

Circulating Vitronectin Predicts Liver Injury and Mortality in Children With Sepsis: A Prospective Observational Study

Clinical and Applied
Thrombosis/Hemostasis
Volume 26: 1-8
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DOI: 10.1177/1076029620935201
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Chunxia Wang, PhD^{1,2}, Yun Cui, MD¹, Huijie Miao, MD¹,
Ting Sun, MD¹, Ye Lu, MD¹, and Yucai Zhang, MD, PhD^{1,2} 

Abstract

Vitronectin (VTN) is a key regulator of coagulation, but clinical relevance of serum VTN in pediatric sepsis remains poorly defined. The aim of this study was to assess the value of serum VTN level on pediatric intensive care unit (PICU) admission in children with sepsis. Pediatric patients with sepsis were enrolled from January 2018 to December 2018. The serum VTN levels were determined on PICU admission, and the association of serum VTN level with PICU mortality and organ dysfunction was assessed. Serum VTN levels were significantly lower in nonsurvivors compared with survivors, in patients with septic shock compared with patients with sepsis, or in patients with sepsis-associated acute liver injury (ALI) compared with patients without ALI. Serum VTN level was associated with PICU mortality (odds ratio [OR]: 0.958, 95% CI: 0.927-0.996; $P = .010$) or ALI (OR: 0.956, 95% CI: 0.915-0.999; $P = .046$), but not shock (OR: 0.996, 95% CI: 0.977-1.016; $P = .716$). The area under receiver operating characteristic curve for VTN in predicting the occurrence of ALI during PICU stay and PICU mortality were 0.760 (95% CI: 0.627- 0.893) and 0.737 (95% CI: 0.544-0.931), respectively. Moreover, VTN plus pediatric risk of mortality (PRISM) III had a better clinical utility according to decision curve analysis compared with VTN or PRISM III alone. These findings suggest that serum VTN level is associated with sepsis-associated ALI and PICU mortality, and VTN plus PRISM III is a powerful predictor of PICU mortality in pediatric patients with sepsis, which have a better clinical benefit compared with VTN or PRISM III alone.

Keywords

vitronectin, mortality, acute liver injury, sepsis, children

Date received: 13 April 2020; revised: 15 May 2020; accepted: 25 May 2020.

Introduction

Sepsis is a leading cause of death in patients with critically ill admitted to intensive care units.¹ Although clinical advancements in early identification and appropriate management to improve outcomes have taken place, the sepsis-associated mortality remains high. Pooled case fatality rates in pediatric severe sepsis and septic shock are higher in developing countries (31.7%) than in developed countries (19.3%).² In China, the hospital mortality of pediatric severe sepsis or septic shock is 18.8% or 80.8% of the cases comprise patients aged less than 5 years.³ Pathologically, uncontrolled activation of the coagulation cascade is a fundamental event that leads to diffuse microvascular thrombosis, multi-organ dysfunction, and death.³⁻⁶ The cross talk between thrombosis and inflammation supports the concept of a thrombo-inflammatory state correlates with septic severity and prognosis,⁷ and thrombus biomarkers such as D-dimer, fibrinogen (Fib), and platelet count are associated with the short-term

adverse outcomes of patients with sepsis.⁷⁻⁹ However, it remains unclear whether specific indicators for thrombosis would be helpful in identifying patients with sepsis who are at an increased risk of death in the early onset of the condition, which is critical for risk identification and treatment decisions.

Vitronectin (VTN) is a multifunctional glycoprotein present in blood that acts as biological “superglue” and a key

¹ Department of Critical Care Medicine, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai, China

² Institute of Pediatric Critical Care, Shanghai Jiao Tong University, Shanghai, China

Corresponding Author:

Yucai Zhang, Department of Critical Care Medicine, Shanghai Children's Hospital, Institute of Pediatric Critical Care, Shanghai Jiao Tong University, No. 355 Luding Road, Putuo District, Shanghai 200062, China.
Email: zyucai2018@163.com



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controller of mammalian tissue repair and remodeling.¹⁰ The concentration of VTN in the peripheral vasculature is high (200-400 $\mu\text{g/mL}$)¹¹ and is involved in immune responses and the regulation of clot formation by binding to complement, heparin, and thrombin antithrombin III complexes. The interaction of VTN with plasminogen activation inhibitor-1 (PAI-1) exerts multiple deleterious effects that induce acute kidney injury (AKI)¹² and exacerbate lung fibrosis in mice.¹³ High levels of PAI-1 are correlated with the severity and mortality of sepsis.^{14,15} Given the inhibitory effectiveness of VTN on PAI-1 activity during coagulation, we hypothesized that serum VTN level is a prognostic predictor for mortality in pediatric patients with sepsis.

To verify this hypothesis, we conducted a prospective observational study, in which we enrolled pediatric patients with sepsis to measure serum VTN levels on pediatric intensive care unit (PICU) admission, and then assessed the potential value in predicting the outcome and organ dysfunction in sepsis.

Materials and Methods

Study Design and Patient Characteristics

Patients with sepsis were enrolled, who were admitted to the PICU at Shanghai Children's Hospital from January 2018 to December 2018. The diagnosis criteria for pediatric sepsis were based on the International Pediatric Sepsis Consensus Conference in 2005,¹⁶ and sepsis-associated liver injury is defined as referenced by Surviving Sepsis Campaign International Guidelines in 2012.¹⁷ The inclusion criteria included the following: (1) aged between 29 days and 18 years, (2) diagnosed with sepsis when admitted to PICU, and (3) the length of PICU stay for over 24 hours. The exclusion criteria were as follows: (1) advanced tumor, (2) lack of the value of serum VTN levels, (3) congenital heart disease, and (4) severe primary diseases or heredity metabolic disease. Patients were treated in accordance to current guidelines.¹⁷ The study protocol was approved by the local ethics committee and conducted in accordance with the ethical standards defined in the Declaration of Helsinki (Ethics Committee of the Children's Hospital affiliated to Shanghai Jiao Tong University, Approval number: 2018R039-F01). The informed consent was provided by the patients' parents or relatives.

Blood Samples

The blood samples were collected within 1 hour after PICU admission in sterile vacutainer tubes for further analysis. Serum was obtained and stored at -80°C for VTN determination.

Observational Variables

Demographic and clinical parameters were collected using a predesigned case report form. These parameters included age, gender, comorbidities, infection sites, pathogens, pediatric risk of mortality (PRISM) III score, ratio of mechanical ventilator support, and ratio of vasoactive agents needed. Etiology

diagnosis was based on the epidemiological and clinical characteristics, the results of routine blood test including white blood cell and C-reactive protein level. Furthermore, procalcitonin and lipopolysaccharide determination were used to identify bacterial infection even Gram-negative bacterial infection. Blood culture was further used to identify the bacterial species. For virus diagnosis, the nucleic acid detection and antibody neutralization test were used in our center. In addition, 1-3- β -D-glucan test kit (fungi G test) was used for early diagnosis of fungi infection. Furthermore, if the conventional tests were failure to identify the pathogenic species, next-generation sequencing would be used. The laboratory parameters included lactate (Lac), international normalized ratio, activated partial thromboplastin time, Fib, alanine aminotransferase (ALT), total bilirubin (TBIL), lactate dehydrogenase, and γ -glutamyl transpeptidase. The outcome variables included the length of PICU stay, organ dysfunction during PICU hospitalization, and PICU survival status.

Serum VTN Analysis Using Enzyme-Linked Immunosorbent Assay

The concentration of serum VTN was determined using ELISA kit (Multi Sciences Co. Ltd, Cat No. 70-EK11992). The range of detection for VTN was from 0.25 to 16 ng/mL. Serum samples were diluted before detection.

Statistical Analyses

Continuous variables were presented as the median (interquartile range) for abnormal distribution data and mean \pm standard deviation for normal distribution data. The Mann-Whitney U test or Student t test was used to compare the continuous variables with abnormally or normally distributed data, respectively.¹⁸ The χ^2 test was used to compare the categorical data presented as percent or number. Correlation analysis was performed using linear regression. The associations between covariates and PICU mortality, shock, or acute liver injury (ALI) were estimated by *multivariate logistic* regression models. To assess the capacity of VTN to act as predictors of PICU mortality or sepsis-associated ALI, a receiver operating characteristic (ROC) curve was generated. To compare the clinical utility of VTN, PRISM III, or VTN plus PRISM III, decision curve analysis was performed as referenced.¹⁹ Data analyses were performed using STATA 15.0 MP. A value of $P < .05$ was considered statistically significant. All P values presented are 2 tailed.

Results

Baseline Characteristics of Patients

During a 1-year period, a total of 101 patients diagnosed with sepsis were eligible. Patient with advanced tumor ($n = 1$), lack of appropriate serum VTN levels ($n = 5$), congenital heart disease ($n = 6$), or severe primary diseases/heredity metabolic disease ($n = 7$) were excluded. Finally, 82 pediatric patients with sepsis were enrolled in this study (Figure 1).

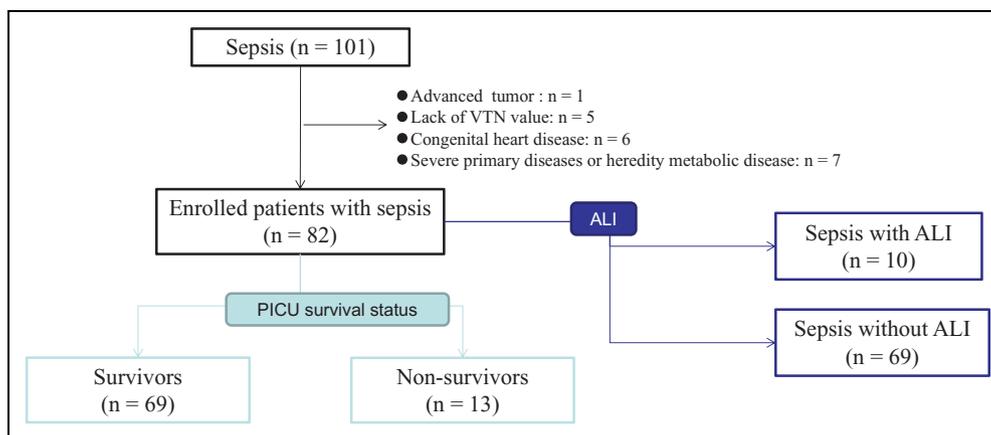


Figure 1. Flowchart of patients' enrollment in this study.

Table 1. Baseline Characteristics of Patients With Sepsis.

Characteristics	Total (n = 82)	Survivor (n = 69)	Nonsurvivor (n = 13)	P value
Age (month)	18.5 (4-51)	19 (5-51)	7 (4-45)	.643
Gender (male, %)	43 (52.4)	37 (53.6)	6 (46.2)	.621
PRISM III	10 (3-12)	8.5 (3-11)	13 (7-18)	.014
Complications				
Respiratory failure, n (%)	50 (61.0)	37 (53.6)	13 (100)	.002
Shock, n (%)	40 (48.8)	29 (42.0)	11 (84.6)	.005
Gastrointestinal disorder, n (%)	31 (37.8)	26 (37.7)	5 (38.5)	.958
Liver injury, n (%)	10 (12.2)	6 (8.7)	4 (30.8)	.026
Acute kidney injury, n (%)	14 (17.1)	10 (14.5)	4 (30.8)	.153
MODS, n (%)	39 (47.6)	26 (37.7)	13 (100)	<.001
Primary infection site				
Respiratory tract, n (%)	40 (48.8)	32 (46.4)	8 (61.5)	.207
Gastrointestinal, n (%)	20 (24.4)	19 (27.5)	1 (7.7)	
Urine system, n (%)	1 (1.2)	1 (1.4)	0 (0)	
Skin/soft tissue/bloodstream, n (%)	13 (15.9)	9 (13.0)	4 (30.8)	
Central nervous system, n (%)	7 (8.5)	7 (10.1)	0 (0)	
Pathogen				
Bacterial, n (%)	45 (54.9)	37 (53.6)	8 (61.5)	.156
Virus, n (%)	24 (29.3)	21 (30.4)	3 (23.1)	
Others, n (%)	7 (8.5)	5 (7.2)	2 (15.4)	
Mechanical ventilator, n (%)	51 (62.2)	38 (55.1)	13 (100)	.355
Vasoactive agents, n (%)	46 (56.1)	33 (47.8)	13 (100)	.001
Length of PICU stay, day	5 (3-9)	5.5 (2-10)	4 (3-12)	.553

Abbreviations: MODS, multiple organ dysfunction syndrome; PICU, pediatric intensive care unit; PRISM III, pediatric risk of mortality III.

The median age of patients was 18.5 (4-51) months and 52.4% of the enrolled patients were male (43/82). Respiratory failure was the most common comorbidity (61.0%), as well as respiratory tract was the most frequently infected site (48.8%). Of the patients with respiratory failure, 62.2% required mechanical ventilation (51/82), and 56.1% received vasoactive infusions (46/82). Among the 13 nonsurvivors, all patients (100%, 13/13) required mechanical ventilation and vasoactive agents. All nonsurvivors were complicated by multiple organ dysfunction syndromes (MODSs) when sepsis was diagnosed (100%, 13/13). The PICU morbidity rate of pediatric sepsis was 15.9% (13/82). There were significant

differences in PRISM III score ($P = .001$), complications with respiratory failure ($P = .002$), shock ($P = .005$), ALI ($P = .026$) or MODS ($P < .001$), and ratio of mechanical ventilator and vasoactive supporting agents ($P = .001$) between survivor ($n = 69$) and nonsurvivor ($n = 13$) individuals (Table 1).

Serum VTN Levels Are Low in Nonsurvivors or Patients With Septic Shock, Sepsis-Associated ALI

Given the coagulation disorder might contribute to multiple organ dysfunction during sepsis, the association between

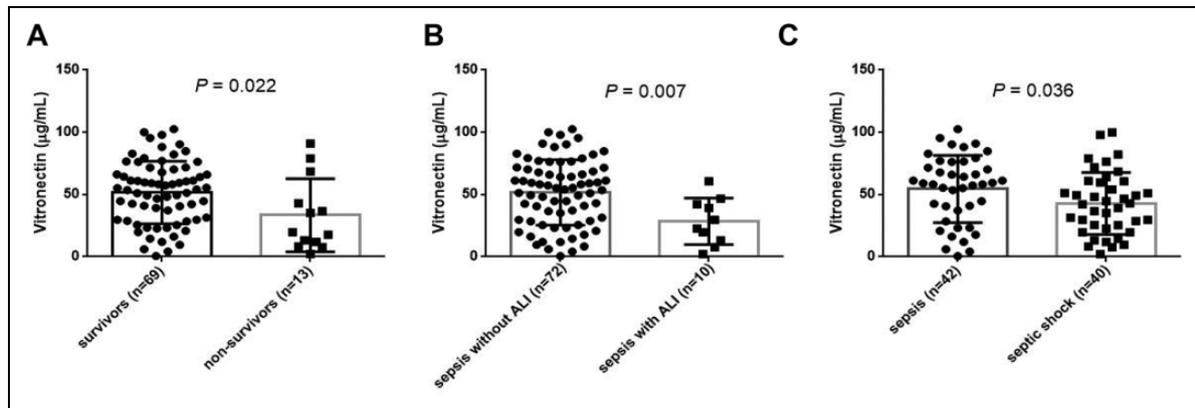


Figure 2. Serum vitronectin levels in patients with sepsis. (A) Survivors vs nonsurvivors, (B) sepsis without acute liver injury (ALI) versus sepsis-associated ALI, (C) sepsis versus septic shock.

Table 2. Comparison of Serum Vitronectin Levels in Patients Complicated by Different Organ Dysfunction.

Organ dysfunction	No		Yes		P value
	Case number	VTN ($\mu\text{g/mL}$)	Case number	VTN ($\mu\text{g/mL}$)	
Shock	42	58.6 (37.1-76.2)	40	42.6 (24.1-60.2)	.036
Respiratory failure	32	50.4 (25.9-63.6)	50	49.6 (25.5-68.6)	.846
AKI	68	54.6 (29.1-69.4)	14	30.6 (17.7-51.1)	.125
ALI	72	54.6 (29.3-70.9)	10	26.2 (13.2-42.2)	.007
Gastrointestinal dysfunction	51	54.0 (28.8-71.5)	31	42.6 (22.7-60.9)	.247
MODS	43	55.2 (28.4-70.2)	39	43.0 (25.4-64.3)	.314
28-day death	69	54.0 (29.7-67.9)	13	19.8 (11.8-43.0)	.022

Abbreviations: AKI, acute kidney injury; ALI, acute liver injury; MODS, multiple organ dysfunction syndrome; VTN, vitronectin.

Table 3. The Laboratory Indexes of Patients With Sepsis.

Variables	Total (n = 82)	Survivor (n = 69)	Nonsurvivor (n = 13)	P
Lac (mmol/L)	1.1 (0.75-2.0)	1.1 (0.75-1.85)	1.45 (0.8-2.3)	.473
INR	1.14 (1.06-1.24)	1.13 (1.06-1.24)	1.16 (1.07-1.25)	.436
APTT(s)	36.8 (31.4-43.1)	37.95 (32.25-42.65)	35.1 (30.5-44.9)	.787
Fib (g/L)	2.79 (1.79-4.09)	2.82 (1.91-4.29)	2.21 (1.04-2.86)	.131
ALT (U/L)	20 (14-47)	19 (13-43)	29 (16-71)	.112
TBIL ($\mu\text{mol/L}$)	7.57 (4.68-15.44)	7.21 (4.68-12.3)	8.73 (4.79-17.94)	.281
LDH (U/L)	352 (288-478)	350.5 (280-466)	414 (317-665)	.375

Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; Fib, fibrinogen; INR, international normalized ratio; Lac, lactate; LDH, lactate dehydrogenase; TBIL, total bilirubin; γ -GT, γ -glutamyl transpeptidase.

serum VTN levels and organ dysfunction was analyzed. The results indicated that serum VTN levels on PICU admission were lower in nonsurvivors (19.8 [11.8-43.0] $\mu\text{g/mL}$ vs 54.0 [29.7-67.9] $\mu\text{g/mL}$, $P = .022$; Figure 2A), in patients complicated by ALI (26.2 [13.2-42.2] $\mu\text{g/mL}$ vs 54.6 [29.3-70.9] $\mu\text{g/mL}$, $P = .007$; Figure 2B) or septic shock (42.6 [24.1-60.2] $\mu\text{g/mL}$ vs 58.6 [37.1-76.2] $\mu\text{g/mL}$, $P = .036$; Figure 2C), but there were no differences among other subgroups with respiratory failure, AKI, gastrointestinal dysfunction, or MODS (all $P > .05$; Table 2).

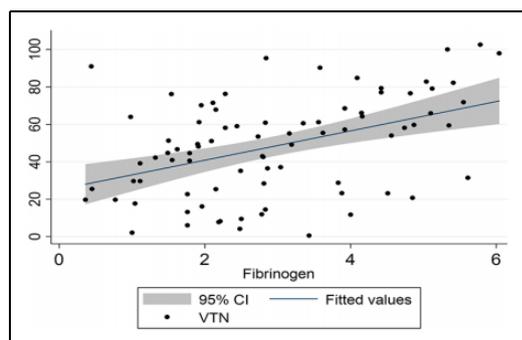
Level of Circulating VTN Is Linearly Correlated With Blood Fib Level

Serum VTN levels were specifically decreased in patients with septic shock or sepsis-associated ALI; therefore, we compared the values of indicators for shock and liver function on PICU admission between survivors and nonsurvivors (Table 3). Lactate levels on PICU admission in nonsurvivors were higher tendency than that in survivors without statistic difference ($P = .473$, Table 3), and ALT levels were mildly increased

Table 4. Correlation Analysis of Serum Vitronectin Levels and Laboratory Indexes of Patients With Sepsis.

VTN	Coefficient	SE	Adjusted R^2	P value
Lac	-1.29072	1.543133	-0.005	.406
INR	-16.81055	10.30262	0.020	.107
APTT	-0.0815349	0.1347131	-0.008	.547
Fib	7.828576	1.8104	0.181	<.001
ALT	-0.0069021	0.0109847	-0.008	.532
TBIL	-0.0441454	0.0229823	0.032	.058
LDH	-0.0049734	0.003624	0.011	.174
Age	-0.0973787	0.0624041	0.0174	.123
Gender	3.166593	5.888459	-0.0089	.592

Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; Fib, fibrinogen; INR, international normalized ratio; Lac, lactate; LDH, lactate dehydrogenase; SE, standard error; TBIL, total bilirubin; VTN, vitronectin; γ -GT, γ -glutamyl transpeptidase.

**Figure 3.** Correlation analysis of serum vitronectin with fibrinogen levels.

in nonsurvivors but were not statistically significant ($P = .112$, Table 3).

We then performed correlation analysis to explore the potential relationship between circulating VTN and indicators for liver function. Serum VTN levels were positively correlated with Fib levels ($P < .001$, Table 4, Figure 3), but not with other indicators of liver function (all $P > .05$, Table 4). While the VTN levels were lower in patients with septic shock compared to those without shock, there was no significant correlation between VTN and Lac, which is a well-known indicator for shock ($P = .406$, Table 4). Moreover, serum VTN concentration was not correlated with age ($P = .123$) or gender ($P = .592$; Table 4).

Serum VTN Level Is Associated With PICU Mortality and Sepsis-Associated ALI in Pediatric Patients With Sepsis

Based on the clear correlations between VTN and shock, sepsis-associated ALI, and PICU mortality, we hypothesized that serum VTN measurements could predict the occurrence of shock, sepsis-associated ALI, and poor outcome in pediatric patients with sepsis. Multivariate logistic analysis indicated that serum VTN level and PRISM III score were independent

Table 5. Multivariate Logistic Analysis About the Association Between Laboratory Parameters and PICU Mortality or Organ Dysfunction in Patients With Sepsis.

Variables	OR	95% CI	P
PICU mortality			
VTN	0.958	0.927-0.990	.010
PRISM III	1.187	1.042-1.353	.010
Shock			
VTN	0.996	0.977-1.016	.716
Lac	1.995	1.110-3.585	.021
Acute live injury			
VTN	0.956	0.915-0.999	.046
TBIL	1.030	0.990-1.072	.140
ALT	1.035	1.004-1.067	.025

Abbreviations: ALT, alanine transaminase; Lac, lactate; OR, odds ratio; PICU, pediatric intensive care unit; PRISM III, pediatric risk of mortality III; TBIL, total bilirubin; VTN, vitronectin.

factors for PICU mortality prediction (odds ratio [OR]: 0.958 [95% CI: 0.927-0.990], $P = .010$; OR: 1.187 [95% CI: 1.042-1.353], $P = .010$; respectively; Table 5). Furthermore, serum VTN and ALT levels were significantly associated with the occurrence of sepsis-associated ALI (0.956 [0.915-0.999], $P = .046$; OR: 1.035 [95% CI: 1.004-1.067], $P = .025$; respectively; Table 5). However, serum VTN level was not independent factor for shock (OR: 0.996 [95% CI: 0.977-1.016], $P = .716$) in pediatric sepsis adjusted by Lac (OR: 1.995 [95% CI: 1.110-3.585], $P = .021$; Table 5).

Receiver operating characteristic analysis was further used to evaluate the potential value of serum VTN level for predicting PICU mortality and sepsis-associated ALI. Given that both serum VTN level and PRISM III score are associated with PICU mortality in pediatric sepsis, the predictive utility of VTN or PRISM III alone and VTN plus PRISM III was analyzed and compared. The area under the ROC curve (AUC) for VTN plus PRISM III was 0.802 (95% CI: 0.655-0.949), which is superior to the predictive utility of VTN alone (AUC = 0.737 [95% CI: 0.544-0.931]) or PRISM III alone (AUC = 0.719 [95% CI: 0.548-0.890]; $P = .054$; Figure 4A). For assessing PICU mortality, the specificity was 87.88% and sensitivity was 53.85% at a cutoff value of 20 μ g/mL (Figure 4A). According to the result of decision curve analysis, it appears that the VTN + PRISM III model was superior to the simple model across a wide range of threshold probabilities, with the highest difference at a threshold probability around 0.6. At that threshold, the net benefit was 0.015 for the PRISM III model and 0.075 for the VTN + PRISM III model (Figure 4B). For predicting sepsis-associated ALI, the AUC of serum VTN level for predicting ALI occurrence was 0.737 (95% CI: 0.544-0.931) with a sensitivity of 90.00% and a specificity of 59.72% with a threshold cutoff value of 47 μ g/mL (Figure 4C).

Discussion

Coagulation disorder is a well-known key characteristic of sepsis pathophysiology, but an adequate laboratory index for

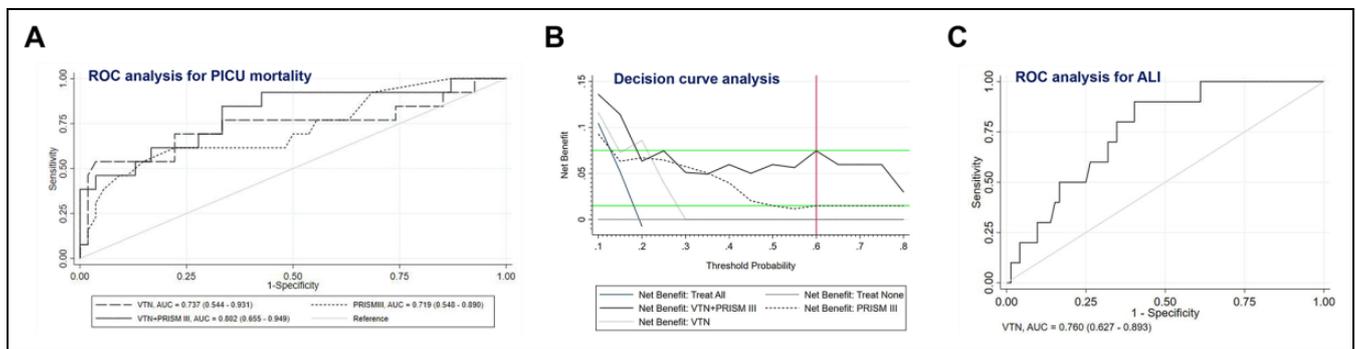


Figure 4. ROC and decision curve analysis (DCA) for predicting PICU mortality or acute liver injury (ALI). (A) ROC analysis of VTN, PRISM III, or VTN plus PRISM III for PICU mortality, (B) DCA analysis of VTN, PRISM III, or VTN plus PRISM III for PICU mortality (C) ROC analysis for ALI. PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality; ROC, receiver operating characteristic; VTN, vitronectin.

its early assessment is not available. To the best of our knowledge, this is the first study to report that serum VTN level on PICU admission is associated with the occurrence of ALI and PICU mortality in pediatric patients with sepsis, and serum VTN level plus PRISM III is a predictor of PICU mortality in pediatric sepsis.

Liver injury is a common risk factor for poor mortality in patients with sepsis.²⁰ The incidence rate of sepsis-associated ALI in patients enrolled in this study during a 1-year period was 12.2% (10/82), which is consistent with our previous retrospective study on the sepsis-associated ALI incidence rate (9.7%, 72/745)²¹; however, the incidence rate observed in the current study was lower than that of a recent study conducted in Southwest China (19.6%).³ The PICU mortality of patients with sepsis-associated ALI was 40% in the present study, which is consistent with the observation of our previous retrospective study (36.1 [26/72]).²¹ The mortality rate was significantly higher in patients with sepsis-associated ALI (40%, 4/10) than in patients without ALI (12.5%, 9/72) in our present study. Therefore, early identification of liver injury during sepsis needs more clinical and research attention and will be helpful for developing strategies for improving the outcome of sepsis.

Inflammation-induced changes in coagulation play a pivotal role in the pathogenesis of sepsis, and inflammation and coagulation interact with each other and are involved in sepsis-induced organ failure.²² Platelet function, pro- and anticoagulant proteins concentrations, and fibrinolytic pathway protein concentrations are developmentally regulated in the liver. Therefore, coagulation disorders result in liver dysfunction. Early assessment of coagulation disorders could be useful for early identification of liver injury. Increased PAI-1 or activation of thrombin-activatable fibrinolysis inhibitor is hallmark of sepsis,^{23,24} and the polymorphisms of PAI-1 might be related to patient susceptibility to sepsis.^{25,26} Given the important role of VTN as an inhibitor of PAI-1 through the direct binding of PAI-1, changes in serum VTN levels might be superior to PAI-1 as a predictor for coagulation disorders. To the best of our knowledge, this is the first study to investigate the role of serum VTN level in predicting sepsis-associated ALI occurrence.

Hypercoagulability and endothelial injury can cause disseminated intravascular coagulation (DIC) and is found in 25% to 50% of patients with sepsis, which may contribute to organ failure and high patient mortality.^{5,6,27,28} D-dimer, as a biomarker for early identification of DIC,^{9,29} was associated with the prognosis of patients with sepsis.^{9,30} High level of PAI-1 was also associated with the severity and mortality of sepsis.^{14,15} Consistently, as an inhibitor of PAI-1, serum VTN levels were significantly lower in nonsurvivors than survivors on PICU admission, which was associated with PICU mortality. Our previous study indicated that a TBIL value >64.5 $\mu\text{mol/L}$ within 72 hours after PICU admission is an independent risk factor for mortality in patients with sepsis-associated ALI.²¹ In the present study, the level of TBIL on PICU admission was 11.995 $\mu\text{mol/L}$ (95% CI: 8.34-77.95) in patients with sepsis-associated ALI, and it was not associated with prognosis of pediatric sepsis. These results suggested that serum VTN is an earlier prognostic predictor compared with TBIL. More importantly, we found that serum VTN level plus PRISM III got a higher AUC and a better clinical benefit for predicting PICU mortality than PRISM III alone. At the highest difference at a threshold probability around 0.6, the net benefit was 0.015 for the PRISM III model, and 0.075 for the VTN + PRISM III model. This means that one can administrate about $7.5 - 1.5 = 6$ more profitable assessment (of 100 patients) when using the VTN + PRISM III model rather than the PRISM III model to predict PICU mortality. This clinical benefit of serum VTN in predicting mortality of pediatric sepsis needs more attention in the future.

There were a few limitations in this study. As a prospective observational study, the sample size was small, and the conclusions drawn from the present pediatric population need further investigation in a larger population. For early detection of coagulation changes in pediatric patients, blood samples were collected on PICU admission, but the changes about serum VTN levels during PICU hospitalization were lack. In addition, the values of other indicators for coagulation such as PAI-1 and D-dimer were unavailable due to the limited volume of blood samples collected from infants and younger children enrolled in this study. Nevertheless, we believe our results show that

serum VTN level can serve as an early-response marker and effective predictor for sepsis-associated ALI or PICU mortality in pediatric patients with sepsis.

In summary, serum VTN level is associated with occurrence of sepsis-associated ALI and PICU mortality. Serum VTN level plus PRISM III is a powerful predictor for PICU mortality in children with sepsis, which have a better clinical benefit compared with VTN or PRISM III alone.

Authors' Note

C.W. and Y.Z. conceived and designed the study. C.W., Y.C., H.M., T.S., and Y.L. collected and analyzed data. C.W., Y.C., and Y.Z. contributed analysis tools and discussion. C.W. and Y.Z. wrote the paper. Our present study was a prospective observational study. The datasheet for this study is available from the corresponding author upon reasonable request. This study was approved by Ethical Committee of Children's Hospital Affiliated to Shanghai Jiao Tong University and conducted in accordance with provisions of the Declaration of Helsinki (Approval number: 2018R039-F01). The written informed consents were obtained from all patients' relatives.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Science and Technology Commission of Shanghai Municipality (18411951000), the Shanghai Municipal Education Commission—Gaofeng Clinical Medicine Grant support (20171928). C.W. is supported by Talents Program of Shanghai Jiao Tong University School of Medicine (17XJ11018).

ORCID iD

Yucai Zhang  <https://orcid.org/0000-0002-4905-3600>

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