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ORIGINAL RESEARCH

Hematocrit and Albumin Levels at Admission Predict in-Hospital Mortality in Pediatric COVID-19 Omicron Variant Patients

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Introduction: The Omicron variant is the present predominant COVID-19 strain worldwide. Accurate mortality prediction can facilitate risk stratification and targeted therapies. The study aimed to evaluate the feasibility of the difference in hematocrit and albumin (HCT-ALB) levels, alone or combined with the pediatric Sequential Organ Failure Assessment (pSOFA) score and lactate level, to predict the in-hospital mortality of COVID-19 Omicron variant-infected pediatric patients.

Methods: A multicenter retrospective cohort study was performed for children with COVID-19 Omicron variant infection between December 2021 and January 2022. The demographics, clinical characteristics, hospital admission laboratory test results, and treatments were recorded. The in-hospital mortality was documented. The associations between HCT-ALB levels and mortality, and between HCT-ALB+pSOFA+lactate and mortality were analyzed.

Results: A total of 119 children were included. The median age was 1.6 (interquartile range: 0.5–6.2) years old. There were 70 boys and 49 girls. The mortality rate was 14.3% (17/119). The univariate and multivariate Cox regression analysis revealed that HCT-ALB was associated to in-hospital mortality (hazard ratio: 1.500, 95% confidence interval: 1.235–1.822, $p<0.001$). The receiver operating characteristic curve analysis revealed that HCT-ALB can be used to accurately predict in-hospital mortality at a cut-off value of −0.7 (area under the curve: 0.888, sensitivity: 0.882, specificity: 0.225, Youden index: 0.657, $p<0.001$). These patients were assigned into three groups based on the HCT-ALB level, pSOFA score, and lactate level (low-, medium-, and high-risk groups). The Kaplan-Meier analysis revealed that the mortality increased in the high-risk group, when compared to the medium-risk group ($p<0.01$). The latter group had a higher mortality, when compared to the low-risk group ($p<0.01$).

Conclusion: The HCT-ALB level can be applied to predict the in-hospital mortality of children infected with the COVID-19 Omicron variant. Its combination with other variables can improve prediction performance.

Keywords: COVID-19, omicron variant, hematocrit, albumin, mortality

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Introduction

With the introduction of coronavirus disease 2019 (COVID-19) vaccines and antiviral medications, the hospital admission and mortality rates of SARS-CoV-2-infected patients have significantly decreased.[1,2] However, COVID-19 remains as one of the leading infectious causes of death in young children, with a mortality rate of 1.0 per 100,000 population. This could be due to the limited use of COVID-19 vaccines and antiviral medications in this population.[3–5] Compared to the 12–15 year-old adolescents with a vaccination rate of 53.5%, merely 7.9% of young children under five years old have received the vaccine.[6] The most common mediation for COVID-19 infection, Paxlovid (nirmatrelvir and ritonavir), was only approved for children above 12 years old.[7] Furthermore, studies have reported higher hospital admission rates in young children, when compared to adults, especially in children infected by the COVID-19 Omicron variant.[8,9] It was reported that the peak hospitalization rate was approximately five times for the Omicron variant, when compared with the Delta variant infection.[10] Furthermore, it was suspected that the mutant spike glycoprotein in the Omicron variant can lead to increased binding affinity to the human angiotensin-converting enzyme 2 receptor, and elevated infectivity, resulting in rapid spreading of the Omicron variant infection.[11] Risk stratification and accurate mortality prediction can optimize the targeted therapeutic intervention and supportive care for children with suspected poor outcomes. Several studies have reported the risk factors associated to critical illness in children with COVID-19.[12–14] However, more studies are required to identify risk factors to facilitate the severity stratification for targeted management in children with suspected poor outcomes.

Blood tests, such as blood cell count, chemistry profile, and hepatic function (including protein, bilirubin, and liver enzyme levels), are routinely performed for every sick child admitted to the hospital. The biomarkers obtained from the blood test results are cost-effective and easy to obtain. Previous studies have reported that several blood tests, such as C-reactive protein, lactate dehydrogenase and procalcitonin, are associated to severe illness in COVID-19 children. However, these tests carry low specificity.[15,16] Under normal physiological conditions, hematocrit (HCT) and albumin (ALB) levels remain stable, and are balanced by the semi-selective permeable microvascular endothelial barrier. Due to inflammatory reactions, such as SARS-CoV-2 infection, inflammatory cytokines can damage endothelial cells, and enlarge the intercellular space, disrupting the capillary endothelial barrier, and inducing the leakage of macromolecules.[17] Since the size of red blood cells is significantly larger than ALB, more leakage of ALB occurs, when compared to red blood cells, from the intravascular lumen to the interstitial space. This would decrease the ALB level, and cause the HCT level to remain unchanged or increase (due to the fluid shift into the third space), enlarging the difference between HCT and ALB levels (HCT-ALB level). Previous studies have revealed that the HCT-ALB level can be applied to diagnose infectious diseases, and predict the severity and mortality of patients with sepsis and eclampsia.[18–20] Patients with severe SARS-CoV-2 infection often present with systemic inflammation. Strong systemic inflammation commonly implies a worse outcome in COVID-19 patients.[21] Thus, the investigators explored whether the HCT-ALB level can be used as a biomarker to predict the poor outcome and mortality of patients with severe SARS-CoV-2 infection.

Therefore, the present study aimed to determine the association between the HCT-ALB level and mortality of COVID-19 Omicron variant-infected pediatric children, in order to provide a cost-effective evidence-based biomarker, and a risk stratification strategy to facilitate personalized targeted therapies for high-risk pediatric patients.

Materials and Methods

Study Design and Participant Selection

The present multicenter, retrospective cohort study was conducted between December 2021 and January 2022. The medical charts of pediatric patients in the Affiliated Hospital of Qingdao University and its alliance hospitals in China were reviewed. The study protocol was approved by the ethics committee of each participating hospital. The requirement for a written informed consent was waived due to the retrospective design of the study. The study was performed in strict compliance with the Declaration of Helsinki, and the protection of patient confidentiality.

Inclusion criteria: (1) pediatric patients ≤14 years old, and (2) the hospital admission diagnosis for the COVID-19 Omicron variant was confirmed by reverse transcription-polymerase chain reaction. Exclusion criteria: (1) history of

anemia, autoimmune disease, cirrhosis, congenital heart disease, chronic pulmonary illness, or sleep apnea; (2) abnormal body mass index; (3) patients with no records on HCT and ALB levels; (4) patients with incomplete medical records; (5) patients who gave up the treatment, and signed out of the hospital against medical advice.

Data Collection

Two research assistants independently reviewed the hospital medical records and extracted the necessary information. The retrieved information was compared. Any discrepancy was clarified back in the hospital medical records. The following baseline information of patients was collected: age, gender, medical history, clinical symptoms, and admission laboratory test results. Then, the HCT-ALB (%-g/L) was calculated. In addition, the following treatments received during the hospital stay were recorded: antibiotics, antivirals, intravenous immunoglobulin infusion, and glucocorticoid usage. Furthermore, the in-hospital death or survival was documented. If the patient had multiple hospital admissions, merely the first admission was counted.

Statistical Analysis

Continuous data was presented in mean ± standard deviation (SD), or median with interquartile range (IQR). This data was compared using Student's *t*-test, ANOVA, Mann–Whitney *U*-test, or Kruskal–Wallis rank sum test, depending on the normality test results. Categorical data was presented in numbers with percentages. This data was compared using Chi-square test or Fisher's exact test. The patients were initially assigned into two groups: survival and non-survival groups. Then, the patient characteristics were compared. Characteristics with statistically significant differences between the two groups, including HCT-ALB, were entered into the univariate and multivariate Cox regression analysis, in order to determine the relationships with in-hospital mortality. The hazard ratio (HR) and 95% confidence interval (CI) were reported. Receiver operating characteristic curve (ROC) analysis was performed to evaluate the predictive performance of different variables for in-hospital mortality. Then, all patients were assigned into three risk groups, based on the HCT-ALB level, pediatric Sequential Organ Failure Assessment (pSOFA) score, and lactate level. Each test result received a score of 0 or 1 (HCT-ALB received 0 if <10 or 1 if ≥1; pSOFA score received 0 if <7 or 1 if ≥7; lactate received 0 if <3.5 mmol/L or 1 if ≥3.5 mmol/L). The total score of 0, 1, and 2 or 3 was used to assign the patients into the following three groups: low-risk, medium-risk, and high-risk groups. Kaplan-Meier analysis was performed to determine the in-hospital mortality of patients in these three risk groups. All statistical analyses were performed using SPSS (version 28.0; IBM, NY, USA). A *p*-value of <0.05 was considered statistically significant.

Results

Characteristics of the Study Participants

A total of 119 children infected with the COVID-19 Omicron variant were included for the present study (Figure 1). Among these patients, 70 patients were boys, and 49 patients were girls. The median age of these patients was 1.6 years old (IQR: 0.5–6.2 years old). The overall in-hospital mortality rate was 14.3% (17/119).

Characteristic Comparisons Between the Survival and Non-Survival Groups

The clinical characteristic comparisons revealed that patients in the non-survival group had an older age, presented with cough, and received immunoglobulin or glucocorticoid treatment, when compared to patients in the survival group (Table 1).

The laboratory test result comparisons revealed that patients in the non-survival group had higher white blood cell, lymphocyte and platelet counts, and HCT-ALB, C-reactive protein, ferritin, procalcitonin, D-dimer, interleukin-6, interleukin-10, lactate dehydrogenase, alanine transaminase, aspartate transaminase, lactate, creatine kinase-MB, and creatinine levels, when compared to patients the survival group (Table 2).

Association Between HCT-ALB and in-Hospital Mortality

Variables with statistically significant differences between the survival and non-survival groups were selected (Tables 1 and 2). Then, univariate and multivariate Cox regression analysis was performed (Table 3). The multivariate Cox

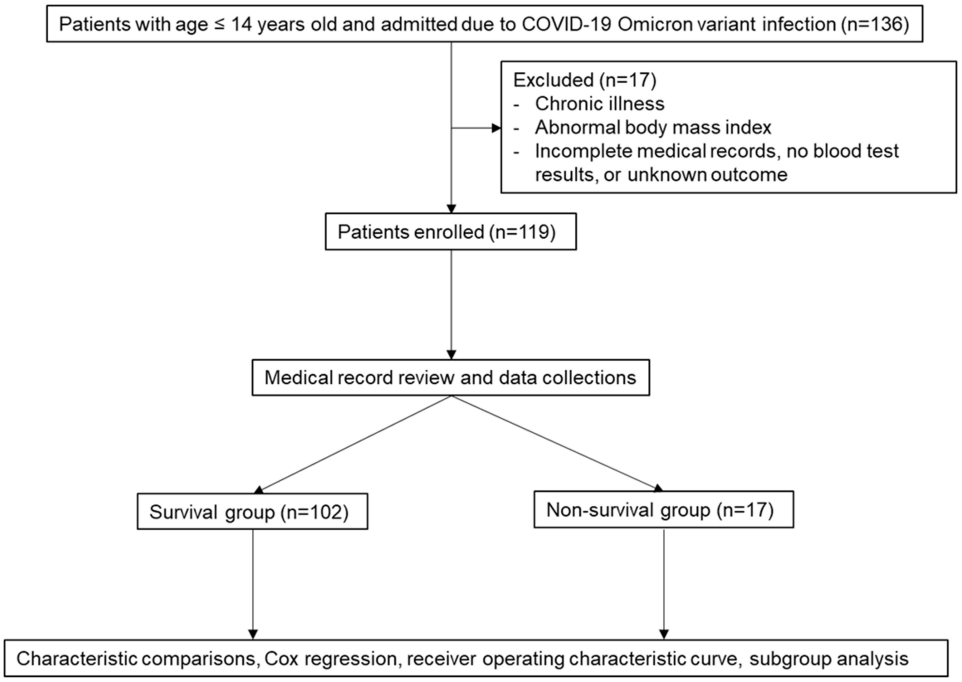


Figure 1 Patient selection and data analysis flowchart.

regression analysis results revealed that HCT-ALB, lymphocyte count, procalcitonin, C-reactive protein, interleukin-6, creatine kinase-MB, and immunoglobulin treatment were associated to in-hospital mortality.

ROC analysis was conducted to determine the performance of variables that were statistically and significantly associated to in-hospital mortality in the multivariate Cox regression analysis. The results revealed that HCT-ALB can be used to accurately predict in-hospital mortality at a cut-off value of −0.7 (area under the curve: 0.888, sensitivity: 0.882, specificity: 0.225, Youden index: 0.657, $p<0.001$; Table 4).

Survival Analysis Among the Different Risk Groups

The patients were assigned into three groups, based on the HCT-ALB level, pSOFA score, and lactate level: high-risk (n=13), medium-risk (n=15), and low-risk (n=91) groups. From the low-risk and medium-risk groups, and to the high-risk group, the HCT-ALB level, pSOFA score, and lactate level gradually increased. The difference among these three variables was statistically significant in the three risk groups, but not for the pSOFA score and HCT-ALB level between the medium-risk and low-risk groups (Figures 2–4). The Kaplan-Meier analysis revealed that the survival chance decreased in the high-risk group, when compared to the medium-risk group ($p<0.01$). Furthermore, the survival chance decreased in the medium-risk group, when compared to the low-risk group ($p<0.01$, Figure 5).

Discussion

Children infected with the COVID-19 Omicron variant can develop severe illness, or even die. In the present study, it was found that HCT-ALB can be used as a biomarker to accurately predict the in-hospital mortality of children infected with the COVID-19 Omicron variant. After combining the HCT-ALB level with the pSOFA score and lactate level, the patients were stratified into three groups. Patients in the high-risk group had higher mortality, when compared to patients in the medium-risk group, and patients in the medium-risk group had higher mortality, when compared to patients in the low-risk group. Therefore, the HCT-ALB level can be used alone, or together with the pSOFA score and lactate level to predict the mortality, and guide the appropriate management of children infected with the COVID-19 Omicron variant.

Due to the high prevalence of SARS-CoV-2 infection, it is important to identify patients with potential poor outcomes, in order to administer prompt management. Previous studies on adult patients infected with SARS-CoV-2

Table 1 Clinical Characteristic Comparisons Between the Survival and Non-Survival Groups

Characteristics	Survivor Group (*n*=102)	Non-survivor Group (*n*=17)	*p*
Age, years	1.4 (0.30–6.20)	5.7 (0.90–8.80)	0.045
Gender, male, *n* (%)	61 (59.80)	9 (52.94)	0.595
Medical history, *n* (%)			0.001
None	95 (93.10)	11 (64.70)	
Cerebral palsy	0 (0.00)	1 (5.90)	
Growth retardation	3 (2.90)	1 (5.90)	
Systemic lupus erythematosus	0 (0.00)	1 (5.90)	
Nephrotic syndrome	1 (1.00)	1 (5.90)	
Pompe disease	0 (0.00)	1 (5.90)	
Mitochondrial encephalomyopathy	1 (1.00)	0 (0.00)	
Epilepsy	1 (1.00)	0 (0.00)	
Little Fat Willy syndrome	0 (0.00)	1 (5.90)	
Metachromatic leukodystrophy	1 (1.00)	0 (0.00)	
Symptoms on admission, *n* (%)			
Fever, ≥38.0°C	100 (98.00)	16 (94.10)	0.373
Cough	60 (58.80)	5 (29.40)	0.024
Croup	5 (4.90)	0 (0.00)	1.000
Shortness of breath	15 (14.70)	5 (29.40)	0.250
Laryngeal obstruction	1 (1.00)	1 (5.90)	0.266
Vomiting	12 (11.80)	5 (29.40)	0.121
Abdominal pain	4 (3.90)	1 (5.90)	0.544
Conjunctivitis	1 (1.00)	0 (0.00)	1.000
Rash	3 (2.90)	2 (11.80)	0.148
Diarrhea	8 (7.80)	2 (11.80)	0.946
In-hospital treatments, *n* (%)			
Antibiotics	65 (63.73)	14 (82.35)	0.132
Antiviral	8 (7.84)	4 (23.53)	0.120
Intravenous immunoglobulin	23 (22.55)	14 (82.35)	<0.001
Glucocorticoids			<0.001
None	23 (22.55)	3 (17.65)	
Methylprednisolone 1–2 mg/kg/d (2–3 days)	46 (45.10)	9 (52.94)	
Methylprednisolone 10–20 mg/kg/d (2–3 days)	1 (0.98)	5 (29.41)	
Dexamethasone 0.2 mg/kg·d (2–3 days)	32 (31.37)	0 (0.00)	

reported that older age, male gender, medical history (such as immunosuppressed status), and Black race can increase the risk for mortality.[22] Vaccination is a protective factor for disease severity and death.[23] For children infected with SARS-CoV-2, comorbidities (such as respiratory conditions), symptoms, and laboratory test results can be associated to mortality.[24] Most studies that determined the mortality established clinical prediction models that commonly included various clinical characteristics and laboratory test results.[12–14] However, most of these models could not be easily calculated, and are difficult to use in clinic. Therefore, there is a need to identify biomarkers that can accurately predict the mortality of children infected with the COVID-19 Omicron variant. Thus, the investigators aimed to identify a simple and easy biomarker that is feasible for the routine daily care of these children.

HCT is part of the report for the complete cell count test. Complete cell count is a routine test for patients admitted to the hospital. The serum ALB level is analyzed during the hepatic function test, and is a routine laboratory examination performed during hospital admission. Previous studies have revealed that the HCT-ALB level is correlated to disease severity. Wang et al conducted a retrospective study on two large databases, which included 16, 127 and 3043 sepsis patients. They found that high HCT-ALB level is an independent risk factor for in-hospital mortality.[19] Dai et al analyzed the HCT-ALB level in healthy controls, normal pregnant women, pregnant women with hypertension, and pregnant

Table 2 Laboratory Test Result Comparisons Between the Survival and Non-Survival Groups

Laboratory Results	Survivor Group (*n*=102)	Non-survivor Group (*n*=17)	*p*
pSOFA score	5.00 (3.80, 5.00)	9.00 (8.00, 11.50)	<0.001
White blood cell, $\times 10^9$/L	6.50 (4.80, 10.10)	11.50 (8.60, 14.40)	0.002
Lymphocyte, $\times 10^9$/L	1.60 (1.10, 3.00)	3.20 (1.60, 5.20)	0.003
Platelet, $\times 10^9$/L	273.10 ± 101.90	200.80 ± 87.30	0.200
HCT-ALB, %-g/L	−4.50 (−7.40, −1.20)	11.40 (0.40, 14.80)	<0.001
C-reactive protein, mg/dL	5.00 (1.50, 15.60)	44.50 (26.80, 112.10)	<0.001
Ferritin, ng/mL	356.00 (244.30, 454.50)	3,476.00 (671.50, 7,217.00)	<0.001
Procalcitonin, ng/mL	0.20 (0.10, 0.50)	66.90 (20.10, 113.50)	<0.001
D-dimer, μg/mL	1.10 (0.60, 1.70)	9.40 (5.40, 40.40)	<0.001
Interleukin-6, pg/mL	24.70 (8.00, 39.50)	746.60 (144.10, 1,568.60)	<0.001
Interleukin-10, pg/mL	10.50 (6.90, 22.80)	119.00 (86.40, 168.40)	<0.001
Lactate dehydrogenase, U/L	400.50 (312.50, 511.80)	7,912.00 (3,075.00, 9,968.00)	<0.001
Alanine transaminase, U/L	20.00 (15.20, 29.00)	310.60 (96.60, 1,292.50)	<0.001
Aspartate transaminase, U/L	42.80 (30.00, 59.30)	568.30 (182.80, 3,074.00)	<0.001
Total bilirubin, μmol/L	6.90 (4.10, 12.30)	7.20 (4.40, 15.40)	0.579
Lactate, mmol/L	2.30 (1.70, 2.80)	5.80 (2.60, 8.60)	<0.001
Creatine kinase-MB, ng/mL	2.10 (1.10, 3.50)	9.20 (3.70, 16.20)	<0.001

Notes: All data were presented in median (interquartile range), except for the platelet count, which was presented in mean ± standard deviation.
Abbreviations: pSOFA score, pediatric Sequential Organ Failure Assessment score; HCT-ALB, hematocrit and albumin.

Table 3 Univariate and Multivariate Cox Regression Analysis

Variables	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Age	1.125	0.097–1.270	0.057	–	–	–
pSOFA score	62091839.970	0.000–0.000	0.991	–	–	–
White blood cell	1.107	1.025–1.195	0.009	–	–	–
Lymphocyte	1.436	1.131–1.823	0.003	0.645	0.460–0.902	0.011
HCT-ALB	1.314	1.174–1.472	<0.001	1.500	1.235–1.822	<0.001
C-reactive protein	1.022	1.010–1.034	<0.001	1.018	1.003–1.033	0.019
Ferritin	1.003	1.001–1.006	0.004	-	-	-
Procalcitonin	1.112	1.054–1.173	<0.001	1.035	1.017–1.053	<0.001
D-dimer	2.240	1.485–3.380	<0.001	-	-	-
Interleukin-6	1.013	1.004–1.022	0.006	1.003	1.001–1.004	<0.001
Interleukin-10	1.000	0.999–1.002	0.421	-	-	-
Lactate dehydrogenase	1.005	1.000–1.010	0.062	-	-	-
Alanine transaminase	1.008	1.003–1.013	0.002	-	-	-
Aspartate transaminase	1.007	1.003–1.012	<0.001	-	-	-
Lactate	2.899	1.740–4.829	<0.001	0.749	0.561–0.999	0.490
Creatine kinase-MB	1.291	1.136–1.468	<0.001	0.836	0.756–0.925	<0.001
Creatinine	1.831E+10	0.000–0.000	0.999	-	-	-
Cough	0.292	0.096–0.890	0.030	-	-	-
Glucocorticoids	0.772	0.468–1.273	0.311	-	-	-
Immunoglobulin	16.029	4.237–60.643	<0.001	61.920	5.840–656.484	<0.001

Abbreviations: CI, confidence interval; pSOFA score, pediatric Sequential Organ Failure Assessment score; HCT-ALB, hematocrit and albumin.

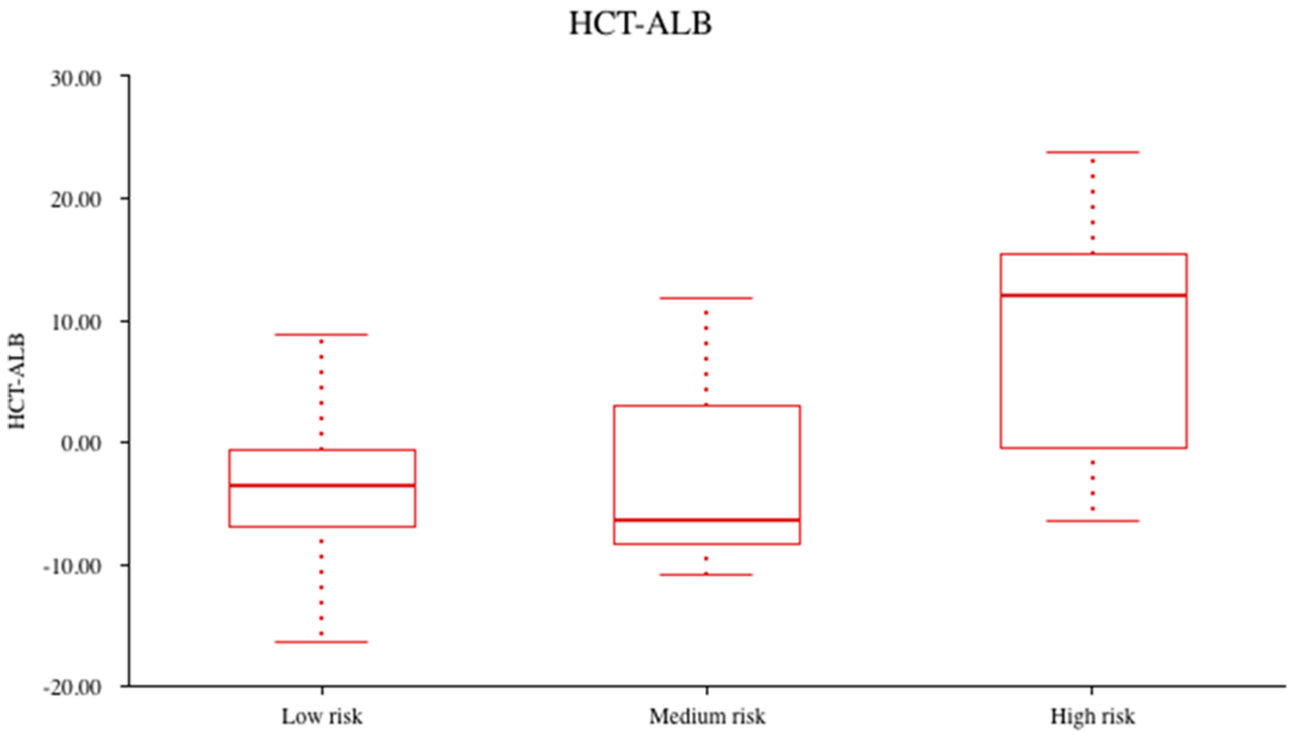
women with preeclampsia or eclampsia. They concluded that an HCT-ALB level of >12.65 can be used to facilitate the diagnosis of preeclampsia and eclampsia in pregnant women.[18] The same research group also retrospectively compared patients with and without infection to healthy controls, and recommended that HCT-ALB >10.25 can be used to make

Table 4 Receiver Operating Characteristic Curve Analysis for Predictive Performance

Variables	AUC (95% CI)	Sensitivity	Specificity	Youden Index	Cut-off Value	*p*
Lymphocyte	0.724	70.60%	31.40%	0.392	2.40	0.003
HCT-ALB	0.888	88.20%	22.50%	0.657	−0.70	<0.001
C-reactive protein	0.909	88.20%	16.70%	0.716	21.50	<0.001
Procalcitonin	0.987	100.00%	5.90%	0.941	4.10	<0.001
Interleukin-6	0.897	82.40%	7.80%	0.745	83.40	<0.001
Lactate	0.819	64.70%	0.00%	0.647	4.80	<0.001
Creatine kinase-MB	0.885	70.60%	10.80%	0.598	5.00	<0.001
Intravenous immunoglobulin	0.799	82.40%	22.50%	0.597	0.50	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; HCT-ALB, hematocrit- albumin.

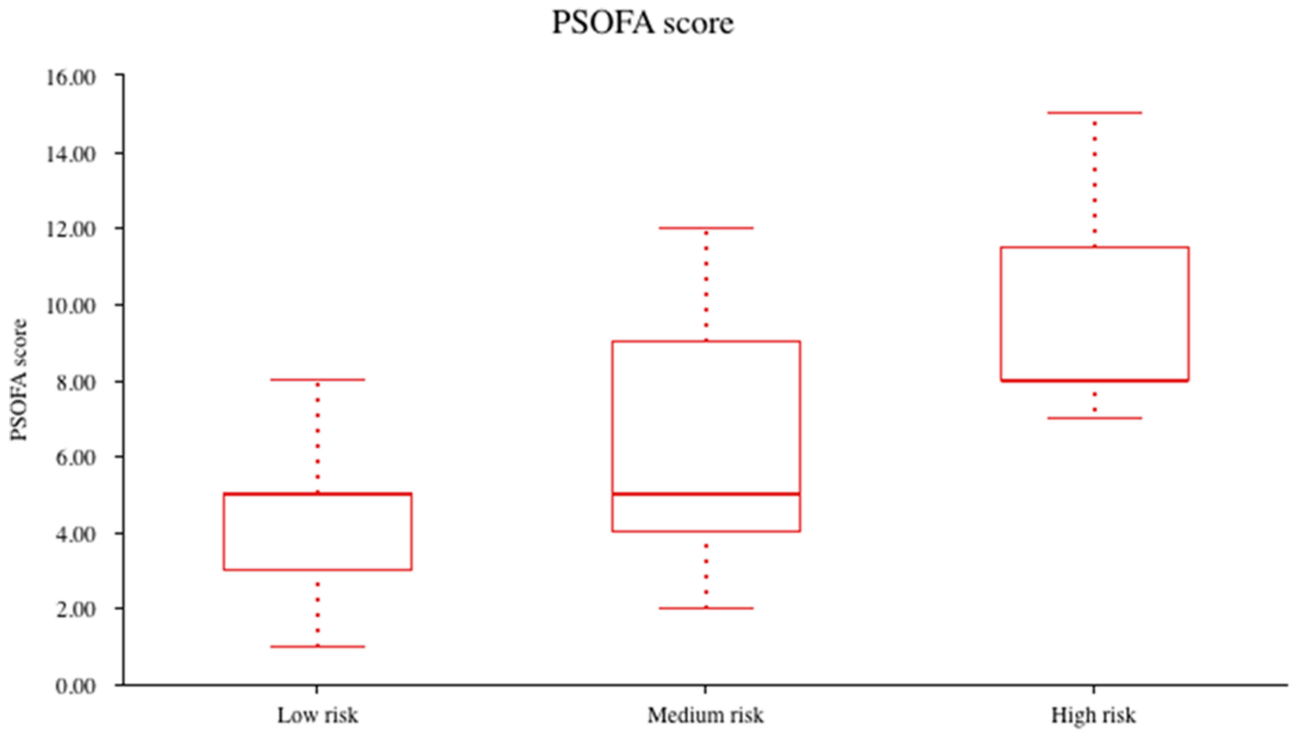
a quick diagnosis of infection for early antibiotic treatment.[20] This study result was consistent with another study result, which revealed that high HCT-ALB levels can be used to differentiate septic shock from hemorrhagic shock.[25] Another two studies reported that high HCT-ALB levels are correlated to more severe scrub typhus disease or acute paraquat poisoning.[26,27] For all these studies, the investigators suggested that the potential underlying rationale to use HCT-ALB to predict disease prognosis was the systemic inflammatory reaction. Systemic inflammation can increase capillary permeability, with subsequent ALB leakage, intravascular fluid escape, and hemoconcentration. This would finally result in decreased ALB levels and increased HCT levels, thereby enlarging the difference between HCT and ALB levels. Since



HCT-ALB	Group	Median	Group	Median	Inter-group difference	p
	Low-risk group	-3.580	Medium risk	-6.470	2.890	0.891
	Low-risk group	-3.580	High risk	12.040	-15.620	<0.001
	Medium-risk group	-6.470	High risk	12.040	-18.510	0.001

HCT-ALB, hematocrit- albumin

Figure 2 Comparison of HCT-ALB levels in the low-risk, medium-risk, and high-risk groups.



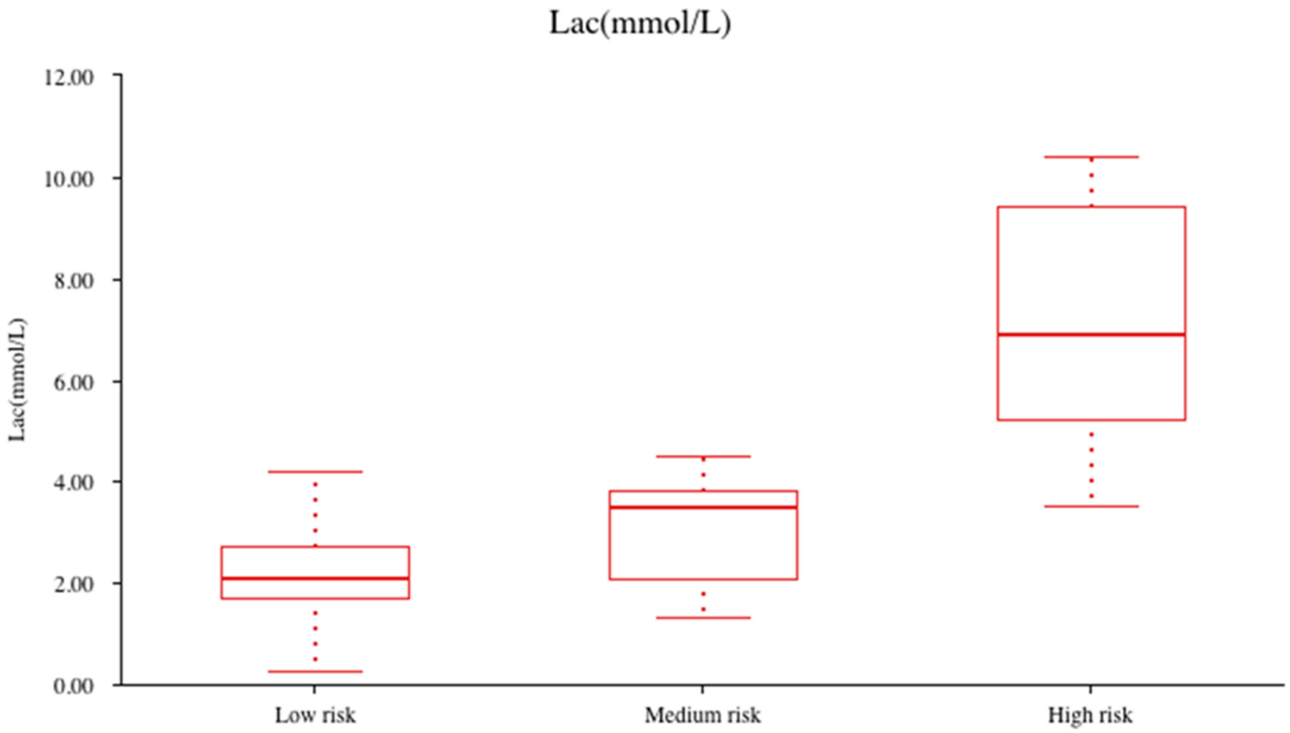
pSOFA score	Group	Median	Group	Median	Inter-group difference	p
	Low-risk group	5.000	Medium risk	5.000	0.000	0.268
	Low-risk group	5.000	High risk	8.000	-3.000	<0.001
	Medium-risk group	5.000	High risk	8.000	-3.000	0.004

pSOFA, pediatric Sequential Organ Failure Assessment

Figure 3 Comparison of pediatric Sequential Organ Failure Assessment (pSOFA) scores in the low-risk, medium-risk, and high-risk groups.

patients with severe SARS-CoV-2 infection commonly present with the cytokine storm and overwhelming systemic inflammation,[28] the investigators hypothesized that HCT-ALB changes with the severity of COVID-19, and that this might be used as a biomarker to predict mortality.

In the present study, it was found that the difference in HCT-ALB was statistically significant between the survival and non-survival groups. Furthermore, the multivariate regression analysis revealed that HCT-ALB can be used to independently predict mortality. Moreover, the ROC curve analysis revealed an AUC of 0.888 when HCT-ALB was tested to predict mortality. Since an AUC of >0.8 commonly indicates good performance, and the clinical applicability of a diagnostic test,[29] the investigators considered that HCT-ALB can be used to predict the in-hospital mortality of children infected with the COVID-19 Omicron variant in clinic. For all the markers that had significant associations with mortality in the multivariate analysis, the ROC curve revealed that only three biomarkers had an AUC higher than that of HCT-ALB. These three biomarkers were C-reactive protein, procalcitonin, and interleukin-6. These had a specificity lower than that for HCT-ALB. The C-reactive protein level can increase due to various different disease statutes, and this might explain its low specificity.[30] Procalcitonin is a marker for bacterial infection. This is often used to discriminate between bacterial and viral infection. Children with COVID-19, who present with high procalcitonin levels, might have concurrent bacterial infection.[31] The role of procalcitonin to predict mortality in children with COVID-19, who do not have bacterial infection, requires further studies. Interleukin-6 is a cytokine that can be used to predict mortality in COVID-19 patients.[32] However, interleukin-6 is not a routine test performed for the majority of patients, and this is not widely tested in every hospital laboratory. Considering all these evidences, the investigators considered that HCT-ALB has great value as a valid biomarker to predict mortality in children infected by the COVID-19 Omicron variant. This is simple and easy to calculate, and is widely available in clinic. Thus, this should be considered by clinicians who treat this patient population.



Lactate	Group	Median	Group	Median	Inter-group difference	p
	Low-risk group	2.100	Medium risk	3.500	-1.400	0.017
	Low-risk group	2.100	High risk	6.900	-4.800	0.000
	Medium-risk group	3.500	High risk	6.900	-3.400	0.030

Figure 4 Comparison of lactate levels in the low-risk, medium-risk, and high-risk groups.

Previous studies have revealed that the pSOFA score is associated to poor outcomes in children infected with SARS-CoV-2.[33] Furthermore, lactate has been proposed to be a biomarker for the unfavorable prognosis of patients infected with SARS-CoV-2.[34] In the present study, the investigators combined the HCT-ALB level, pSOFA score, and lactate level, and stratified children with COVID-19 into three risk groups. The HCT-ALB level, pSOFA score, and lactate level gradually increased from the low-risk and medium-risk groups, to the high-risk group. Patients in the high-risk group had higher mortality, when compared to patients in the medium-risk group, and patients in the medium-risk group had higher mortality, when compared to patients in the low-risk group. Therefore, the strategy applied by the investigators to group COVID-19 subjects based on the HCT-ALB level, pSOFA score, and lactate level can be used as a reliable method to predict in-hospital mortality in children infected with the COVID-19 Omicron variant.

Overall, the present study provides evidence that routine blood tests on HCT and ALB can provide valuable insights, and might impact the clinical management of children with COVID-19 Omicron variant infection. Combining the HCT-ALB level with the pSOFA score and lactate level allows for the further classification of patients into different risk groups. The present innovative finding for the HCT-ALB level, as a predictive biomarker for pediatric COVID-19 patients, can facilitate risk stratification, targeted treatments, and better resource allocation. The simplicity and wide availability of HCT and ALB tests enable the study results to be easily applicable in routine clinical practice, which can impact the prognosis of children infected by the COVID-19 Omicron variant.

The strength of the present study was that the study results proposed a biomarker that is simple, widely available, and easy to be obtained from routine laboratory test results, in order to predict the mortality of children with COVID-19. Furthermore, the results suggested a stratification strategy to group children with COVID-19 based on three measurements, in order to predict the risk of mortality. The limitations of the present study were the retrospective design of the study, the small number of participants, and the short follow-up period only for in-hospital mortality. Furthermore, patients with self-reported history of anemia or liver

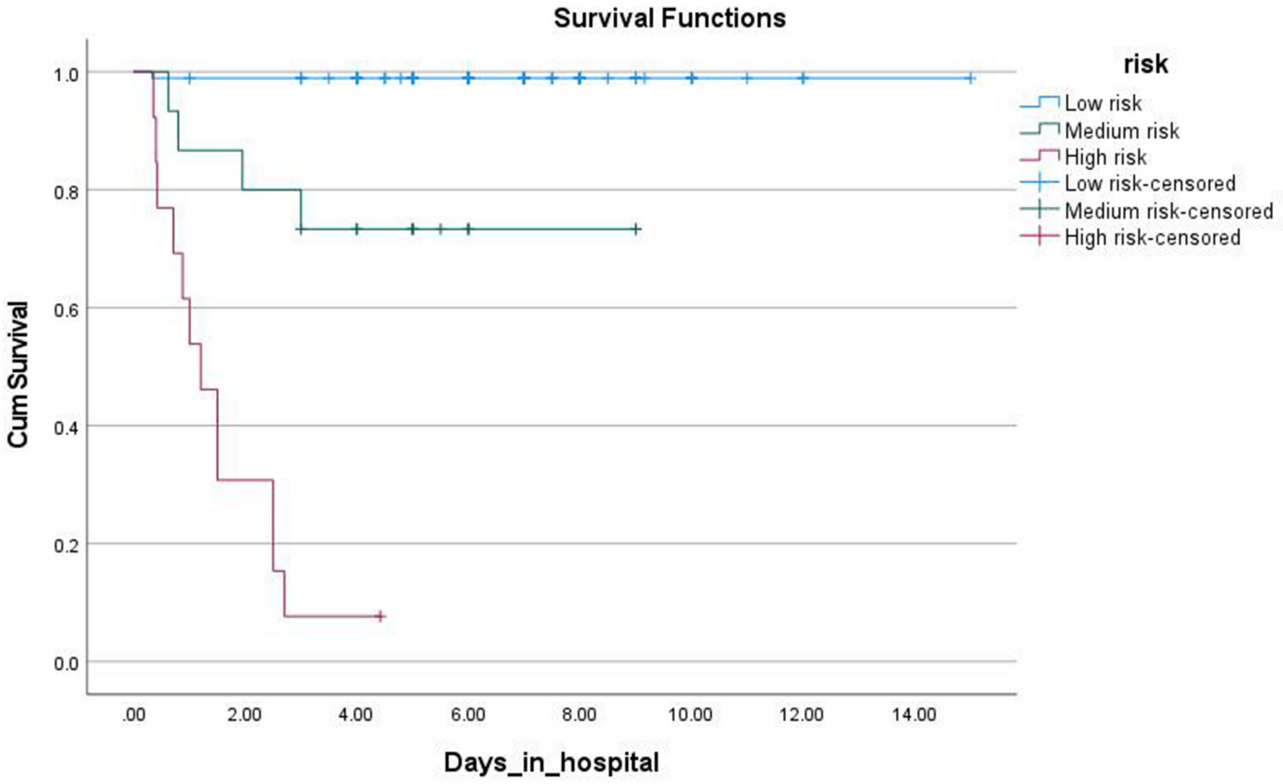


Figure 5 Kaplan-Meier analysis of in-hospital survival in the three risk groups.

disease, which can affect the HCT and ALB measurements, were excluded. Moreover, the present study might have had children with abnormal baseline HCT and ALB levels. Thus, the HCT and ALB levels were detected at the time of hospital admission. However, various factors, such as hydration status, could have affected the HCT measurement. The HCT and ALB levels can present with dynamic changes after management during hospital stay. Daily checking the HCT and ALB levels might help to better predict the disease prognosis, and guide in the adjustment of appropriate treatments.[35] In addition, the vaccination status of the children was unknown, which could certainly affect the disease prognosis. As the availability of anti-viral medication for COVID-19 increases, the management and prognosis of COVID-19 can also change. Various factors, such as socioeconomic status, access to healthcare, and possible co-infections, could have influenced the underlying health conditions, laboratory test results, and disease severity. The present study did not include these other potential confounders, which could certainly bring biases, and affect the result generalizability. Further prospective studies are required to confirm the present study results, in order to facilitate the early identification of children with COVID-19, who have a potential poor prognosis.

Conclusion

In summary, HCT-ALB can be used as a simple and easily available test to predict the in-hospital mortality of children infected with the COVID-19 Omicron variant. This carries high sensitivity and moderate specificity. Its combination with the pSOFA score and lactate level can help to stratify these children into different groups with distinct prognoses, in order to guide therapeutic approaches. Laboratory tests based on HCT and ALB can provide valuable prediction, and guide the treatments to children with COVID-19 Omicron infection.

Abbreviations

ALB, albumin; COVID-19, coronavirus disease 2019; HCT-ALB, hematocrit and albumin; HCT, hematocrit; HR, hazard ratio; IQR, interquartile range; pSOFA, pediatric Sequential Organ Failure Assessment; ROC, receiver operating characteristic curve.

Data Sharing Statement

The datasets generated and analyzed in study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study protocol was approved by the ethics committee of each participating hospital listed below. The requirement for a written informed consent was waived due to the retrospective design of the study.

Ethics committee of each hospital:

Ethics committee of the Affiliated Hospital of Qingdao University, Ethics committee of Zibo Maternal and Child Health Hospital, Ethics committee of Yantai Yuhuangding Hospital, Ethics committee of Qingzhou People's Hospital, Ethics committee of Laizhou City People's Hospital, Ethics committee of Haiyang People's Hospital, Ethics committee of Jining First People's Hospital, Ethics committee of West Coast New District Hospital of Chinese Medicine, Ethics committee of People's Hospital of Wulian, Ethics committee of Linyi Central Hospital, Ethics committee of Rehabilitation University Qingdao Central Hospital, Ethics committee of Qingdao Traditional Chinese Medicine Hospital, and Ethics committee of Weihai Municipal Hospital.

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Disclosure

The authors declare that they have no conflicts of interest.

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