Predictive Value of Pragnostic Nutritional

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Original Article

Predictive Value of Prognostic Nutritional Index in Children with COVID-19

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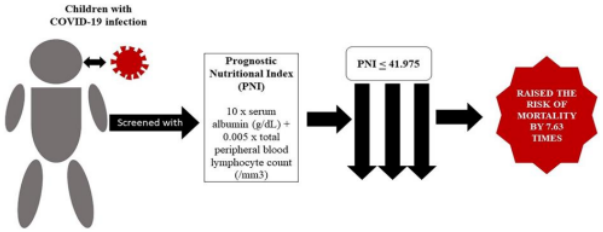
ABSTRACT

Background and aim: Severe malnutrition might contribute the poor outcomes in COVID-19. This study aims to investigate the relationship between prognostic nutritional index (PNI) and mortality in children with COVID-19 infection and its predictive value for predicting poor prognosis.
Methods: A case control study using medical records of paediatric patients with COVID-19 was conducted from June 2020-July 2022. Subjects were divided into two groups: non-survived and survived. PNI value were calculated as 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (/mm^3). PNI was compared with nutritional status and several markers that have been used in COVID-19, including (1) neutrophil to lymphocyte ratio (NLR), (2) systemic immune inflammation index (SII), and (3) platelet to lymphocyte ratio (PLR).
Results: Among 124 eligible subjects, 34 (27.41%) were in the non-survived group and 90 (72.58%) children in the survived group. Children with severe malnutrition had lower albumin and a greater risk of death than those with good nutrition. PNI, NLR, and SII were significantly correlated with the mortality children with COVID-19 except for PLR; P = 0.001, P = 0.001, P = 0.021, and P = 0.118, respectively. Receiver operating characteristic curves stated that PNI (AUC = 0.741, P < 0.0001). The cut-off values of PNI were 41.975 with sensitivities of 73.5% and specificities of 73.3%. PNI value <41.975 had a 7.64 times greater risk of mortality (P < 0.0001).
Conclusion: PNI might be used as predictive value for predicting poor outcome in children with COVID-19 infection.

GRAPHICAL ABSTRACT



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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the agent causing the 2019 coronavirus disease (COVID-19) pandemic [1]. The prognostic nutritional index (PNI), is one of the tools originally used for the nutritional assessment of elective surgery patients. PNI was obtained based on the calculation of number of peripheral blood lymphocytes and serum albumin levels. Some evidence has shown that PNI can predict clinical outcomes in various diseases [2-6].

Several investigations on COVID-19 infection in children have found that infection, symptom, and fatality rates differ from those in adults [7, 8]. In paediatric patients with SARS-CoV-2 infection, 83% of children had a relatively mild to moderate infection, 13% of confirmed cases were asymptomatic, and only 3% of confirmed cases had severe to critical disease manifestations [9]. Risk factors for poor outcomes in COVID-19 pneumonia include poor nutrition and low uptake of immunizations [10]. One in every ten deaths in children under the age of five in low-income countries is due to severe malnutrition, because these children are at higher risk of contracting infectious infections. Prior to the COVID-19 pandemic, an estimated millions of children under five years old were either wasted or severely wasted. Over the first 12 months of the COVID-19 pandemic, 6.7 million children are projected to become wasted, with 80% occurring in Africa and South Asia [11].

Various studies have been conducted to identify factors that predict the severity of COVID-19 infection [12, 13]. In COVID-19 patients, the neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) have a relationship with the outcome [14]. Several studies have integrated clinical and laboratory variables to create prognostic scores for the clinical management of COVID-19 patients to determine disease prognosis at admission [15]. Although numerous prognostic factors or models for predicting outcomes in COVID-19 patients have been described, no examination of predictive factors for disease severity or death in the paediatric patient subgroup has been reported [16].

The Prognostic Nutritional Index (PNI) value is able to represent the patient's nutritional status and immunity. The first component of PNI is serum albumin level which is a popular indicator of protein status used in non-inflammatory patients. The spread of a cytokine storm, which causes systemic inflammation, has been identified as a major driver of disease development in COVID-19 patients. In this case, hypoalbuminemia is an indicator of adverse inflammatory status and poor outcome in COVID-19 patients. The lymphocyte count, another important component of PNI, is relatively low in patients who died compared to those who are still surviving. Direct viral invasion of lymphocytes, which, together with excessive release of cytokines, can induce lymphocyte apoptosis. Some evidence has indicated that PNI can predict clinical outcome in various diseases [2]. There has been no research to date on predictors of COVID-19 death in children. Early detection and prediction of COVID-19 mortality will allow for earlier intervention. Therefore, this study aims to investigate whether PNI has a relationship with the mortality incidence in children with confirmed COVID-19 infection and its predictive value for predicting the poor prognosis.

Martials and Methods

We conducted an analytic observational study with a case control in the paediatric ward of Dr. Soetomo General Academic Hospital, Surabaya. This study used the medical records of paediatric patients from June 2020 to July 2022. For the inclusion criteria, we collected paediatric patients aged 1 month–18 years old with COVID-19 infection, as evidenced by positive confirmation results via polymerase chain reaction (PCR) swab test and undergoing treatment in the hospital isolation room. Paediatric patients who are confirmed to have COVID-19 will undergo several interventions, including basic data collection and complete blood tests, albumin levels, and clinical outcomes of COVID-19. Participants in this study could be excluded if they met several criteria,

including (1) a history of haematological diseases that affect lymphocyte and platelet levels, (2) a history of nephrology and hepatology diseases that affect albumin levels, (3) insufficient medical record data, and (4) early discharge before or during treatment. We requested parents of paediatric patients to sign an informed consent form allowing medical record data to be utilized as research material. We calculated the PNI value with the formula: 10 x serum albumin (g/dL) + 0.005 x total peripheral blood lymphocyte count (/mm3). This research has been granted ethical clearance issued by the Health Research Ethics Committee at Dr. Soetomo General Academic Hospital, Surabaya, No. 0953/LOE/301.4.2/VI/2022.

Data analysis

Data calculation were performed using Microsoft Excel 2019 and IBM SPSS Statistics Version 24.0. tables and figures will be used to display the data. A descriptive analysis was performed on the frequency distribution table using a statistical measure of frequency (n), percentage (%), mean, and standard deviation (SD). The Kolmogorov-Smirnov test is used to determine the normality of the study variables. The Chi-square test was used to compare the characteristics of children with COVID-19 infection who did not survive versus those who did survive. If it does not meet the Chi-square test, the Fisher Exact test will be carried out. A p-value below 0.05 was declared as statistically significant. Bivariate analysis to determine the differences between the proportions of the qualitative variables. The ANOVA test is used to compare PNI to nutritional status in children with COVID-19. Independent T-test and/or Mann-Whitney U test is used to determine the comparison of the prognostic nutritional index, NLR, SII, and PLR, to the outcome of COVID-19. ROC analysis is used to determine the sensitivity and specificity of several parameters including PNI, NLR, SII, and PLR in predicting mortality due to COVID-19 in children. The Youden Index is used to determine the best threshold value of PNI, NLR, SII, and PLR in predicting mortality in children with COVID-19 infection.

Results and Discussion

We collected a total of 468 children with confirmed COVID-19 through medical record data from June 2020 – July 2022. Of the 468 children with COVID-19, 377 were treated in the hospital isolation room. In this study, we excluded six children with a history of haematology, two children with a history of nephrology, and five children with a history of haematology, and then eight paediatric patients who had an early discharge before or even during therapy and 232 children who had incomplete medical records were eliminated. As a result, 124 children with COVID-19 met the inclusion criteria for this study (Figure 1).

Table 1 lists the data on the characteristics of children with COVID-19 who were included in this study. Approximately, 54.8% are dominated by male children. Most children in the 0-2-year age group were treated in the isolation room; as many as 41 (33.1%). Twenty-four children (19.4%) had a primary diagnosis in respirology. No significant differences were found between the variables of sex, age, and primary diagnosis in the mortality incidence in children with confirmed COVID-19, with P-values of 0.140, 0.153, and 0.460 respectively. We found that 45 children (36.3%) had a normal nutritional status, 35 children (28.2%) were severely underweight, 26 children (21%) were underweight, and 18 children (14.5%) were overweight. In terms of nutritional status, a significant relationship was found with the mortality incidence in children with confirmed COVID-19.

The PNI parameter in non-survived pediatric COVID-19 patients had lower values than those who survived (P <0.0001). Meanwhile, there was a significant difference in the NLR and SII parameter values between two groups of children with COVID-19, with p-values of 0.001 and 0.021, respectively. However, no significant differences in PLR parameters were found between both groups (Table 2).

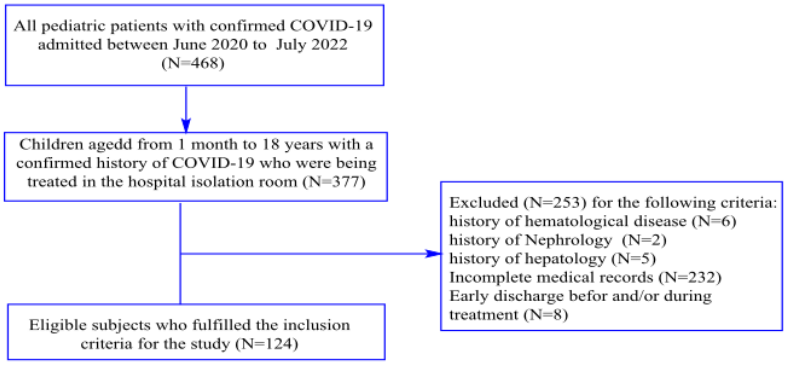

Figure 1: Flowchart of research subject's collection

Table 1: The characteristic of research subjects

Variables	Non-survived n = 34	Survived n = 90	P-value
Sex			
Male	14 (44.1)	53 (58.9)	0.140†
Female	19 (55.9)	37 (41.1)	
Age (year)			
0-2	7 (20.6)	34 (37.8)	
>2-5	3 (8.8)	11 (12.2)	0.153†
>5-12	9 (26.5)	22 (24.4)	
>12-18	15 (44.1)	23 (25.6)	
Primary diagnosis			
Allergy	0 (0)	1 (1.1)	
Surgery	4 (11.8)	17 (18.9)	
Cardiology	3 (8.8)	7 (7.8)	
Endocrinology	0 (0)	3 (3.3)	
Gastroenterology	4 (11.8)	6 (6.7)	0.460†
Hepatology	2 (5.9)	1 (1.1)	
Nephrology	5 (14.7)	10 (11.1)	
Neurology	1 (2.9)	12 (13.3)	
Oncology	5 (14.7)	13 (14.4)	
Respirology	9 (26.5)	15 (16.7)	
Tropic-Infection	1 (2.9)	5 (5.6)	
Nutritional status			
Severely underweight	12 (35.3)	23 (25.4)	
Underweight	9 (26.4)	17 (18.9)	0.003†
Normal	4 (11.8)	41 (45.7)	
Overweight	9 (26.5)	9 (10)	
Parameters			
PNI	39.25 ± 2.34	48.45 ± 1.21	<0.001‡
NLR	7.04 ± 1.14	3.16 ± 0.33	0.001§
SII	1242.4 ± 164	902 ± 114	0.021§
PLR	228.0 ± 52	146.2 ± 16.21	0.118§

Data was presented as number (percentage) and mean ± standard deviation (SD); † Chi-square test and/or Fisher Exact Test; ‡ Independent T-test; § Mann-Whitney U test; PNI = Prognostic Nutritional Index; NLR = Neutrophil to lymphocyte ratio; SII = Systemic immune inflammatory index; and PLR = Platelet to lymphocytes ratio.

Table 2: The comparison of albumin levels and nutritional status in children with COVID-19 infection

Nutritional status	Albumin levels (g/dL)		P-value
	n	Mean ± SD	
Severely underweight	35	3.099 ± 0.548	0.040
Underweight	26	3.233 ± 0.491	
Normal	45	3.389 ± 0.426	
Overweight	18	3.091 ± 0.128	

ANOVA test was used; SD = Standard deviation.

Table 3 presents the mean of albumin levels in the nutritional status of children with COVID-19. Children with COVID-19 who are severely underweight and overweight have lower albumin levels compared to others. The post-hoc analysis showed that albumin levels in children with good nutritional status were significantly different between severely underweight (P = 0.010) and overweight (P = 0.032).

PNI in children infected with COVID-19 was analyzed based on their nutritional status. Table 4 demonstrates that there is no significant difference between PNI and the nutritional status of children with COVID-19. Figure 2 inllustrates the ROC curves of PNI, NLR, SII, and PLR parameters of children infected with COVID-19 analyzed based on mortality. The Youden Index determines the cut-off values for PNI, NLR, SII, and PLR in predicting mortality in children with COVID-19 infection (Table 4). PNI shows the highest Youden Index value compared to other parameters (AUC 0.741, P < 0.0001).

Table 3: The comparison of the PNI to the nutritional status in children with COVID-19 infection

Nutritional status	Prognostic Nutritional Index		P-value
	n	Rerata ± SD	
Severely underweight	35	44.07 ± 12.92	0.064
Underweight	26	47.11 ± 13.03	
Normal	45	48.98 ± 11.88	
Overweight	18	40.16 ± 12.67	

ANOVA test was used.

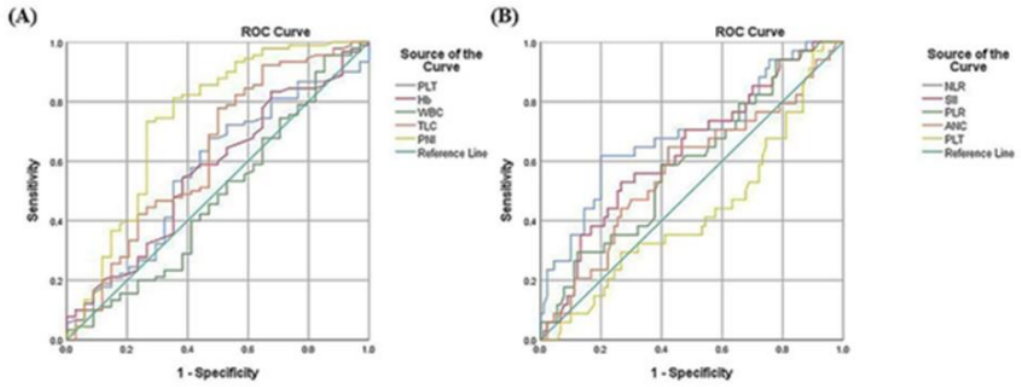

Figure 2: ROC analysis of various parameters for predicting mortality in COVID-19 children (A) ROC analysis on PNI to determine the cut-off value for predicting mortality in COVID-19 children (B) ROC analysis on NLR, and SII determine the cut-off value for predicting mortality in COVID-19 infection

Table 4: The comparison of AUC values on the PNI, NLR, PLR, and SII parameters on the incidence of mortality in children with COVID-19 infection

Parameters	AUC	P-value	95% CI (Lower – Upper)	Cut-off	Youden Index
PNI	0.741	<0.0001	0.629 – 0.852	41.975	0.469
NLR	0.691	0.001	0.581 – 0.801	3.997	0.418
SII	0.635	0.021	0.526 – 0.744	1041.0	0.263
PLR	0.591	0.118	0.480 – 0.702	136.5	0.188

ROC analysis was used. AUC = Area under curve; CI = Confidence interval; PNI = Prognostic Nutritional Index; NLR = Neutrophil to lymphocyte ratio; SII = Systemic immune inflammatory index; and PLR = Platelet to lymphocytes ratio.

Table 4 indicates that the PNI cut-off value is 41,975 with a sensitivity of 73.5% and a specificity of 73.3%, which may be a predictor of death risk in children with COVID-19 infection. Cross-tabulation analysis also showed a negative predictive value (NPV) of 51% and a positive predictive value (PPV) of 88% in predicting death in children with COVID-19 infection. In addition, the PNI parameter shows a positive likelihood ratio of 2.76 and a negative likelihood ratio of 0.36. It may be concluded that children with COVID-19 infection with a PNI value of <41.975 have a 7.63 times higher risk of death than children with a high PNI value (Table 5).

The proportion of COVID-19 infections in children was higher in boys than in girls in this study and several other studies, although no association with increased mortality was found [17, 18]. The results of this study are similar to those of another study mentioned that there was no significant difference between male and female sexes [9]. Boys have a greater risk of death than girls. Two studies stated that 63-69% of those who died from COVID-19 were men [19, 20].

In this study, the age group of 0-2 years old had higher COVID-19 infections, though this was not significantly different from other age groups. This finding is in line with a study that found that based on inpatient data, 27% of patients admitted to the hospital were infants under 1 year of age, and most of the patients (31.6%) who required treatment in the paediatric intensive care unit (PICU) were under 1 year old [21]. Another study indicated that the case fatality rate (CFR) based on age and intensive care unit (ICU) admission rate of infants <1 year has the highest CFR and ICU admission rate [21]. The relationship between COVID-19 severity and mortality by age is controversial. According to one study, children aged >15 years were the most likely to die, accounting for 58% of those who died, whereas children aged 1 year old represented only 7% of those who died [19].

Table 5: Cross-tabulation analysis of PNI, NLR, and SII parameters for predicting mortality in children with COVID-19 infection

Prognostic Nutritional Index	Non-survived n = 34	Survived n = 90	OR	P-value
PNI				
Low (<41.975)	25 (73.5)	24 (26.7)	7.63	<0.0001
High (>41.975)	9 (26.5)	66 (73.3)		
NLR				
High (>3.99)	21 (61.8)	18 (20)	6.46	<0.0001
Low (<3.99)	13 (38.2)	71 (80)		
SII				
High (>1041)	18 (52.9)	24 (26.7)	3.00	0.006
Low (<1041)	16 (47.1)	66 (73.3)		

Chi-square test was used. Data was viewed as number (percentage). OR = Odd ratio; PNI = Prognostic Nutritional Index; NLR = Neutrophil to lymphocyte ratio; and SII = Systemic immune inflammatory index.

A comparison of primary diagnoses in paediatric patients with COVID-19 infection against mortality reveals that some patients (19.4%) have respiratory comorbidities. Several studies have found that the primary diagnoses most frequently associated with mortality are respiratory, cardiovascular, and oncological diseases, obesity, asthma, and developmental disorders [19, 22]. Different results were shown by Patel's study: out of 444 children with COVID-19, 349 had no comorbidities (78.6%), and 95 of the 444 children had comorbidities (21.4%) [17]. COVID-19 increases the risk of significant disease due to structural abnormalities that reduce lung function, which is more common in children with a primary diagnosis in the field of respirology.

Our study found a relationship between nutritional status and the risk of death in children with a COVID-19 infection. Malnutrition with a weight for length or weight for height with a z-score of 3 was associated with up to 50% mortality among hospitalized children [23]. Death due to malnutrition was found in the majority (85.7%) of patients in the ICU, compared to the recovered patients (14%) [20]. Numerous factors influencing immune system function are related to the patient's nutritional status. Protein-energy malnutrition or subclinical micronutrient deficiencies can affect the immune system's ability to respond properly to pathogens. This exacerbates immune suppression and development retardation as energy and micronutrients are diverted to the acute phase of immunological response to fight infection and the risk of bacterial translocation. Obesity has been further associated with poor COVID-19 outcomes, which are mediated by an intensified inflammatory response, increased cardiac injury, and increased coagulation activity [23].

Serum albumin levels in children infected with COVID-19 show lower values in children who are severely underweight and overweight. The relationship between inflammation and low serum albumin levels is still controversial [25, 26]. Hypoalbuminemia is more severe in children with kwashiorkor-type malnutrition than in those with marasmus. The inflammation severity from comorbidities and obesity causes a proportional decrease in serum albumin levels [27, 28]. Malnutrition and inflammation are the main mechanisms by which hypoalbuminemia occurs. Undernutrition is associated with normal plasma albumin levels or conversely, low serum albumin levels seen in chronic disease despite adequate nutritional intake [29].

The PNI parameter in this study showed that there was no significant difference between nutritional status groups. A study in China was conducted on 122 patients infected with COVID-19 and hospitalized, comparing PNI values in populations with normal body mass index (BMI) values, overweight, and obesity, the results of this study stated that lower PNI was found in normal nutritional population compared to overweight and obese [30]. However, another study suggests that malnutrition and PNI have a weak correlation. This corresponds to PNI related to albumin level, more reflective of the severity of the underlying cirrhosis than the poor nutritional status of the patient [31].

PNI, NLR, SII, and PLR were found to be associated with the mortality occurrence in the group of children with COVID-19, particularly in children with low PNI values, high NLR, and high SII, but not with PLR parameters. According to our study, the best NLR cut-off for predicting death in children with COVID19 infection is 3.99. A retrospective analysis of 289 COVID-19 patients compared NLR in patients treated in intensive care and non-intensive care, with ICU patients having considerably higher NLR than non-ICU patients [32].

Our study states that NLR may identify a high risk of death in patients with COVID-19. The exact mechanisms by which NLR differs in its prognostic role as a differentiator for the outcome of COVID-19 patients remain unknown. NLR is influenced by genetic and environmental factors, including BMI and smoking status, to varying degrees. The increase in NLR value, in particular, better reflects the neutrophilia status of COVID-19 patients. Neutrophilia produced by high circulating levels of pro-inflammatory cytokines has been associated with poor outcomes in COVID-19 patients. In addition, lung autopsies of deceased COVID-19 patients have revealed neutrophil infiltration in the pulmonary capillaries, extravasation of neutrophils into the

alveolar spaces, and neutrophilic mucositis. An increase in neutrophil frequency can be a source of excessive reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) and result in severe lung damage. According to this study, the optimal cut-off value of SII in predicting death in children with COVID19 infection is 1041. According to one study, SII was higher in paediatric cancer patients with COVID-19 who died, with 863 in the group that died compared to 302 who survived [33]. Different results were shown by the study of Bilge *et al.*, where SII did not differ between two groups as seen by age, sex, and malignancy both in the non-survivor and survivor groups. These results may indicate that COVID-19 does not trigger an adequate inflammatory response in patients with malignancy [34-36].

The PNI in our study showed lower parameter values in the non-survived group of children with COVID-19 infection. This statement is supported by several studies which state that PNI score was found to be lower in the group that experienced death in patients with COVID-19 [2]. Likewise, another study stated that the group with a low PNI score was 11.2 times more at risk of dying in hospital compared to the group with a normal PNI score [37]. PNI is an index calculated from albumin and lymphocyte levels, which is an objective reflection of inflammatory and nutritional status [38]. In addition, it has been confirmed as having prognostic value in various cardiovascular diseases and malignancies [33, 37].

The correlation between poor outcomes and low albumin levels may be mediated by several mechanisms. First, because albumin is synthesized by hepatocytes, its level is an indicator of liver function. Inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) can inhibit hepatocyte synthesis ability so that serum albumin levels decrease. Cytokine storm occurs due to the release of large amounts of cytokines, including IL-6, interleukin-1 (IL-1), TNF-α, monocyte chemoattractant protein 1 (MCP-1), inducible Interferon-γ (IFN-γ), protein-10 (IP-10), and granulocyte colony-stimulating factor (G-CSF), which cause severe organ damage in COVID-19 patients [35-37]. Therefore, decreased albumin levels may indicate the severity of cytokine storm and organ damage, including liver dysfunction in COVID-19 patients. The second mechanism, low albumin levels can lead to exudation of intravascular fluid that exacerbates the severity of pulmonary edema. Serum albumin levels have been verified to be inversely related to the development of acute respiratory distress syndrome (ARDS) in COVID-19 patients. ARDS is a risk factor for poor prognosis in COVID-19 patients [39-41]. Albumin is a general marker of nutritional status; low albumin levels may suggest a status of mass consumption due to the tissue damage and hypermetabolism in critically ill patients. Poor nutritional status, as indicated by albumin levels, causes failure of tissue repair and recovery in COVID-19 patients [42].

Our study states that PNI can be a predictor of mortality in pediatrics patients with COVID-19 with an AUC value of 0.741 ($P < 0.0001$) which is better than the other two parameters we tested in this study, namely NLR (AUC = 0.691, $P = 0.001$) and SII (AUC = 0.635, $P = 0.021$). The cut-off value of PNI parameter in our findings is 41.975. The cut-off value we obtained is different from various studies related to PNI and mortality in adult patients with COVID-19. The investigation of relationship between PNI levels and disease severity in COVID-19 has a cut-off value that varies from 34 to 49 [37, 39, 40]. The PNI parameter that we evaluated for COVID-19 was initially identified as a clinical predictor of postoperative complications following gastrointestinal surgery. A low serum albumin level, also an important mortality indicator for patients following up in the ICU, has been found to be correlated with a poor prognosis in pneumonia caused by COVID-19. We understand that our study has limitations because the data we used originates from patient medical records. After all, research bias cannot be controlled. However, we believe that this study might be used as an alternative for health workers to determine the prognosis in paediatric patients with COVID-19.

Conclusion

The PNI has been correlated with a poor prognosis, and in children with COVID-19 infection, it may even cause mortality. Our findings show that a PNI value of <41.975 raises the risk of death in pediatric patients with COVID-19 infection by seven times. In this case, the PNI value may be used quickly and effectively, making it particularly helpful to medical personnel working in units with limited health facilities.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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