical Infectious Diseases Jared Bullard et al 2020	SARS-CoV-2 Vero cell infectivity was only observed for RT-PCR Ct < 24 and symptom onset to test (STT) < 8 days. The odds of a positive culture were decreased by 32% for each unit increase in Ct. The study's data, if confirmed, may help guide isolation, contact tracing, and testing guidelines.	To determine the relationship between E gene SARS-CoV-2 RT-PCR cycle threshold (Ct) values from respiratory samples, symptom onset to test (STT), and infectivity in cell culture. Better understand the duration of infectivity of SARS-CoV-2 and its impact on public health guidelines, infection control practices, and occupational health.	The methodology used in the study involved a retrospective cross-sectional design using SARS-CoV-2 RT-PCR-confirmed positive samples to determine their ability to infect Vero cell lines. Viral titers were determined through median tissue culture infectious dose (TCID50) assays, and multivariate logistic regression and receiver operating characteristic curves were used for data analysis.	Ct values from respiratory samples, Symptom to test time (STT), Age, Sex	Ability of SARS-CoV-2 RT-PCR-confirmed positive samples to infect Vero cell lines, Positive viral culture as a binary predictor variable, Odds of a positive culture for every 1-unit increase in Ct	The article primarily focuses on laboratory and diagnostic aspects related to SARS-CoV-2 infectivity, such as RT-PCR cycle threshold values and viral culture results. While it does not delve deeply into clinical manifestations of COVID-19, it does mention the importance of understanding infectivity duration for informing public health measures, infection control practices, and occupational health decisions	Canada
Epidemiological and clinical features of	The main findings of the study are: - The study	The study aimed to understand the	The methodology involved collecting	The independent variables in the study	The dependent variables in this study are the risks of	The specific health conditions that the	Shanghai, China

SARS-CoV-2 infection in children during the outbreak of Omicron variant in Shanghai Xiangshi Wang et al 2022	observed a significant number of pediatric COVID-19 cases, with a majority being symptomatic, and a substantial proportion being asymptomatic. - Two-dose COVID-19 vaccination was found to reduce the risks of symptomatic infection and febrile disease among confirmed cases by 35% and 33%, respectively. - The wide dissemination of the Omicron variant in the community was reflected in the surge of pediatric COVID-19 cases, and asymptomatic infection was found to be common among Omicron-infected children. Additionally, COVID-19 vaccination was shown to provide some protection against symptomatic infection and febrile disease.	epidemiological and clinical characteristics of pediatric SARS-CoV-2 infection during the early stage of the Omicron variant outbreak in Shanghai.	clinical data, epidemiological exposure, and vaccination status from pediatric COVID-19 cases in Shanghai. Data analysis was performed using SPSS, and relative risks were calculated to explore the effect of vaccination on symptomatic infection and febrile disease.	are time (specifically the time period from March 7 to March 31, 2022), epidemiological exposure, COVID-19 vaccination status (including dose and date), demographic information, clinical symptoms, laboratory findings, chest imaging, and treatment.	symptomatic infection and febrile disease in pediatric COVID-19 cases, which depend on the vaccination status and other factors.	study participants have are symptomatic and asymptomatic cases of COVID-19, fever, cough, transient leukopenia, pneumonia, Omicron variant infection, severe Omicron infection, reinfection with Omicron variant, and live SARS-CoV-2.	
COVID-19 associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group Dilek Yilmaz Ciftdogan et al 2022	- Almost half of the patients with MIS-C had clinical features that overlapped with KD, with a higher rate than reported in the literature. - Patients with MIS-C and overlap with KD were younger compared to those without overlap. - Patients with overlap with KD had lower lymphocyte and platelet counts, as well as significantly elevated procalcitonin levels.	The study objectives are to highlight the clinical and laboratory features and outcomes of patients with MIS-C whose clinical manifestations overlap with or without Kawasaki disease, compare the clinical features, laboratory findings, treatment methods, and outcomes of patients with MIS-C from multiple centers with or without overlap with KD, and provide insights into the understanding of MIS-	The methodology used in the study includes retrospective analysis of a case series, data collection from medical records, descriptive statistics, comparison of variables using appropriate statistical tests, and univariate and multivariate logistic regression analysis (confidence: 95)	Age groups, sex, underlying disease, complaints, clinical and laboratory findings, need for ICU stay	Overlap risk in MIS-C patients with KD, Risk of overlap with KD, Clinical characteristics that overlapped with KD	Some common clinical manifestations in children with MIS-C include: Fever: All children who were subjects of this study had fever, with the fever lasting for an average of 5 days. Fatigue: Fatigue was the most common complaint, experienced by 81.8% of total patients. Gastrointestinal symptoms: Symptoms such as abdominal pain, vomiting, or	Turkey

		C and its potential relationship with KD. (confidence: 95)				diarrhea occurred in 77% of patients. Changes in the mucous membrane: Changes in the mucous membrane, such as conjunctival injection and changes in the mucous membrane, are found in the majority of patients. Respiratory symptoms: Respiratory symptoms may also occur, with a higher incidence in the age group over 12 years. Shock: Shock occurs in a small proportion of patients, with a higher incidence in the age group above 12 years. In addition, most patients with MIS-C also have clinical manifestations that overlap with Kawasaki disease, such as conjunctival injection, rash, and changes in the mucous membranes.	
Pulmonary Dysfunction after Pediatric COVID-19 Heiss, R et al 2023	The paper provides a clinical-practical guideline for diagnosing and treating Long/Post-COVID symptoms, suggests the existence of at least four subtypes within the overall group of patients with Long/Post-COVID syndrome, and emphasizes the important role of general practitioners as primary caregivers.	The study objectives are to provide a clinical-practical guideline for diagnosing and treating Long/Post-COVID symptoms based on limited data, considering the clinical care pathway, and updating the guideline promptly as evidence increases.	The methodology involves the development of a practical guideline for diagnosing and treating Long/Post-COVID symptoms based on limited evidence, considering the correlation with comorbidities, the influence of study design on reported frequency,	Presence and severity of comorbidities, Presence of somatic or psychosomatic symptoms, Time since acute COVID-19 infection, Updates in evidence and data, Severity of functional limitations	The dependent variables in the paper include subtypes of Long/Post-COVID-Syndrome, functional status assessment, symptoms and quality of life in patients, vital and laboratory parameters, imaging findings related to potential complications, development of mental health conditions, and long-term physical,	The population health conditions in the study are comorbidities, somatic or psychosomatic complaints, and immune deficiencies.	Not spesific

			and the identification of potential subtypes within the patient group.		emotional, and cognitive impairments post-COVID-19. The impact of physical inactivity on the severity of COVID-19 is also considered as a dependent variable.		
COVID-19 in 7780 pediatric patients Ansel Hoang et al 2020	- The review provides evidence that children diagnosed with COVID-19 have an overall excellent prognosis. - The study summarizes the clinical, laboratory, and radiologic features of COVID-19 in neonates, children, and adolescents. - The paper has several key advantages compared to other COVID-19 pediatric systematic reviews, including a large number of included studies and patients, synthesis of underlying pediatric medical conditions and delineation of bacterial and viral coinfections, quantitative description of clinical symptoms and imaging findings, presentation of antiviral therapies by specific agents, and a preliminary comparison of patients with/without MIS-C.	The study objectives are to summarize the clinical symptoms, laboratory, and imaging findings of confirmed pediatric cases of COVID-19 and to provide a characterization of the therapies provided to these patients. The authors also highlight the need for future longitudinal studies to confirm their findings and better understand which patients are at increased risk for developing severe inflammation and multiorgan failure.	The methodology involved adherence to PRISMA guidelines, comprehensive database searches, independent screening and data extraction, assessment of risk of bias, and statistical analyses using STATA v¢13.	Underlying medical conditions, exposure to a family member diagnosed with COVID-19, need for intensive care unit observation or treatment, symptoms associated with severe inflammation and MIS-C, laboratory markers associated with MIS-C	Clinical signs, Imaging findings, Laboratory results, Development of MIS-C in children with confirmed diagnosis of SARS-CoV-2	Immunocompromised status, respiratory or cardiac disease, co-infections, and multisystem inflammatory syndrome in children (MIS-C)	United States, China
Haematological parameters predicting cardiac involvement in children with COVID-19 infection Ufuk U Güllü et al 2022	- Certain haematological parameters and cardiac biomarkers such as NLR, proBNP, CKMB, and troponin-I can predict the development of MIS-C in COVID-19 patients with high sensitivity and specificity. - The study provided cutoff values, sensitivity-specificity levels, and a risk analysis to predict MIS-C using	The study objectives are to evaluate haematological parameters and cardiac biomarkers to predict cardiac involvement by COVID-19 infection, assess the correlation of MIS-C with cardiac biomarkers, and provide cutoff values, sensitivity-specificity	The methodology involves a retrospective study conducted in a single center, including pediatric patients with a positive COVID-19 PCR test but no comorbidity, and healthy children as the control group. The study collected demographic characteristics, clinical, and laboratory findings	Haematological parameters, Cardiac biomarkers, Age of the patients, Time of admission	NLR value, proBNP value, troponin-I value	The specific health conditions that the study participants have, if any, are not mentioned. However, the study explicitly states that patients with comorbid conditions such as cardiac or neurological sequelae, asthma, immunodeficiency,	Turkey

	several laboratory parameters, which can aid in the early detection of MIS-C in patients with suspected COVID-19 infection. - The study involved low-risk patients and demonstrated the value of cost-effective haematological parameters in predicting cardiac involvement and prognosis in paediatric patients with COVID-19.	levels, and a risk analysis to predict MIS-C using several laboratory parameters for low-risk patients.	at the time of admission and used specific criteria to diagnose MIS-C. (confidence: 90)			haematological disorders, or malignancy were excluded from the study. The control group consisted of healthy children of the same age without complaints.	
Local and systemic responses to SARS-CoV-2 infection in children and adults Masahiro Yoshida et al 2021	- The study provides several mechanisms that explain the milder clinical syndrome observed in children.	To examine the differences between children and adults in their response to SARS-CoV-2 infection, analyze paediatric and adult patients with COVID-19 as well as healthy control individuals using single-cell multi-omic profiling of matched nasal, tracheal, bronchial, and blood samples. Provide evidence of dendritic cells initiating interferon signaling in early infection and identify epithelial cell states associated with COVID-19 and age. Characterize the epithelial and immune cell compartments at a high granularity, identifying previously undescribed cell types and states in airways and blood.	The methodology used in the study includes single-cell multi-omic profiling of matched nasal, tracheal, bronchial, and blood samples from paediatric and adult patients with COVID-19, as well as healthy control individuals. The dataset generated from the study can be explored interactively through a web portal and is available in public repositories for further analysis.	Donor, Age group, Sex, Ethnicity, Tissue, Smoking status, COVID-19 status, Batch, 10x kit version, Number of expressed genes, Number of mapped fragments	The dependent variables in this study are the cell type composition in response to COVID-19, which is influenced by factors such as age, sex, inferred ethnicity, tissue, and COVID-19 status.	Severe pneumonia, viral pneumonia, other pneumonia, non-pneumonia controls	UK and the US.
Viral load dynamics and disease severity in patients infected with	- The duration of SARS-CoV-2 is significantly longer in stool samples	The study objectives are to evaluate viral loads at different	The methodology involved the collection of samples from patients	The independent variables in this study are numerous and	Severity of illness, Duration of the virus, Viral	The specific health conditions that the study participants have	Zhejiang province, China

SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study Shufa Zheng et al 2020	than in respiratory and serum samples - Patients with severe disease showed a longer duration of SARS-CoV-2 in respiratory samples, higher viral load, and a later shedding peak compared to patients with mild disease - The viral loads peaked in respiratory samples in the second week from disease onset in the mild group, while viral load continued to be high during the third week in the severe group	stages of disease progression in patients infected with SARS-CoV-2 and to analyze the temporal change in viral loads and the correlation between viral loads in different sample types and disease severity.	infected with SARS-CoV-2, extraction of viral RNA, quantitative reverse transcription PCR (qRT-PCR) analysis, and statistical analysis of the data. It was a retrospective case series study without direct patient involvement in study design or outcome measures.	include type of sample, time since symptom onset, antiviral treatment, severity of illness, comorbidities, personal characteristics, timing of antiviral treatment, progression and resolution of clinical illness, age, gender, presence in Wuhan, presence in the severe group or mild group, presence in the intensive care unit, presence of specific symptoms, presence of specific clinical indicators, presence of specific viral RNA in different samples, and presence of specific treatments.	load, Correlation between age and duration of virus	are COVID-19, with some patients experiencing mild disease and others experiencing severe disease. The most common underlying health conditions among the participants were hypertension and diabetes mellitus. Fever and cough were the most common symptoms reported. (confidence: 95)	

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CT Value as an Indicator of Clinical Symptoms in Pediatric COVID-19

This analysis demonstrates that CT values derived from respiratory samples can offer valuable information on the progression of juvenile COVID-19 patients **(Heiss *et al.,* 2023**). Elevated CT values have been linked to asymptomatic or moderate infection, indicating reduced viral particles and potentially less severe disease progression. This aligns with prior observations in adult COVID-19 cases, wherein elevated CT readings were linked to less severe illness. (**Martin *et al.,* 2022**).

The existing information indicates that Ct levels, gastrointestinal symptoms, and proportion of asymptomatic cases are crucial in predicting clinical symptoms in pediatric patients with COVID-19. **[4]** emphasized that Ct values over 19 were linked to asymptomatic infections, indicating that Ct values could predict disease severity in pediatric patients [4] underscored the significance of gastrointestinal symptoms in children with COVID-19, with vomiting being the prevailing symptom. These findings indicate that the clinical symptoms observed in pediatric patients are distinct from those observed in adults (**Gisi *et al.,* 2022**). In addition, **Chen *et al.* (2020)** provided evidence that juvenile patients with COVID-19 have distinct clinical manifestations and CT imaging features compared to adults. This underscores the importance of identifying unique indicators for predicting clinical symptoms in pediatric instances **(J. Chen *et al.,* 2020).**

A study conducted by **Cui *et al.* (2020)** found that fever and cough are the predominant clinical symptoms in juvenile patients with COVID-19, but they occur less frequently compared to adults (**Cui *et al.,* 2021**). These findings indicate that the manifestations of COVID-19 in children may vary from those in adults, highlighting the importance of identifying specific indicators for this age group. Furthermore, **Wang *et al.* (2022)** documented that most instances of COVID-19 in children had no symptoms, hence emphasizing the diverse range of clinical manifestations observed in pediatric patients (**Wang *et al.,* 2022**).

The wide range of ways pediatric COVID-19 patients might manifest themselves highlights the intricate Nature of diagnosing and forecasting their clinical progression. The unusual clinical symptoms observed in children and the changing characteristics of the virus emphasize the necessity for a distinct strategy for diagnosing and treating the disease (**Yoshida *et al.,* 2022**).

Multiple studies emphasize the significance of CT and NLR levels in forecasting clinical symptoms and the severity of the disease in juvenile COVID-19 cases. Gaining insight into the prognostic significance of CT readings can facilitate the detection of asymptomatic or mild cases, enabling prompt management and surveillance (**Bullard *et al.,* 2020**). Furthermore, the significant occurrence of gastrointestinal symptoms and the greater incidence of asymptomatic cases in pediatric patients highlights the unique range of clinical manifestations of COVID-19 in this specific population (**Abrams *et al.,* 2020**). This study investigates the utilization of CT and NLR values as prognostic indicators for the clinical progression of pediatric COVID-19 cases. It is by the requirement for comprehensive guidelines based on solid data for managing pediatric cases. The results of this study can provide valuable insights for creating precise recommendations and protocols customized to the distinct clinical features of juvenile COVID-19 patients.

The systematic review undertaken in this study technique provides a detailed analysis of pertinent papers, enabling a meticulous assessment of the predictive significance of CT and NLR values. This methodology guaranteed that the conclusions derived from the study were well-supported by a robust body of evidence **(Zheng *et al.,* 2020**).

Neutrophil-to-lymphocyte ratio as a prognostic indicator of clinical manifestations in pediatric patients with COVID-19.

The comprehensive study additionally discovered that the neutrophil-to-lymphocyte ratio (NLR) can potentially forecast the clinical progression in juvenile cases of COVID-19. The studies analyzed in this review consistently found that elevated NLR values were linked to more severe illness and unfavorable outcomes, such as admission to the intensive care unit. Furthermore, there was a notable correlation between NLR and laboratory indicators of inflammation, including C-reactive protein and procalcitonin (**Nugroho *et al.*, 2023**).

The neutrophil-to-lymphocyte ratio (NLR) has been recognized as a potential indicator of clinical symptoms in pediatric patients with COVID-19. In their study, **Güllü *et al.* (2022)** demonstrated that having an NLR value of 5.03 or higher raised the probability of multisystem inflammatory syndrome in children (MIS-C) by 19.3 times. This suggests that NLR can predict severe clinical outcomes in pediatric COVID-19 patients (**Güllü *et al.*, 2022**). Furthermore [4] discovered that Ct levels exceeding 19 were correlated with asymptomatic infection, indicating a possible connection between NLR and the seriousness of the disease in pediatric patients **[4]**. In addition, **Hoang *et al.* (2020)** emphasized the significance of CT features in COVID-19, suggesting that certain imaging observations could be valuable in predicting clinical manifestations in juvenile cases (**Hoang *et al.*, 2020**). Furthermore, **Gisi *et al.* (2022)** documented the potential of measuring immature granulocyte count, percentage of immature granulocytes, and NLR values as indicators for predicting COVID-19. This study provides additional evidence for the significance of NLR as a predictor of clinical symptoms in pediatric patients **(Gisi *et al.*, 2022**)

These data indicate that the NLR, CT values and particular hematological parameters can be used to predict clinical symptoms in children with COVID-19. This information can help determine the risk level and develop appropriate therapeutic strategies for this group of patients (**Balashov *et al.*, 2021**). Investigating the significance of inflammatory indicators in predicting the clinical progression of juvenile COVID-19 cases is a crucial focus in the present medical field . This study investigates the possibility of NLR (neutrophil-to-lymphocyte ratio) as a predictor of clinical symptoms. It supports the increasing evidence that emphasizes the significance of inflammatory markers in assessing risk and managing diseases (**Yu *et al.*, 2020**).

Aside from neutrophil-to-lymphocyte ratio (NLR), other hematological measures, including immature granulocyte count, percentage of immature granulocytes, and platelet-to-lymphocyte ratio, have demonstrated potential in predicting COVID-19 outcomes in pediatric patients (**E.P.Lee *et al.*, 2023**). Incorporating these factors in this study enhances the breadth of predictive indicators under investigation, providing a comprehensive methodology for comprehending the progression and intensity of the disease in this particular group (**Balashov *et al.*, 2021**). The diverse characteristics of these inflammatory indicators highlight the intricate Nature of juvenile COVID-19 and emphasize the significance of evaluating different clinical and laboratory factors in predicting risk and managing patients **(Kociolek *et al.*, 2021**). This study offers a comprehensive perspective on potential indicators of clinical symptoms in pediatric COVID-19 cases by combining different markers. This contributes to a deeper comprehension of how the disease progresses and assists in developing personalized management strategies for this vulnerable population. Existing literature demonstrates that hematological measures, such as the neutrophil-to-lymphocyte ratio, can be utilized as cost-effective and predictive predictors of prognosis in many diseases (**Güllü *et al.*, 2022**).

This study specifically examines juvenile instances of COVID-19 and assesses the predictive significance of specific hematologic markers, such as the neutrophil-to-lymphocyte ratio, about clinical symptoms and prognosis. The results of this study have significant consequences for categorizing risk and creating tailored approaches for managing pediatric COVID-19 cases. This study seeks to provide useful insights into risk assessment and disease treatment in pediatric patients with COVID-19 by analyzing the correlation between hematological markers and the clinical course of the disease. This systematic review emphasizes the significance of hematological measures, such as the neutrophil-to-lymphocyte ratio and other markers of inflammation, in forecasting the progression and result of COVID-19 cases in children (**Addetia *et al.*, 2020**).

Based on the reviewed research, CT and NLR values serve as valuable indicators for predicting the progression of pediatric COVID-19 cases. Specifically, higher CT values are linked to less severe symptoms and a lower amount of virus, but higher NLR values suggest more severe symptoms and poorer outcomes (**Sacco *et al.*, 2022**). Furthermore, the systematic review emphasized that age plays a crucial role in determining the clinical progression of pediatric COVID-19 patients. Hence, the amalgamation of CT and NLR values along with patient age can enhance the precision in forecasting the clinical trajectory and outcome in pediatric COVID-19 cases (**Hao *et al.*, 2022**).

Various variables have been examined to forecast the clinical manifestations in pediatric patients with COVID-19. The clinical symptoms observed in children with COVID-19 include fever and cough, which are less common than adults (**Young *et al.*, 2020**) **(Cui *et al.*, 2021**). Furthermore, pediatric patients often experience gastrointestinal symptoms such as diarrhea, nausea/vomiting, and abdominal discomfort (**Gisi *et al.*, 2022**) Ct levels over 19 have been linked to asymptomatic infections, possibly indicating disease severity in pediatric patients [4] Furthermore, it has been discovered that C-reactive protein and chest CT scans provide further diagnostic benefits in suspected instances of COVID-19 (**Kassas *et al.*, 2020**). Significantly, the outlook for children undergoing immunosuppressive therapy who contract new COVID-19 infection is more favorable compared to individuals with other concurrent medical problems (**Balashov *et al.*, 2021**). It is crucial to acknowledge that while there is extensive

reporting on the occurrence and symptoms of COVID-19 in adults, our knowledge regarding the spread and consequences of COVID-19 in children is restricted (**Otto *et al.,* 2020**). Investigating the potential value of CT, C-reactive protein, and other hematologic markers in predicting disease severity and clinical outcomes in pediatric COVID-19 cases is a crucial and intricate area of research (**Korkmaz *et al.,* 2020**).

In addition, including CT values, NLR, patient age, and other clinical manifestations as prognostic factors in this study offers a comprehensive method for evaluating the risk and managing the disease in pediatric COVID-19 cases (**Smith *et al.,* 2022**). By adopting a comprehensive perspective, one can gain a more refined comprehension of the progression of the disease and guarantee the creation of tailored approaches to managing the needs of this susceptible group (**Woodruff *et al.,* 2022**). The Intricate Nature of the connection between hematologic markers and clinical outcomes in juvenile COVID-19 emphasizes the necessity for a comprehensive strategy to evaluate disease severity and prognosis in this group (**Cevik *et al.,* 2021**). This study assesses these parameters, providing useful insights into the categorization of risk, managing the condition, and creating customized strategies for pediatric COVID-19 cases.

Future research should focus on identifying the factors that accurately predict the occurrence of COVID-19 in children

According to this comprehensive analysis, there are multiple suggestions for future studies on factors that can predict the progression of pediatric COVID-19 cases. It is crucial to conduct future research to investigate the predictors of pediatric COVID-19 to further our comprehension of the disease. Longitudinal investigations are necessary to validate the results and ascertain those at a heightened risk of experiencing severe inflammation and multiorgan failure (Celik et al., 2021). Furthermore, it is crucial to update the existing evidence-based clinical guidelines when new data emerges to direct the treatment of multisystem inflammatory syndrome in children with SARS-CoV-2 and hyperinflammation in pediatric COVID-19 (Henderson et al., 2022). Further work is needed to determine the usefulness and relevance of using Ct values higher than 19 to predict pediatric illness severity in silent infections in clinical settings. Furthermore, it is crucial to continuously monitor and research the effects of the COVID-19 pandemic on the rates of routine pediatric vaccination and the percentage of vaccinated children in different healthcare systems. This is necessary to minimize any potential long-term impacts (Desilva et al., 2022). It is crucial to comprehend the range of mucocutaneous disease and related clinical features in children and adolescents with COVID-19 and multisystem inflammatory disorders to enhance diagnostic and therapeutic approaches (Rekhtman et al., 2021).

This comprehensive assessment and analysis of hematological data establishes a strong basis for future investigations into prognostic factors in pediatric COVID-19 cases. The recommendations presented in this study provide significant guidance for further research and comprehension of this illness. Longitudinal investigations validate the results and pinpoint individuals at a heightened risk of experiencing severe inflammation and multiorgan failure (Zheng et al., 2020). The ever-changing Nature of COVID-19 and its effects on children necessitates a thorough and ongoing evaluation to guide medical treatment effectively and determine risk levels. This research promotes longitudinal studies to facilitate a more comprehensive comprehension of disease progression and the factors that impact its severity in pediatric cases (Brown et al., 2021). Furthermore, it is crucial to consistently update evidence-based clinical guidelines as new data emerges, specifically with multisystem inflammatory syndromes in children linked to SARS-CoV-2 and hyperinflammation in pediatric COVID-19 (Dailey et al., 2022) . The dynamic Nature of the disease and its varied presentations in juvenile patients necessitate a flexible and adaptable approach to clinical guidelines (Shen et al., 2020).

Further work is needed to explore the possibility of Ct values exceeding 19 as a predictor of asymptomatic infection and illness severity in pediatric patients. It is crucial to verify the dependability and relevance of these predictors in the clinical environment to ensure precise evaluation and control of pediatric COVID-19 cases (Machura et al., 2023). It is crucial to closely observe the influence of the COVID-19 pandemic on the rates of routine childhood immunization and the percentage of immunized children in various healthcare systems. The study's suggestion to persist in monitoring and investigating this domain is crucial to alleviate potential enduring repercussions and guarantee the ongoing safeguarding of youngsters against avoidable illnesses during the pandemic (Singanayagam et al., 2020).

Moreover, it is crucial to enhance diagnostic and therapeutic strategies by comprehending the diversity of mucocutaneous disease and related clinical features in children and adolescents with COVID-19 and multisystem inflammatory syndromes (Nooh et al., 2022). The study's focus on research requirements underscores significant deficiencies in existing knowledge. It establishes the foundation for progress in diagnostic and therapeutic methods for children with COVID-19 and its associated problems. Ultimately, this comprehensive examination and evaluation of hematological factors in children with COVID-19 offers significant perspectives and suggestions for future investigations. To enhance clinical management, risk assessment, and outcomes for children afflicted by the virus, it is crucial to implement these suggestions and enhance our comprehension of factors that indicate the severity of pediatric COVID-19.

4. CONCLUSION

A thorough examination of blood-related measurements and clinical characteristics in children with COVID-19 shows an urgent requirement for a multifaceted strategy to comprehend the seriousness of the disease and predict its outcome in this susceptible group. This study emphasizes the intricate relationships among biomarkers, clinical symptoms, and disease advancement, underscoring the significance of a comprehensive evaluation in instances of pediatric COVID-19.

The Multifaceted Nature of pediatric COVID-19 needs a detailed understanding of prediction markers and risk variables to enable individualized disease management and intervention. By underlining the relevance of adding CT values, NLR, patient age, and other clinical symptoms as prognostic criteria, your study provides a solid platform for improving pediatric COVID-19 research and clinical practice. Based on the findings gathered from this study, various recommendations for future research and clinical practice can be established. First, continued longitudinal investigations are necessary to confirm the findings and identify patients at high risk of severe inflammation and multiorgan failure. This research will contribute to ongoing evidence-based clinical guidelines that should be changed routinely as further information becomes available, notably in multisystem inflammatory syndrome and hyperinflammation in pediatric COVID-19. Furthermore, the reliability and application of Ct values greater than 19 as predictors of asymptomatic infection and disease severity in pediatric patients deserve further exploration and validation in varied clinical contexts. In addition, continued monitoring and research efforts are essential to assess the impact of the pandemic on routine pediatric vaccination rates and to understand the variability of mucocutaneous disease and associated clinical characteristics in children and adolescents with COVID-19 and multisystem inflammatory syndrome.

This study's emphasis on the need for advancements in diagnostic and treatment approaches for children with COVID-19 and related problems highlights the necessity of continued research and clinical vigilance. Contributions to the understanding of pediatric COVID-19 and its predictors are invaluable, and the recommendations presented by this study offer strategic routes for further exploration and action. By incorporating these insights into continuing research and clinical practice, we can continue to enhance risk assessment, illness management, and, ultimately, outcomes for pediatric patients afflicted by COVID-19.

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