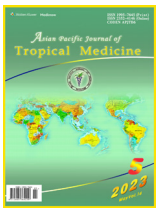

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Association between serum albumin levels and disease severity in adult patients with dengue: A 7-year retrospective cohort study in mainland China

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ABSTRACT

Objective: To identify the association between serum albumin levels and disease severity among adult patients with dengue in mainland China.

Methods: This retrospective cohort study analyzed the data of adult patients (aged ≥ 18 years) hospitalized with laboratory-confirmed dengue in a tertiary center for infectious diseases from 2013 to 2019 in mainland China. Serum albumin levels were estimated and compared between patients with severe dengue and non-severe dengue. Additionally, the association between serum albumin levels and severe dengue was evaluated using a generalized linear model [relative risks (*RR*)]. Multivariate logistic regression analysis was performed to identify the potential predictors of severe dengue.

Results: Overall, 1 568 patients were included in this study. Of these patients, 34 (2.17%) developed severe dengue. The median serum albumin levels were significantly lower in patients with severe dengue than that in those with non-severe dengue (33 g/L *vs.* 37 g/L, $P<0.001$). After adjustment for age, sex, and comorbidities, hypoalbuminemia (*RR* 4.877, 95% *CI* 2.193-11.461, $P<0.001$) was found to be a predictor of severe dengue. Serum albumin levels (*OR* 1.303, 95% *CI* 1.161-1.462, $P<0.001$)] and age (*OR* 1.038, 95% *CI* 1.017-1.061, $P<0.001$) were significant risk factors for severe dengue. The area under the curve for serum albumin levels to distinguish severe dengue was 0.787.

Conclusions: Lower serum albumin levels were significantly associated with disease severity in adult patients with dengue. Hypoalbuminemia on admission resulted in at least a four-fold increased risk of severe dengue.

Keywords: Dengue; Severe dengue; Serum albumin; Hypoalbuminemia; Prediction

1. Introduction

As a major international public health problem designated by the World Health Organization (WHO), dengue fever (DF) is the most prevalent and rapidly spreading mosquito-borne viral disease, caused by four serotypes of dengue virus (DENV-1–4)[1]. Most DENV infections are asymptomatic or mild; however, a fraction of these patients develop severe dengue (SD), approximately three–seven days after illness onset, thus providing a potential window of opportunity to identify patients with possible progression[2,3]. Currently, early detection and access to appropriate medical care can reduce the mortality rate by <1%[2,4]. Since SD pathogenesis is complex and not yet fully understood[5], it impacts patient health significantly, making early diagnosis and treatment critical.

Significance

The association between serum albumin levels and dengue in the Chinese population has not been established. This study showed that lower serum albumin levels were significantly associated with disease severity in adult patients with dengue, allowing a simple scheme for risk stratification of patients with dengue.

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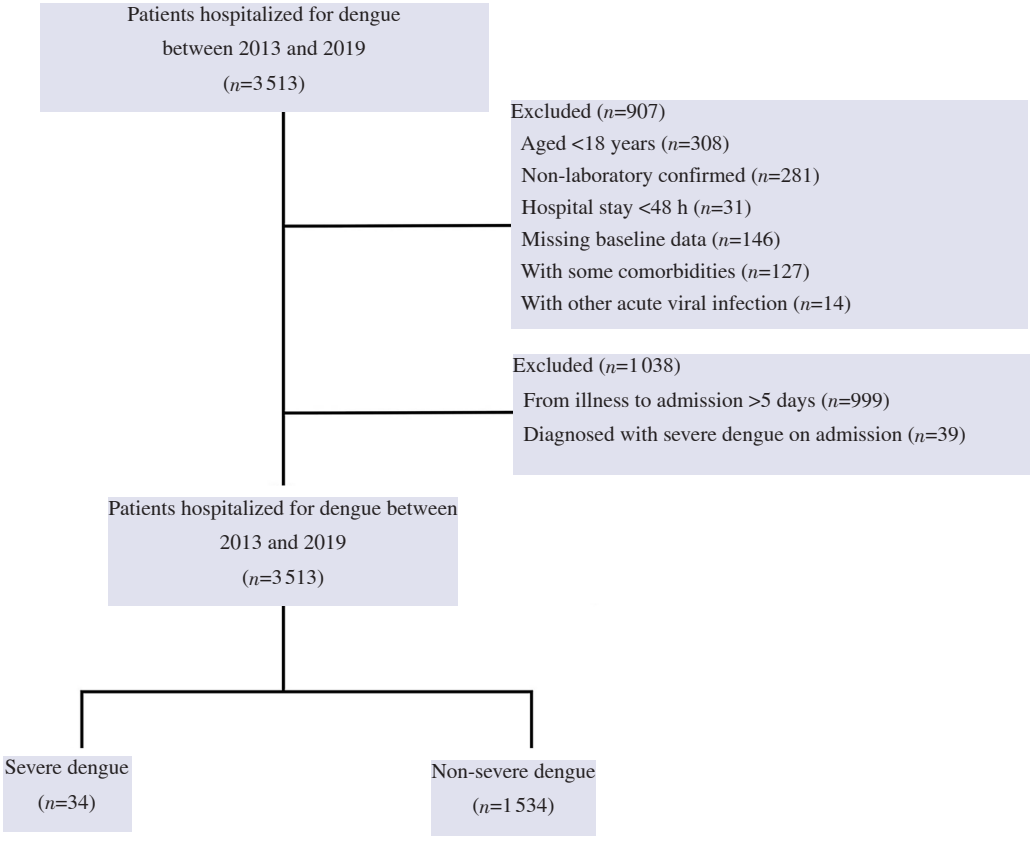

Figure 1. Flowchart of the case selection process.

The 2009 WHO guidelines categorized dengue based on disease severity into dengue without warning signs (WS), dengue with WS, and SD[2]. However, the sensitivity of the utilized warning signs remains limited, and some signs are subjective, particularly those in adult patients[6,7]. In addition to hematocrit and platelet count[2], other biomarkers, such as alanine aminotransferase (ALT)[8], aspartate aminotransferase (AST)[7,8], and activated partial thromboplastin time[9], are used to predict SD. Despite extensive research, clinically feasible and reliable biomarkers for adult patients with dengue are still lacking[10].

Serum albumin, the most abundant circulatory protein, is associated with regulating metabolic and vascular functions, immunomodulatory and anti-inflammatory effects[11,12]. Low serum albumin levels have been associated with poor prognosis in infectious diseases[13,14]. A decrease in serum albumin levels is the most reliable predictor of entry into the critical phase of dengue. The lowest serum albumin levels occurs two days prior to the maximum peak of fluid leakage; therefore, it can serve as an early warning indicator[15,16]. Serum albumin levels may be useful as a biomarker associated with predicting dengue severity and mortality[7,17,18]. However, the role of serum albumin levels in dengue severity has not been determined[10,19,20]. Therefore, to investigate the utility of serum albumin measurement for the risk prediction of dengue, these results require validation in a large sample.

Despite being classified by the WHO as a non-endemic country for dengue, China has experienced multiple outbreaks of DF[21,22]. During the 2014 DF outbreak, the reported cases in Guangdong Province accounted for >90% of all reported cases[23]. Dengue was more prevalent (>85%) in adults, and a higher proportion of older adults presented with atypical symptoms[24]. This finding differed from the pattern observed in other Southeast Asian countries, where dengue was highly prevalent among children[21,25]. However, the association between serum albumin levels and dengue in the Chinese population has not been established. Hence, this study determined the serum albumin levels in adult patients with dengue and evaluated its role in predicting dengue severity in a relatively large adult population.

2. Subjects and methods

2.1. Study design and settings

This retrospective study was conducted on adult patients with dengue who were admitted to Guangzhou Eighth People's Hospital, Guangzhou Medical University, a tertiary center for infectious diseases located in Guangzhou City, mainland China, from January 2013 to December 2019.

Adult patients (aged ⩾18 years) with confirmed dengue and a length of hospital stay of ⩾ two days were included in the study. However, the study's exclusion criteria were as follows: (1) patients with missing data of serum albumin levels on admission; (2) patients with a history of liver cirrhosis, chronic kidney disease, malignant tumors, hyperthyroidism, malnutrition, and pregnancy; (3) patients who had a delay in the hospitalization of more than five days from illness onset; (4) patients who were diagnosed with SD upon admission; and (5) dengue combined with acute viral infections such as Zika virus, Japanese encephalitis virus, and influenza (Figure 1).

2.2. Data collection and laboratory testing

Specially trained researchers collected the patients' data. Patient data during hospitalization were extracted from electronic medical records, which included the following aspects: (1) demographic and admission status data; (2) laboratory data, such as levels of white blood cell (WBC), hemoglobin, hematocrit, platelet (PLT) count, ALT, AST, serum albumin, serum creatinine (SCr), creatine kinase (CK), lactate dehydrogenase (LDH), prothrombin time (PT), and international normalized ratio (INR); (3) dengue-specific nonstructural protein 1 (NS1) antigen, viral RNA, immunoglobulin IgM/IgG antibodies test results; and (4) imaging tests. At the end of the clinical follow-up, the patient was classified as SD or non-SD patients. The exact day the patients fulfilled the criteria for SD was determined.

Fasting blood samples were taken on the day or the next day after admission, and submitted for complete blood count, blood biochemistry and coagulation tests. Serum albumin levels and other biochemical indicators were performed on a Roche Cobas c702 (Roche Diagnostics, Indianapolis, IN, USA) automatic biochemical analyzer. Complete blood count was performed using a Sysmex xn2800 (Sysmex America, Inc., Lincolnshire, IL, USA) automatic blood analyze. The coagulation parameters were measured using a Stago (Stago Diagnostica, Parsippany, NJ, USA) automatic blood coagulation meter. The preparation and use of the above reagents were conducted following the manufacturer's instructions. The dengue-specific RNA, NS1 antigen or IgM/IgG antibodies were assessed using the methods described in previous studies[26].

2.3. Ethical approval

The study was approved by the Clinical Research Ethics Committee of Guangzhou Eighth People's Hospital, Guangzhou Medical University (no.20160264) and retrospectively registered in the Chinese Clinical Trial Registry (ChiCTR2100046696). Written informed consent was obtained from the patients.

2.4. Definitions

Dengue diagnostic criteria have been previously described; briefly, laboratory-confirmed dengue was defined as a positive DENV RNA detected through real-time (RT)-polymerase chain reaction (PCR) assay or the presence of dengue-specific NS1 antigen detected through enzyme–linked immunosorbent assay[2,27]. According to the 2009 WHO criteria and national guidelines, patients with any of the following conditions were diagnosed SD: (1) severe plasma leakage, plasma leakage leading to shock, and/or respiratory distress, (2) severe bleeding, and (3) severe organ impairment, such as ALT/AST 1 000 U/L, or evidence of myocarditis, heart failure, encephalopathy, or encephalitis[2,27,28]. All patients with SD were comprehensively evaluated by two or more clinical experts.

Serum albumin levels were classified as follows: normal albumin (⩾35 g/L), hypoalbuminemia (<35 g/L), mild hypoalbuminemia (30–34.9 g/L) and severe hypoalbuminemia (<30 g/L). Older patients are referred to those aged >65 years.

2.5. Statistical analysis

The clinical characteristics were compared between the groups. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as frequency and percentage. Student's *t*-test analysis or Mann–Whitney *U*-test were used to compare the continuous variables, and *Chi*–square or Fisher's exact test was used to compare the categorical variables, respectively. The correlation between serum albumin levels and other clinical and laboratory parameters was analyzed using Spearman's correlation coefficients. The association between serum albumin levels and SD was evaluated using a generalized linear model [relative risks (*RR*)] with the R software, version 4.2.2. A multivariate logistic regression model was used to determine the independent risk factors following the Wald (Forward Wald) method, and the odds ratio (*OR*) and 95% confidence interval (*CI*) were calculated. The area under the curve (AUC) of the receiving operating characteristic (ROC) curve, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated as described by DeLong *et al.*[29]. Statistical analyses were performed using the IBM SPSS Statistics software, version 25 (IBM Corp., Armonk, NY, USA). All tests were two-tailed, and a *P*-value of <0.05 was considered statistical significance.

Table 1. Demographic and baseline characteristics of 1568 adult patients with dengue.

Variables	All patients (n=1568)	Severe dengue (n=34)	Non-severe dengue (n=1534)	P
Demographic				
Age (years)*	43 (30-58)	72 (48-83)	42 (30-57)	<0.001
⩽65	1315 (83.86)	13 (38.24)	1302 (84.88)	<0.001
>65	253 (16.14)	21 (61.76)	232 (15.12)	
Male	715 (45.60)	20 (58.82)	695 (45.31)	0.118
Comorbidities				
Hypertension	197 (12.56)	11 (32.35)	186 (12.13)	0.002
Diabetes mellitus	72 (4.59)	3 (8.82)	69 (4.50)	0.203
Chronic lung disease	34 (2.17)	1 (2.94)	33 (2.15)	0.529
Cerebrovascular disease	43 (2.74)	4 (11.76)	39 (2.54)	0.013
Baseline laboratory data*				
WBC ($\times10^9$/L)	2.79 (2.01-4.23)	3.35 (2.28-4.98)	2.78 (2.00-4.22)	0.062
Hemoglobin (g/L)	136 (125-148)	134 (117-144)	136 (125-148)	0.078
Hematocrit (%)	40.0 (36.8-43.0)	39.9 (36.3-42.9)	40.0 (36.9-43.0)	0.319
PLT ($\times10^9$/L)	80 (47-122)	38 (19-92)	81 (47-122)	0.006
ALT (U/L)	36 (24-60)	41 (27-65)	36 (24-59)	0.653
AST (U/L)	54 (34-90)	88 (52-120)	54 (34-89)	0.034
Serum albumin (g/L)	37 (35-40)	33 (31-36)	37 (35-40)	<0.001
CK ($\times10^9$/L)	174 (102-358)	249 (155-398)	172 (101-353)	0.034
LDH (U/L)	327 (239-481)	432 (316-724)	324 (238-481)	0.005
SCr (umol/L)	77.6 (65.0-90.6)	62.7 (75.3-94.6)	65.0 (77.7-90.5)	0.673
PT (s)	13.4 (12.9-14.1)	13.3 (12.8-14.0)	13.4 (12.9-14.1)	0.709
INR	1.03 (0.97-1.09)	1.01 (0.97-1.08)	1.03 (0.97-1.09)	0.482

*Data are expressed as median (interquartile range). Categorical variables are shown as the number and percentage of patients. Continuous variables are shown as the median and interquartile range. WBC: white blood cell; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; LDH: lactate dehydrogenase; SCr: serum creatinine; PT: prothrombin time; INR: international normalized ratio.

Table 2. Association between serum albumin levels classification and severe dengue using a generalized linear model.

Serum albumin levels	Unadjusted		Adjusted*	
	RR (95% *CI*)	*P* value	*RR* (95% *CI*)	*P*
Normal (⩾35 g/L)	1		1	
Hypoalbuminemia	9.325 (4.540–20.620)	<0.001	4.877 (2.193–11.461)	<0.001
Mild hypoalbuminemia	7.911 (3.716–17.885)	<0.001	4.042 (1.751–9.739)	<0.001
Severe hypoalbuminemia	29.048 (8.456–89.661)	<0.001	15.753 (3.469–64.086)	<0.001

*Other factors enrolled in a generalized linear model included age, sex, and hypertension, chronic lung disease, diabetes mellitus, cerebrovascular disease. *RR* : relative risk; *CI*: confidence interval.

3. Results

3.1. Patient demographic and baseline characteristics

A total of 1568 hospitalized patients with laboratory-confirmed dengue were identified. The demographic and baseline characteristics of the enrolled patients are presented in Table 1. Of 1568 patients, 34 (2.17%) and 1534 (97.83%) had SD and non-SD, respectively. The median age of the patients was 43 years, and 715 (45.60%) were males. The most common comorbidities were hypertension (12.56%), diabetes mellitus (4.59%), and cerebrovascular disease (2.74%). Among the clinical manifestations of patients with SD, severe organ impairment was the most common (50.00%), followed by severe bleeding (35.29%) and severe plasma leakage (32.35%). The SD group had significantly decreased PLT count and serum albumin levels (P<0.05), with elevated AST, CK, and LDH levels (P all <0.05).

3.2. Associations between serum albumin levels and dengue severity

The median baseline serum albumin levels were lower in the SD group than in the non-SD group [33 (31-36) g/L *vs.* 37 (35-40) g/L, P<0.001) (Figure 2A). Further analysis showed that the rate of SD progressively decreased from the low to high serum albumin levels group (P<0.001, Figure 2B). After adjusting the multivariable logistic regression models for age, sex, and comorbidity factors, patients with hypoalbuminemia (*RR* 4.877, 95% *CI* 2.193-11.461, P<0.001), mild hypoalbuminemia (*RR* 4.042, 95% *CI* 1.751-9.739, P<0.001) and severe hypoalbuminemia (*RR* 15.753, 95% *CI* 3.469-64.086, P<0.001) were more likely to develop SD than those with normal albumin levels (Table 2).

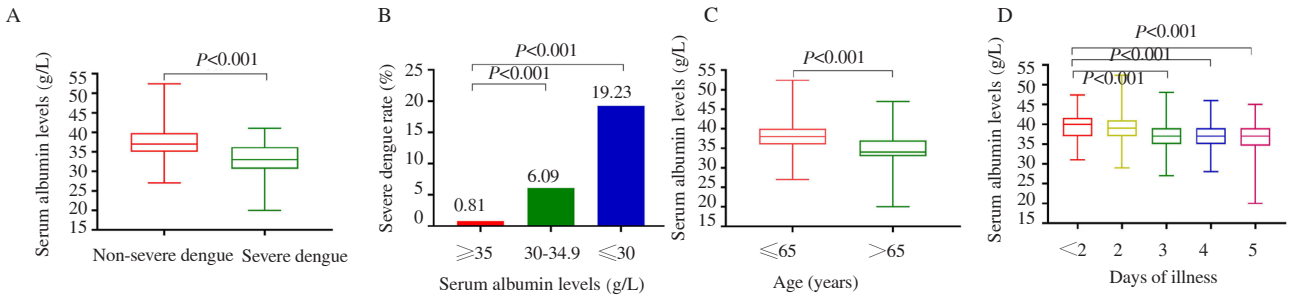

Figure 2. Serum albumin levels in different patient groups. A: Disease classification; B: Severity rate in different groups; C: Age groups; D: Day of illness upon admission.

Table 3. Correlations between serum albumin levels and baseline data.

Variables	*r*	*P*
Age (years)	-0.397	<0.001
WBC ($\times10^9$/L)	-0.066	0.009
Hemoglobin (g/L)	0.201	<0.001
Hematocrit (%)	0.175	<0.001
PLT ($\times10^9$/L)	0.397	<0.001
ALT (U/L)	-0.056	0.027
AST (U/L)	-0.209	<0.001
CK ($\times10^9$/L)	-0.126	<0.001
LDH (U/L)	-0.306	<0.001
SCr (umol/L)	0.008	0.758
PT (s)	0.136	<0.001
INR	0.150	<0.001

WBC: white blood cell; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; LDH: lactate dehydrogenase; SCr: serum creatinine; PT: prothrombin time; INR: international normalized ratio.

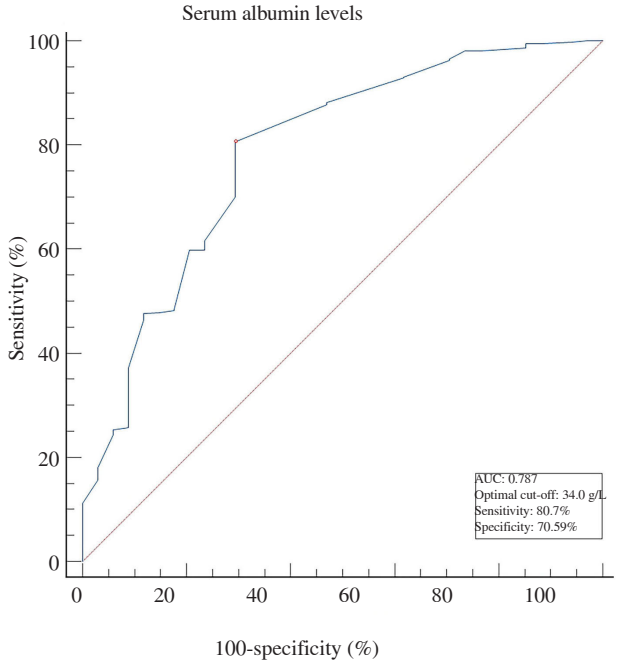

Figure 3. Receiver operator characteristic curves for predicting dengue severity by serum albumin levels. AUC: area under the curve.

Table 4. Independent risk factors for severe dengue by univariable and multivariable analysis.

Variables	Univariable analysis		Multivariable analysis*	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Male (*vs.* women)	0.580 (0.291-1.156)	0.122	-	
Age (years)	1.063 (1.042-1.085)	<0.001	1.038 (1.017-1.061)	<0.001
Hypertension (yes *vs.* no)	3.466 (1.663-7.226)	<0.001	-	
Diabetes mellitus (yes *vs.* no)	2.055 (0.613-6.886)	0.243	-	
Chronic lung disease (yes *vs.* no)	1.378 (0.183-10.381)	0.755	-	
Cerebrovascular disease (yes *vs.* no)	5.111 (1.717-15.211)	0.003	-	
WBC ($\times10^9$/L)	1.117 (1.004-1.243)	0.041	-	
Hemoglobin (g/L)	0.983 (0.965-1.002)	0.076	-	
Hematocrit (%)	0.965 (0.899-1.035)	0.317	-	
PLT ($\times10^9$/L)	0.989 (0.981-0.997)	0.007	-	
ALT (U/L)	0.998 (0.991-1.006)	0.652	-	
AST (U/L)	1.003 (1.000-1.006)	0.040	-	
Serum albumin (g/L)	1.413 (1.273-1.568)	<0.001	1.303 (1.161-1.462)	<0.001
CK (U/L)	1.000 (1.000-1.001)	0.073	-	
LDH(U/L)	1.001 (1.00-1.001)	0.005	-	
SCr (umol/L)	1.019 (1.004-1.035)	0.015	-	
PT (s)	1.061 (0.778-1.446)	0.709	-	
INR	2.886 (0.152-54.874)	0.481	-	

*Only significant variables are shown. WBC: white blood cell; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; LDH: lactate dehydrogenase; SCr: serum creatinine; PT: prothrombin time; INR: international normalized ratio.

3.3. Correlation between serum albumin levels and baseline data

Serum albumin levels were significantly lower in older patients than in younger patients (P<0.001) (Figure 2C). Serum albumin levels were significantly decreased from onset to 3 days after admission (P all<0.001) (Figure 2D). Serum albumin levels were negatively correlated with age (r=-0.397, P<0.001), LDH levels (r= -0.306, P<0.001), and AST levels (r= -0.209, P<0.001), and positively correlated with PLT count (r=0.397, P<0.001) and hemoglobin levels (r=0.201, P<0.001) (Table 3).

3.4. Predictor of disease severity in patients with dengue

Based on the baseline clinical and laboratory results, we included univariable and multivariable analysis models in determining the indicators of SD. Age, presence of hypertension and cerebrovascular disease, WBC and PLT counts, AST, serum albumin, LDH and SCr levels were significant individual predictors in the univariable model. The multivariate analysis revealed that serum albumin levels (*OR* 1.303, 95% *CI* 1.161-1.462, P<0.001) and age (*OR* 1.038, 95% *CI* 1.017 1.061, P<0.001) were independent risk factors for SD (Table 4). Furthermore, the AUC for SD diagnosis was 0.787 (95% *CI* 0.766-0.807) for serum albumin levels, and 0.770 (95% *CI* 0.749-0.791) for age (Figure 3 and Supplementary Table S1). Serum albumin levels of >34 g/L had 80.7% sensitivity, 70.59% specificity, and 99.2% PPV in detecting SD.

4. Discussion

This large-scale study assessed the association between serum albumin levels and disease severity in hospitalized adult patients with dengue from non-endemic countries. Serum albumin levels early during the disease were associated with SD, even after adjusting for related covariates. Hypoalbuminemia on admission increased the risk of SD by at least four-fold. To date, these findings provide the most robust evidence for the relationship between serum albumin levels and the severity of dengue and demonstrate the potential utility of serum albumin levels measured early during the infection.

SD is a severe form of DENV infection. However, with timely intervention, the mortality of SD can be reduced from more than 20% to less than 1%[2,4]. In the endemic areas, SD was frequently found in children, with severe plasma leakage as its main clinical manifestation; In contrast, it was common in adults living in non-endemic areas, with severe organ impairment as the main clinical manifestation[30–34]. Here, the clinical manifestations of patients with SD are mainly severe organ impairment, which is common in older patients. Clinical symptoms and physical examination, and laboratory examination findings help in the early warnings of SD[10,19,20]. However, due to the differences in the clinical characteristics of SD, early warning of SD is still challenging, particularly in non-endemic areas. Therefore, developing simple and feasible biomarkers for early warning of SD is necessary.

Serum albumin levels have been widely used to assess nutritional status and inflammation in humans[35,36], since it is a well-established, inexpensive and readily available clinical test in healthcare settings. These characteristics make it an attractive option for implementation as a prognostic tool in resource-constrained settings with the greatest burden of dengue. Hypoalbuminemia prevalence in patients with dengue is approximately 10% to 30%, and it is a risk factor for SD and death[7,17,37,38]. Therefore, it is necessary to evaluate the relationship between serum albumin levels and disease severity in patients with dengue.

Two meta-analyses suggested that serum albumin levels have a predictive value in patients with SD[10,19], whereas, other sutdies showed contradicting results[20], which can be attributed to the heterogeneity of the included samples. Therefore, it remains unclear whether serum albumin levels or hypoalbuminemia can be used as early predictors in adult patients with SD. Here, the early predictive value of serum albumin levels for SD was analyzed through rational design and strict screening of dengue cases in the hospital. Results showed that severe hypoalbuminemia was associated with a 15-fold increased risk of SD, and patients with mild hypoalbuminemia had a four-fold increased risk. Multivariate analysis showed that serum albumin levels were a predictor of SD (*OR* 1.303), which possesses a good predictive value. Our findings are consistent with those of a previous study conducted on 326 patients, which reported that a serum albumin level of <35 g/L was a predictor of SD in the first three days and on the fourth to the sixth day of illness[7]. Serum albumin levels have a predictive value for dengue pleural effusion and/or ascites in adult patients[18,38]. Additionally, other study have shown that the decrease in serum albumin levels is related to the prolongation of hospitalization days, which is common in patients with SD[24,39]. Therefore, serum albumin levels can be used as an early predictor of SD.

Although the mechanism underlying the association between lower serum albumin levels and SD remains unclear, it is considered to be associated with protein leakage through the vessel wall due to increased vascular permeability. Plasma leakage is a known feature of dengue, and its status may be related to disease severity[5]. In two previous studies by Suwarto *et al*[18,38], serum albumin levels of $\leqslant$ 34.9 g/L were associated with an increased risk of pleural effusion and/or ascites in adults with dengue. This study also demonstrated lower serum albumin levels in patients with pleural effusion or ascites (data not shown). Furthermore, significantly decreased serum albumin levels indirectly reflect an increase in vascular permeability and lead to plasma leakage[40]. Hypoalbuminemia commonly occurs in older patients or the presence of comorbidities such as hypertension and diabetes, and is statistically the most likely to develop SD[24,41]. In this study, the between-group differences in serum albumin levels may be partly attributable to the higher

disease severity typically observed in older patients or the presence of comorbidities. Low serum albumin levels may be due to hepatic impairment or increased renal excretion. However, no significant correlation was found between serum albumin levels and ALT or SCr levels. Additionally, hypoalbuminemia might be due to a systemic inflammatory reaction to infectious disease[36]. However, further research is warranted to elucidate the exact mechanism.

Beside serum albumin levels, multivariate logistic regression analysis revealed that age was associated with SD. Rowe *et al.*[24] reported that older patients with dengue in Singapore are at a higher risk of developing SD. Age-induced immune dysregulation and impaired cytokine responses are possible mechanisms[42]. The incidence of hypertension and cerebrovascular disease was significantly higher in the SD group than in the non-SD group. However, they were not independent risk factors of SD in the multivariate analysis, possibly because they are commonly observed in older patients[24]. Therefore, we should be alert to the intensification of older patients with dengue, particularly those with comorbidities.

Several other laboratory findings have been identified as potential prognostic markers[10,19,20]. PLT count and hematocrit levels are suggested as early warning of SD[2,43]. However, this study showed that PLT count was lower among individuals who progressed to SD, and no difference in hematocrit levels was found. This is consistent with the findings of another previous study[7]. Additionally, this study also found that AST, CK, and LDH levels were significantly increased in patients with SD, and similar results have been reported in previous studies[24,44,45]. However, multivariate analysis showed that these had not significant independent predictive value for SD. These differences may be related to sample size, age of enrolled patients and DENV serotype; therefore, further research is needed.

The main limitation of our study was that it was retrospective. It was difficult to control the time of enrollment, which may lead to differences in the time of included patient data and inadequate continuous measurement of serum albumin levels. In addition, this study was based on a single center, and hospital-based adult patients do not reflect the entire DENV-infected population. Some patients may be hospitalized longer during dengue outbreaks; however, this should be verified during the outbreak. Furthermore, this study lacked data on primary and secondary dengue infection, serotypes, and viral load. Therefore, these results should be verified using multi-center prospective research. Despite these limitations, this study characterized the early predictive value of serum albumin levels in hospitalized adult patients with dengue. Therefore, these results provide a useful reference for clinicians encountering adult patients with dengue in non-endemic areas. Overall, future prospective studies are necessary to validate our findings in different populations for better generalization.

In conclusion, this study provides important insights into the association between low serum albumin levels and the risk of disease progression in adult patients with dengue. Hypoalbuminemia on admission increased the risk of SD by at least four-fold. Our findings suggest that the inclusion of baseline serum albumin levels as a prognostic indicator of SD can further improve the risk prediction of SD and aid clinicians in improving risk stratification and treatment decisions.

Conflict of interest statement

We declare that there is no conflict of interest.

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Authors' contributions

CTW contributed to the study concept, design, analysis, interpretation of data and wrote the manuscript. HQY contributed to the experimental studies, data acquisition and analysis, and manuscript preparation. JLX contributed to the data statistical analysis, and manuscript preparation. JW contributed to the study design, manuscript editing and review. LZZ contributed to the studie design, and manuscript editing. WXH contributed to the clinical studies, and manuscript editing. FCZ contributed to the study concepts, design, manuscript preparation, manuscript editin, manuscript review. All authors have read and approved the final manuscript.

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