Original Article

Effectiveness of S100 calcium-binding protein A12 combined with modified early warning score in the clinical diagnosis of adult community-acquired pneumonia

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Background: Recent studies have found that S100 serum calcium-binding protein A12 (S100A12) has important significance in the expression of acute infectious diseases, and has high clinical application value in the differential diagnosis, prognosis and other aspects of acute infectious diseases. The accuracy of modified early warning score (MEWS) in evaluating the disease risk level of critically ill patients is comparable to Acute Physiology and Chronic Health Evaluation (APACHE II).

Methods: Based on MEWS, 108 adult community-acquired pneumonia (CAP) patients were divided into the low-risk, intermediate-risk, and high-risk groups. The differences in invasive mechanical ventilation rate and mortality rate among each group were compared, and the differences of S100A12 in different levels of MEWS scores were compared through one-way analysis of variance. According to the prognosis after 30 days, the patients were divided into the death group and the survival group. Univariate and multivariate logistic regression analyses were used to study the influencing and independent factors of 30-day death in CAP patients. The sensitivity and specificity of S100A12, procalcitonin (PCT), and MEWS scores in predicting the 30-day death in CAP patients were evaluated using the receiver operating characteristic (ROC) curve, as well as the area under each indicator curve.

Results: The serum S100A12 concentration increased with the increase in the MEWS stratification, and the mechanical ventilation and mortality rates also increased significantly. Univariate and multivariate analyses were used to explore the factors influencing mortality in adult CAP patients after 30 days. The receiver-operating characteristics curve was used to analyze the sensitivity, specificity, and area under the curves of serum S100A12, PCT, and MEWS in predicting mortality in CAP patients after 30 days.

Conclusions: The serum S100A12, PCT, and MEWS can effectively predict the mortality risk in adult CAP patients after 30 days. Serum S100A12 combined with MEWS has a high clinical application value in evaluating the severity and prognosis of adult CAP.

Keywords: S100A12; modified early warning score (MEWS); community-acquired pneumonia (CAP); procalcitonin (PCT); clinical application value

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Introduction

The pathogen that causes community-acquired pneumonia (CAP) has an obvious latent nature. Patients can develop disease within the admission period, which can easily lead to multiple organ dysfunction and become life-threatening. CAP is a global concern, with mortality rates of 5–10% and 25–30% in hospitalized patients and intensive care unit (ICU) patients, respectively. The mortality rate can reach 50% among those who are in septic shock and require vasopressors (1). A large-scale population-based study on hospitalized patients with CAP found that the ICU admission rate was 21%, of which 26% of patients needed mechanical ventilation. The mortality rate of severe CAP ranges from 25% to over 50% (2). In addition to being life-threatening, the high incidence of CAP creates a considerable financial burden on the healthcare system. The estimated cost of managing pneumonia in Germany in 2008 was 500 million to 1 billion USD, and the cost of hospitalization was approximately 900 million USD. Therefore, it is crucial to identify the risk and severity of individual CAP patients (3). Accurate, timely, and rapid assessment of the severity of CAP disease is important for the selection of appropriate treatment sites and empirical anti-infection and adjuvant support therapy, and for the assessment and improvement of the prognosis.

Highlight box

Key findings

- This study aims to explore the value of S100A12 in evaluating the severity and prognosis of community-acquired pneumonia (CAP), as well as the correlation of S100A12 concentration at different levels of modified early warning score (MEWS).

What is known and what is new?

- There are many studies on S100 protein family in various diseases, such as inflammatory bowel disease/pancreatic disease/arthritis/kidney disease and other non infectious diseases, while there are few studies on infectious diseases, especially pneumonia.
- This study explores the value of S100A12 in evaluating the severity and prognosis of CAP.

What is the implication, and what should change now?

- This study found a positive correlation between S100A12 and MEWS. The higher the stratification and concentration, the more severe the condition, and the poorer the prognosis. Therefore, dynamic monitoring of S100A12 concentration and early MEWS scoring have high value in predicting severe pneumonia, which can intervene in the progression of pneumonia and improve prognosis in the early stage.

Several studies have found that the expression of S100 serum calcium-binding protein A12 (S100A12) in acute infectious diseases is of great significance. Compared to other infectious markers, such as serum amyloid A (SAA), C-reactive protein (CRP), and procalcitonin (PCT), serum S100A12 is rapidly expressed in bacterial infection and peaks within a short time. Therefore, S100A12 detection has a high clinical application value in differential diagnosis, disease severity assessment, and treatment guidance. The modified early warning score (MEWS) is comparable to the Acute Physiology and Chronic Health Evaluation (APACHE) II in assessing the disease risk of critical patients. Moreover, the clinical data required for the MEWS calculation is quick and easy to obtain; the parameters do not require advanced or expensive large-scale instruments and are easily available in even primary hospitals. MEWS can effectively predict the in-hospital mortality of adult CAP patients (4). This study aimed to explore the value of S100A12 in evaluating the severity and prognosis of CAP, as well as the correlation of S100A12 concentration in different levels of MEWS. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1114/rc).

Methods

Study design and patient population

This study prospectively analyzed 108 adult patients with CAP admitted to the hospital from January to September 2020. Based on the MEWS, the patients were divided into the low-risk, intermediate-risk, and high-risk groups. According to the prognosis 30 days after admission, they were divided into the death group and the survival group. All the included patients fulfilled the diagnostic criteria described in the "Diagnosis and Treatment of Adult Community-Acquired Pneumonia" (5) guidelines formulated by the Chinese Thoracic Society of Chinese Medical Association in 2016. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Affiliated Hospital of Southwest Medical University (Institutional Review Board File KY2020053). Informed consent was obtained from all participants.

Inclusion and exclusion criteria

This study included all adult patients admitted to the

Affiliated Hospital of Southwest Medical University for the treatment of CAP from January to September 2020, who fulfilled the diagnostic criteria described in the "Diagnosis and Treatment of Adult Community-Acquired Pneumonia" guidelines of 2016 (5).

The exclusion criteria were age <18 years, presence of other systemic diseases (Kawasaki disease, glomerulonephritis, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, severe acute pancreatitis, tumors, acute lung injury, respiratory distress syndrome, human immunodeficiency virus infection, granulocytosis, organ transplantation, and other immunodeficiency conditions with pneumonia); missing patients; and incomplete data.

Research methodology

We collected the demographic data, vital signs, biochemical indexes, and mechanical ventilation rates of the adult CAP patients in this study. On the first day of admission, the S100A12, PCT, CRP, white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), and SAA were measured. The calculation of serum S100A12 concentration was conducted strictly according to the kit specifications and manufacturer's instructions. The MEWS was calculated using the data collected. The prognosis of the condition was assessed after 30 days.

Detection concentration of S100A12 using enzyme-linked immunosorbent assay (ELISA)

Double antibody sandwich ELISA of 96T specification (Human S100 Calcium Binding Protein A12 ELISA kit; Sains Biotechnology Co., Ltd., Luzhou, China) was used for detecting the serum S100A12 concentration. The samples, standard samples, and horseradish peroxidase-labeled antibodies were added to the coated micropores of pre-coated S100A12 antigens. The 3,3',5,5'-tetramethylbenzidine turned blue by peroxidase and eventually turned to yellow under the action of the enzyme. The color depth and S100A12 concentration were positively correlated. The sample concentration was calculated using an enzyme marker to measure the optical depth at a wavelength of 450 nm. The concentration range of the kit used was 1.0–80 ng/mL. We found that the serum S100A12 level reached a peak (60 μg/L) after 3 h of intravenous lipopolysaccharide administration. After 24 h, it returned to the baseline level (6,7), which was much higher than the value in healthy or non-infected individuals (5–10 μg/L) (8).

Relevant definitions

The S100 protein was first found in bovine brains by Moore in 1965 (9). It is a newly identified extracellular advanced glycation end product binding protein receptor (10). Serum S100A12 has a high value in the differential diagnosis of bacterial infections, especially in severe bacterial infections (11). The S100A12 concentration reached a peak (60 μg/mL) after 3 h of intravenous LPS and returned to the baseline level after 24 h (6,7). S100A12 was found to bind to calcitonin kinase II, protein kinase C, phospholipase C, and calcium-regulated and mitogen-activated protein kinase in a rat model of sepsis and to activate and participate in multiple signal transduction pathways (12). S100A12 has chemotactic activity and can act directly as chemokines and activators to expand the response of inflammatory cells (13,14). Several studies have confirmed that S100 proteins play an important role in cytoskeleton establishment, regulation of enzyme activity, regulation of apoptosis, and facilitating inflammation and immune response. Moreover, S100A12 is similar to many antimicrobial peptides, and its antibacterial effect is closely related to inflammation (15).

MEWS is a scoring system used to evaluate the degree of risk of a patient's condition in the comprehensive ward. The patients can be categorized as low risk (MEWS 0–3), intermediate risk (MEWS 4–8), and high risk (MEWS 9–14) based on the following five physiological parameters: body temperature, heart rate, respiratory frequency, systolic blood pressure, and consciousness state (16). Compared with the traditional APACHE Ⅱ, Simplified Acute Physiology Score (SAPS), Sequential Organ Failure Assessment (SOFA), Multiple Organ Dysfunction Score (MODS), and other commonly used clinical scoring systems, the MEWS is simple to calculate. Furthermore, the parameters required for its calculation are accurate, quick, and easy to acquire; therefore, it is more in line with the actual requirements in emergency and ICUs and is widely used. Zografakis-Sfakianakis *et al.* (17) and Lee *et al.* (18) have confirmed through several studies that the MEWS is used to assess the degree of risk of a patient's condition. With the increase in the MEWS, the mortality risk also increases. Therefore, it can evaluate the patient's condition and prognosis effectively and predict the mortality risk accurately. Thus, it has a high clinical application value.

Statistical analysis

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Table 1 Comparison of mechanical ventilation rate and mortality in different levels of MEWS score and their correlation with S100A12

Project	Groups	Score	No. of cases	Invasive mechanical ventilation		Death		S100A12 (ng/mL)		
				No. of cases	Invasive mechanical ventilation rate (%)	No. of cases	Death rate (%)	Concentration (mean ± SD)	F	P
MEWS	Low risk	0–3	79	7	8.9	10	12.7	20.38±16.60	7.563	<0.05
	Medium risk	4–8	22	8	36.4	5	22.7	30.18±27.13*		
	High risk	9–14	7	5	71.4	6	85.7	48.27±27.89#		

*, compared with low-risk groups, P<0.05; #, compared with the medium risk group, P<0.05. MEWS, modified early warning score; S100A12, S100 serum calcium-binding protein A12; SD, standard deviation.

was used for statistical analysis. The count data were represented as frequencies and percentages. The Chi-squared test was conducted for comparing single-factor variables. The measurement data were expressed as means and standard deviations. An independent sample *t*-test was used to compare the two groups. A single-factor analysis of variance and least significant difference-t-test were used for inter-group comparisons. The factors influencing 30-day mortality in adult CAP patients were analyzed using single-factor and multifactor logistic regression analyses. Pearson correlation analysis assessed the correlation between S100A12 and MEWS. The sensitivity and specificity of S100A12, PCT, and MEWS in predicting mortality and the difference in the area under each index curve (AUC) were evaluated using the receiver-operating characteristic (ROC) curves of the participants. P values <0.05 were considered statistically significant.

Results

Comparison of mechanical ventilation and mortality rates in different MEWS groups and their correlation with S100A12

Based on the MEWS of the 108 adult CAP patients, 79, 22, and 7 patients were categorized into the low-risk, intermediate-risk, and high-risk groups, respectively. The S100A12 concentration, invasive mechanical ventilation rate, and mortality rate were recorded on the first day of admission. The study showed that the S100A12 level of the high-risk group was higher than that of intermediate- and low-risk groups, while that of the intermediate-risk group was higher than that of the low-risk group, with a statistically significant difference (P<0.05). As the MEWS increased, the mechanical ventilation and mortality rates increased significantly. The CAP severity changes correlated positively with the S100A12 concentration (*Table 1*).

Comparison of serum indexes and MEWS between the groups

According to the survival status of the 108 patients after 30 days, they were divided into the survival group and the death group. The WBC, NLR, SAA, CRP, S100A12, PCT, and MEWS of the two groups were recorded. The results of univariate analysis revealed no significant differences in age, sex, WBC, NLR, and SAA between the two groups (P>0.05). Notably, CRP, S100A12, PCT, and MEWS were the influencing factors for predicting mortality in the adult CAP patients after 30 days, and the death group showed significantly higher values than the survival group, with a statistically significant difference (P<0.05, *Table 2*).

Correlation analysis of factors affecting 30-day mortality in adult CAP patients

The WBC, NLR, SAA, CRP, S100A12, PCT, and MEWS were recorded in the survival and death groups. Univariate analysis showed that CRP, S100A12, PCT, and MEWS were the risk factors for predicting mortality in adult CAP patients. Multivariate logistic regression analysis showed that S100A12, PCT, and MEWS were independent risk factors for predicting 30-day mortality in adult CAP patients (P<0.05, *Table 3*). Pearson correlation analysis revealed that S100A12 correlated positively with MEWS (r=0.349, P<0.001).

Comparison of the AUCs of S100A12, PCT, and MEWS for predicting mortality in adult CAP patients

The ROC curve analysis showed that after 30 days, the

Table 2 Comparison of serum indexes and MEWS score between the two groups

Project	Groups		t/χ^2	P
	Survival group (n=87)	Death group (n=21)		
Age (years)	61.89±14.44	67.90±16.06	1.677	0.096
Gender (M/F)	64/23	17/4	0.493†	0.584
WBC (10^9/L)	11.08±4.80	10.34±4.71	–0.635	0.527
NLR	11.50±14.76	12.88±11.11	0.401	0.689
SAA (mg/L)	255.14±224.50	311.47±242.23	1.017	0.312
CRP (mg/L)	44.50±41.32	75.14±56.82	2.327	0.028
S100A12 (ng/mL)	19.84±17.00	42.14±26.79	3.642	0.001
PCT (ng/mL)	1.37±1.06	3.31±4.02	2.189	0.040
MEWS (scores)	2.69±1.59	5.81±3.06	4.527	<0.001

In *Table 2,* except for gender, which is represented by 'frequency', all other items are represented by 'mean ± SD'. †, χ^2 value. MEWS, modified early warning score; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; SAA, serum amyloid A; CRP, C-reactive protein; S100A12, S100 serum calcium-binding protein A12; PCT, procalcitonin.

Table 3 Correlation analysis of factors affecting death in adult CAP patients after 30 days

Factors	B	S.E.	Wald	OR	95% CI	P
S100A12	0.038	0.013	7.997	1.039	1.012–1.066	0.005
PCT	0.759	0.282	7.247	2.136	1.229–3.712	0.007
MEWS	0.517	0.148	12.232	1.677	1.255–2.240	<0.001
CRP	0.001	0.007	0.016	1.001	0.987–1.015	0.899

CAP, community-acquired pneumonia; OR, odds ratio; 95% CI, 95% confidence interval; S100A12, S100 serum calcium-binding protein A12; PCT, procalcitonin; MEWS, modified early warning score; CRP, C-reactive protein.

Table 4 Area comparison of S100A12, PCT, MEWS under the ROC curve for predicting CAP deaths

Forecast indicators	Optimal threshold	AUC	95% CI	Sensitivity	Specificity	Jordan index	P
S100A12 (ng/mL)	18.190	0.830	0.744–0.920	0.857	0.724	0.581	<0.001
PCT (ng/mL)	1.715	0.690	0.562–0.812	0.619	0.782	0.401	0.008
MEWS (score)	5.500	0.800	0.692–0.901	0.524	0.954	0.478	<0.001

S100A12, S100 serum calcium-binding protein A12; PCT, procalcitonin; MEWS, modified early warning score; ROC, receiver operating characteristic; CAP, community-acquired pneumonia; AUC, area under the curve; 95% CI, 95% confidence interval.

AUCs of S100A12, PCT, and MEWS for predicting mortality in adult CAP patients were 0.830, 0.690, and 0.800, respectively. Moreover, the optimal thresholds of S100A12, PCT, and MEWS were 18.190, 1.715, and 5.500, sensitivity values were 0.857, 0.619, and 0.524, and specificity values were 0.724, 0.782, and 0.954, respectively (*Table 4*, *Figure 1*).

Discussion

CAP is an important and common cause of disease and death worldwide. Severe pneumonia can lead to systemic multiple organ failure, with acute respiratory failure, hypercapnia, hypoxemia, hemodynamic disorders, and other manifestations. The incidence of CAP is estimated as 4.7–11.3%. When the patient has a high respiratory rate,

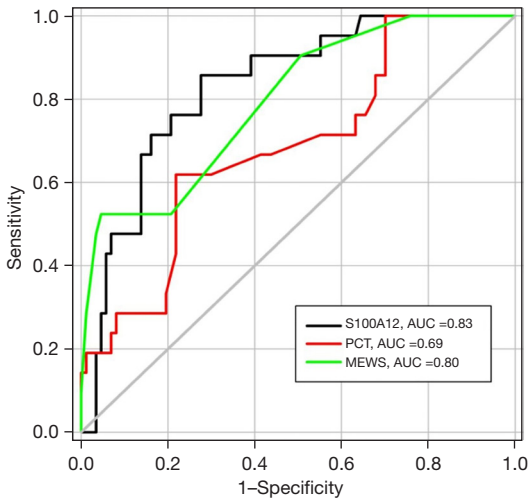

Figure 1 ROC curve of S100A12, PCT, MEWS for predicting CAP deaths. "sensitivity" indicates the sensitivity of serum S100A12, PCT, and MEWS in predicting mortality after 30 days in patients with CAP, and "specificity" indicates the specificity of serum S100A12, PCT, and MEWS in predicting mortality after 30 days in patients with CAP. ROC curve, receiver operating characteristic curve; S100A12, S100 serum calcium-binding protein A12; PCT, procalcitonin; MEWS, modified early warning score; CAP, community-acquired pneumonia.

disturbed consciousness, rapid pulse rate, severe respiratory distress, and apnea symptoms, they should be transferred to the ICU for monitoring and mechanical ventilation (19). Laboratory examination is the first choice for diagnosing severe pneumonia in addition to routine imaging examinations. Laboratory examination mainly includes some infection-related biomarkers. Biomarkers are commonly used to differentiate between infections, assess the disease severity, and predict the prognosis. The commonly used markers include WBC, neutrophils, interleukins, CRP, and calcitonin. Recently, some new serum markers have been used clinically, such as SAA, soluble myeloid cell expression triggers receptor-1, lipopolysaccharide-binding protein, and S100 calcium-binding protein families (20).

The commonly used clinical PCT is the main index of early bacterial infection and has good specificity for severe systemic infectious diseases. SAA is a sensitive acute phase response protein, which can be used as a sensitive index to reflect infection and inflammation control. CRP, an infection index widely used clinically in recent years, rises rapidly after most infectious diseases and is highly sensitive for detecting acute infection. S100A12, a new infection marker, is gradually becoming known globally. As a member of the S100 protein family, S100A12 is mainly expressed in peripheral blood cells, and it can distinguish between acute infections and non-infectious diseases. Moreover, it has shown a good diagnostic value in local and systemic infections (21). Research shows (7,21,22) that S100A12 increases in varying degrees in systemic inflammation (e.g., sepsis, septicemia, and septic shock) and local inflammation (e.g., peritonitis, urinary tract infection, pneumonia, and cystic fibrosis with pulmonary infection). This protein is a new-generation serum marker used to differentiate among acute infectious diseases. Its detection method is simple and fast. It has a high clinical value in the differential diagnosis of acute infectious diseases, especially in CAP, septicemia, and sepsis, evaluation of disease severity, and guidance regarding the anti-infection approach.

The most commonly used scoring systems to evaluate the critical condition of patients are the APACHE II, SAP, SOFA, and MODS. Among them, APACHE II is considered the most authoritative and accurate scoring system to evaluate the degree of risk and prognosis of critical patients. However, the drawback is that the APACHE II, SAP, SOFA, and MODS need many clinical indicators, which are not only complex to obtain but also time-consuming. Therefore, these scoring systems are difficult for widespread use in the whole country. When determining how to evaluate the degree of risk in critical patients quickly, several previous studies reported MEWS to be comparable to APACHE II in evaluating the degree of risk. Moreover, it is easier and faster to obtain the clinical data required to calculate the MEWS, and it can effectively predict the in-hospital mortality of adult CAP patients (4).

With an increase in the MEWS, the mortality risk increases. The MEWS can effectively evaluate the patient's condition and prognosis and accurately predict the mortality; therefore, it has a high clinical value.

According to different groups of analyses conducted, S100A12 combined with MEWS can be used in adult patients to assess the severity and evaluate the prognosis; thus, it has a positive application value. S100A12 correlated positively with MEWS; therefore, the higher the stratification, the higher the concentration, the more severe the disease, and the worse the prognosis. S100A12, PCT, and MEWS can effectively predict the 30-day mortality risk in adult CAP patients. The evaluation efficiency in descending order is S100A12, MEWS, and PCT. S100A12 predicted the 30-day mortality risk in adult CAP patients with the largest area and the highest prediction accuracy,

while the MEWS predicted it with the highest specificity. Moreover, the MEWS system is quite concise, and the results can be obtained conveniently without laboratory investigations.

Some limitations and deficiencies in this study. This is a small sample prospective single center study that may lead to selection bias, so it may be necessary to increase the sample size in clinical practice in the future to verify the results.

Conclusions

This study confirmed that both S100A12 and MEWS positively affect the evaluation of the severity of CAP in adults, and both can effectively predict the prognosis. Therefore, serum S100A12 combined with MEWS scores has a high clinical value in evaluating the severity and prognosis of CAP in adult patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1114/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1114/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1114/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Affiliated Hospital of Southwest Medical University (Institutional Review Board File KY2020053). Informed consent was obtained from all participants.

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