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ORIGINAL RESEARCH

Assessment of Variations in HAPS Scores, CaMK II Expression Levels, and Prognostic Outcomes Among AP Patients with Diverse Disease Severities

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Objective: To analyze the differences in Harmless Acute Pancreatitis Score (HAPS), serum Calcium/Calmodulin-dependent Protein Kinase II (CaMK II) expression, and prognosis among patients with acute pancreatitis (AP) of varying disease severities.

Methods: A retrospective analysis was conducted on the clinical data of 103 patients with acute pancreatitis (AP) treated at our hospital between April 2022 and April 2024. According to the revised Atlanta classification and the International Consensus on Definitions (2012), patients were divided into Group A (59 cases, mild cases) and Group B (44 cases, severe cases). The HAPS score was calculated using relevant examination data obtained upon admission. Fasting venous blood samples (5 mL) were collected from all subjects on the morning of the second day after admission, and serum CaMK II expression levels were measured using a double-antibody sandwich method. Patients were followed up for three months from the date of admission to record local complications, systemic complications, and mortality. Receiver operating characteristic (ROC) curves were plotted to analyze the predictive value of HAPS scores and serum CaMK II levels for mild AP and patient prognosis.

Results: HAPS scores and serum CaMK II levels were assessed at admission. Severe cases showed significantly higher HAPS and CaMK II levels vs mild ($P<0.05$). ROC analysis demonstrated combined detection (AUC=0.902) outperformed individual markers (HAPS=0.827; CaMK II=0.773) in predicting mild AP. Both biomarkers progressively increased with complication severity (local < systemic < death, $P<0.05$), showing predictive value (AUC>0.6) for prognosis.

Conclusion: HAPS scores and CaMK II expression levels in AP patients show a gradual increase with the severity of the disease, and both can serve as predictive indicators of disease severity and prognosis in AP patients. Moreover, combined detection of these indicators has a higher predictive efficiency than single-item detection.

Keywords: disease severity, AP, HAPS score, CaMK II expression, prognosis differences

Introduction

Acute pancreatitis (AP) is a common acute condition of the digestive system with a complex and varied clinical presentation.[1] The disease can progress from a mild, self-limiting condition to severe multi-organ failure, potentially leading to death.[2] Therefore, early identification and accurate assessment of the severity of AP are crucial for improving patient prognosis. Current clinical methods for assessing the prognosis of acute pancreatitis (AP) include the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, the Ranson scoring system, and the Computed Tomography Severity Index (CTSI). However, APACHE II requires the evaluation of multiple physiological parameters, making the scoring process complex and time-consuming, with certain time constraints. The Ranson scoring system is not suitable for early assessment, as it can only be used 48 hours after hospital admission, limiting its clinical practicality. CTSI scoring relies on CT imaging, which is costly and requires 48 to 72 hours of hospitalization to obtain accurate results, making it less favorable for early evaluation.[3] The Harmless Acute Pancreatitis Score (HAPS) has

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recently been introduced as a tool for assessing the severity of AP. Compared to previous evaluation methods, HAPS requires easily accessible clinical parameters, making it more applicable in clinical practice. Studies have shown that the specificity and positive predictive value of HAPS in predicting mild acute pancreatitis (MAP) upon admission are 97.7% and 95.6%, respectively, indicating a high predictive accuracy.[4]

In addition to traditional clinical scoring systems, biomarkers are increasingly being recognized for their role in the diagnosis and severity assessment of AP. Calcium/Calmodulin-dependent Protein Kinase II (CaMK II) is a multifunctional protein kinase widely present in various human tissues, particularly abundant in the myocardium and neurons.[5] Research indicates that CaMK II plays a significant role in pancreatic inflammation and related organ damage, with its expression levels closely linked to the severity of the disease.[6] Serological testing offers the advantages of being easy to perform and non-invasive. Although both HAPS scores and CaMK II expression have significant implications in assessing the severity of AP, studies on the differences between the two in AP patients with varying disease severities are relatively limited. Therefore, this study retrospectively analyzes the clinical data of 103 AP patients to explore the differences in HAPS scores, CaMK II expression levels, and prognosis among AP patients with different disease severities, and to evaluate the application value of combined detection of these two indicators in disease assessment and prognosis prediction. The results of this study are expected to provide a theoretical basis and reference for the early diagnosis and personalized treatment of AP.

Materials and Methods

Basic Information

A retrospective analysis was conducted on the clinical data of 103 patients with acute pancreatitis (AP) treated at our hospital from April 2022 to April 2024. Serum CaMK II quantification was performed exclusively for research purposes and was not part of routine clinical care. All biological samples were obtained from the hospital's biobank, which collects residual specimens after completing standard diagnostic tests (amylase, lipase, CRP, etc). The inclusion criteria were: ① Age ≥18 years, no gender restrictions; ② Meeting the clinical diagnostic criteria for AP;[7] ③ Onset to admission time <48 hours, with relevant treatment interventions after admission; ④ Clear consciousness and sound mind, with complete data available for analysis. The exclusion criteria were: ① AP caused by pancreatic injury, recurrent chronic pancreatitis, or pancreatic cancer; ② Combined with severe organ dysfunction; ③ Combined with malignant tumors; ④ Combined with immune system or hematologic diseases; ⑤ Combined with severe infection; ⑥ Received relevant treatment before admission; ⑦ Combined with congenital pancreatic diseases such as ectopic pancreas or annular pancreas; ⑧ Pregnant or lactating women; ⑨ Combined with cognitive, communication, or mental disorders; ⑩ Did not fully participate in the study or had incomplete clinical data. According to the revised Atlanta classification and the International Consensus on Definitions (2012),[8] patients were divided into Group A (59 cases, mild cases) and Group B (44 cases, severe cases). The basic information of the two groups was comparable, with no statistically significant differences (P>0.05), as shown in Table 1. The study protocol (including waiver of individual informed consent for retrospective analysis of anonymized data) was approved by the Liupanshui People's Hospital Ethics Committee (Approval No. 0212021-LA-115). Patient

Table 1 Comparison of Basic Information [$\bar{x} \pm s$, n (%)]

	Group A (n=59)	Group B (n=44)	t/x^2	P
Gender	–	–	0.022	0.881
Male	34 (57.63)	26 (59.09)	–	–
Female	25 (42.37)	18 (40.91)	–	–
Age (years)	44.65±10.29	44.27±10.86	0.181	0.856
BMI (kg/m²)	22.87±1.95	23.04±1.79	0.453	0.651
Etiology	–	–	0.139	0.709
Alcoholic	22 (37.29)	18 (40.91)	–	–
Biliary	26 (44.07)	21 (47.73)	–	–
Hyperlipidemic	11 (18.64)	5 (11.36)	–	–

records were de-identified prior to analysis, ensuring confidentiality compliance with the Declaration of Helsinki. Informed consent was obtained from all study participants.

Treatment Methods

All patients received severity-stratified standardized therapy in accordance with the Revised Atlanta Classification (2012).[8] Treatment protocols were strictly unified within each severity group to eliminate interventional heterogeneity. For Group A (Mild AP), mandatory interventions included fasting until both Visual Analog Scale (VAS) pain score was ≤3 and serum amylase was ≤3× upper limit of normal (ULN). Aggressive fluid resuscitation was administered using Ringer's lactate at 5–10 mL/kg/h for the initial 24 hours, adjusted based on urine output (>0.5 mL/kg/h). Proton pump inhibitors were given as Pantoprazole 40 mg IV every 12 hours for 72 hours. The nutrition protocol involved initiating oral or enteral feeding within 48 hours of admission, using a nasojejunal tube in cases of oral intolerance. For Group B (Severe AP), first-line therapy included continuous octreotide infusion (50 μg/h for ≥72 hours) and early antibiotic prophylaxis with Meropenem 1 g IV every 8 hours if the CT severity index was ≥6. Organ failure management involved mechanical ventilation for PaO2/FiO2 <300 mmHg and renal replacement therapy if serum creatinine exceeded 2.0 mg/dL with urine output <0.3 mL/kg/h for 24 hours. Surgical intervention was considered if infected necrosis was confirmed and clinical deterioration persisted for more than 72 hours despite antibiotic therapy. To ensure treatment consistency, an independent AP Clinical Pathway Committee reviewed all cases biweekly to verify protocol compliance. Patients with more than 20% deviation from assigned protocols, such as delayed fluid resuscitation in Group A, were excluded from the final analysis (n=2 in Group B).

HAPS Score Measurement

HAPS scores were calculated based on the relevant examination data at the time of AP patients' admission, as follows: ① Abdominal signs: 0 points for no tenderness and muscle tension, 1 point for tenderness and muscle tension; ② Hematocrit: 0 points for males ≤43.0% and females ≤39.6%, 1 point for males >43.0% and females >39.6%; ③ Serum creatinine: 0 points for <176.8 mmol/L, 1 point for ≥176.8 mmol/L. HAPS is the sum of the three scores, with a range of 0–3 points, where a higher score indicates more severe pancreatitis.[9]

Serum CaMK II Expression Level Detection

Fasting morning venous blood samples (5 mL) were collected from all subjects on the day after admission and centrifuged at 3000 r/min for 5 minutes to collect the supernatant. The detection procedure was performed according to the manufacturer's protocol with standardized operations. Briefly, 100 μL of calibrators and samples were added to pre-coated microplate wells in duplicate and incubated for 60 minutes at 37°C. After five cycles of plate washing, 100 μL of biotinylated detection antibody was added, followed by 30-minute incubation. Subsequently, 100 μL of horseradish peroxidase (HRP) conjugate was introduced and incubated for another 30 minutes. Following final washing steps, 90 μL of substrate solution was added for a 15-minute color development before terminating the reaction. Serum CaMK II expression levels were measured using a double-antibody sandwich method. The enzyme-linked immunosorbent assay (ELISA) reader was purchased from Bio-Rad, USA, and the test kit was purchased from Shenzhen Highsan Biotechnology Co., Ltd. (Product number: HAS-51163). The entire procedure requires approximately 3.5 hours of hands-on time with basic laboratory skills, plus 1.5 hours for equipment operation. Results were obtained within the same working day, with an intra-assay coefficient of variation <8%, as specified by the manufacturer.

Follow-up Observation

Patients enrolled in the study were followed up for 3 months from the date of admission through outpatient visits and telephone follow-ups every 2 weeks. Prognostic outcomes were recorded, with the follow-up ending on July 31, 2024, or upon the patient's death. The primary outcomes were classified into local complications (eg, pancreatic necrotic infection, pseudocysts), systemic complications (eg, multiple organ failure, systemic inflammatory response syndrome), and death. Patients were categorized into the local group (n=44), systemic group (n=55), and death group (n=4).

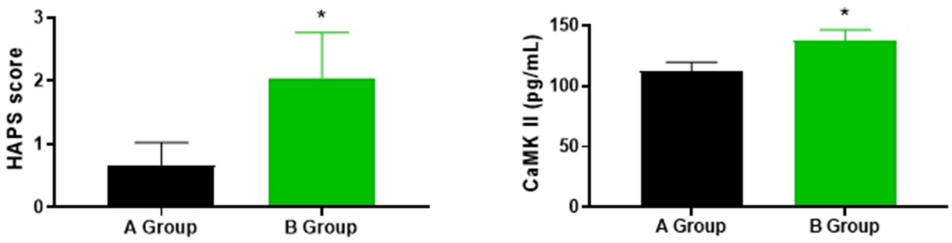

Figure 1 Comparison of HAPS Scores and CaMK II Expression Levels ($\bar{x} \pm s$).
Note: Comparison between groups, *P<0.05.

Statistical Analysis

GraphPad Prism 8 software was used for plotting, and SPSS 22.0 software was used for data processing. Measurement data were described using ($\bar{x} \pm s$), with independent sample *t*-tests for comparisons between groups, one-way ANOVA for multiple group comparisons, and SNK-q tests for pairwise comparisons. Categorical data were described using n (%), with chi-square tests for comparisons between groups. ROC curves were plotted to evaluate the predictive value of HAPS scores and serum CaMK II expression levels for mild AP and patient prognosis. A P-value of <0.05 was considered statistically significant.

Results

Comparison of HAPS Scores and CaMK II Expression Levels

The HAPS scores and CaMK II expression levels were significantly higher in Group B compared to Group A (P<0.05), as shown in Figure 1.

Predictive Value of HAPS Scores and CaMK II Expression Levels for Mild AP

The area under the curve (AUC) for predicting mild AP using HAPS scores, CaMK II levels, and the combination of both were 0.827, 0.773, and 0.902, respectively. The combined detection showed higher predictive efficiency for mild AP compared to individual tests, as shown in Table 2 and Figure 2.

Comparison of HAPS Scores and CaMK II Expression Levels in AP Patients with Different Prognoses

The HAPS scores and CaMK II expression levels were higher in the systemic group and death group compared to the local group, and the death group had higher levels than the systemic group (P<0.05), as shown in Figure 3.

Predictive Value of HAPS Scores and CaMK II Expression Levels for Prognosis in AP Patients with Different Severity

The AUCs of HAPS scores and CaMK II for predicting local complications, systemic complications, and death in AP patients were all >0.600, indicating certain predictive value. The combined detection showed higher predictive efficiency for prognosis in AP patients compared to individual tests, as shown in Table 3.

Table 2 Predictive Value of HAPS Scores and CaMK II Expression Levels for Mild AP

Index	Critical Value	AUC	95% CI	P	Sensitivity	Specificity
HAPS Score	1.36	0.827	0.704~0.896	<0.05	87.69	82.74
CaMK II	120.54	0.773	0.642~0.838	<0.05	83.62	78.95
Combined	–	0.902	0.839~0.941	<0.05	92.47	87.09

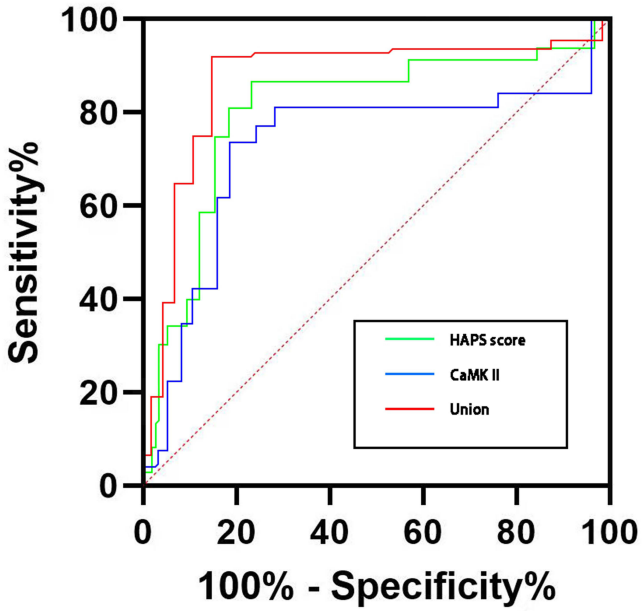

Figure 2 ROC Curve of HAPS Scores and CaMK II Expression Levels for Predicting Mild AP.

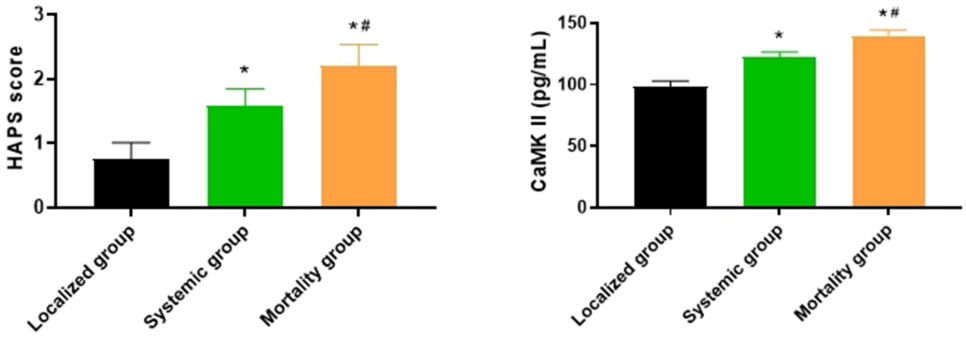

Figure 3 Comparison of HAPS Scores and CaMK II Expression Levels in AP Patients with Different Prognoses ($\bar{x} \pm s$).
Note: Compared with the local group, *P<0.05; compared with the systemic group, #P<0.05.

Discussion

In recent years, with the continuous improvement of China's economic level and the gradual Westernization of dietary habits, the incidence of AP has been steadily increasing, with a trend towards younger and more severe cases.[10] Patients with mild AP typically have a relatively mild condition that generally does not involve organ dysfunction, and timely symptomatic treatment can control the disease. However, if diagnosis is delayed or treatment is inadequate, mild AP can quickly progress to severe AP, leading to serious health consequences.[11] The pathophysiology of severe AP is quite complex, with a rapid onset and a high mortality rate.[12] Patients with severe AP often face the risk of multiple organ failure, making treatment difficult and prognosis poor.[13] Therefore, early identification and effective intervention for severe AP have become key issues that need to be addressed in clinical practice. Previous studies[14] have shown that the mortality rate of AP patients is influenced by various factors, including the patient's age, the etiology of AP, the severity of the disease, the presence of infection, and the type and number of complications. Particularly in severe AP, the condition progresses rapidly and is complex, often leading to multiple complications in a short period, further exacerbating the patient's condition.[15] Therefore, in-depth analysis and accurate screening of these influencing factors, along with early-stage effective treatment measures, are crucial for delaying disease progression and improving patient prognosis.

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Table 3 Predictive Value of HAPS Scores and CaMK II Expression Levels for Prognosis in AP Patients With Different Severity

Index	AUC	95% CI	P	Sensitivity	Specificity
Local Complications	–	–	–	–	–
HAPS Score	0.694	0.615~0.772	<0.05	81.29	78.57
CaMK II	0.673	0.631~0.785	<0.05	79.86	76.32
Combined	0.737	0.654~0.835	<0.05	83.19	80.92
Systemic Complications	–	–	–	–	–
HAPS Score	0.728	0.634~0.812	<0.05	84.63	81.79
CaMK II	0.689	0.647~0.839	<0.05	82.40	80.36
Combined	0.765	0.659~0.858	<0.05	89.76	87.32
Death	–	–	–	–	–
HAPS Score	0.757	0.642~0.841	<0.05	86.79	82.47
CaMK II	0.716	0.628~823	<0.05	83.85	80.56
Combined	0.791	0.658~0.865	<0.05	91.47	88.54

The HAPS score is a simple scale specifically designed to assess the severity of AP in patients, initially intended to quickly identify non-severe AP patients who do not require intensive care unit (ICU) care.[16] The clinical application value of the HAPS score lies in its ability to effectively distinguish mild cases and assist doctors in identifying patients who can be discharged after a short hospital stay in a general ward, or even those who may be managed with home care, thereby optimizing the allocation of medical resources.[17] In this study, we calculated the HAPS score based on the clinical examination data of AP patients upon admission, and the results showed that the HAPS score in Group B was higher than in Group A ($P<0.05$). Through ROC curve analysis, we further evaluated the predictive efficacy of the HAPS score in AP patients with different disease severity. The results showed that the AUC of the HAPS score in mild AP patients was 0.827, indicating that it has a high predictive efficacy for mild AP, which is generally consistent with previous related studies.[18] More importantly, the HAPS score not only predicts the severity of AP but is also closely related to patient prognosis. Studies[19] have shown that the higher the HAPS score, the higher the mortality rate of AP patients, and the longer the hospital stay. Similarly, in another study,[20] the HAPS score demonstrated good sensitivity and specificity in predicting the prognosis of AP patients, making it an effective prognostic assessment tool. In this study, we conducted a 3-month follow-up of all enrolled AP patients to explore the relationship between the HAPS score and different prognostic outcomes. The results showed that the HAPS score in the systemic group and death group was higher than in the local group, and the death group was higher than the systemic group ($P<0.05$). Further ROC curve analysis showed that the AUC of the HAPS score in predicting local complications, systemic complications, and death in AP patients was 0.694, 0.728, and 0.757, respectively. These data indicate that the HAPS score not only effectively predicts the severity of AP but also has significant clinical value in prognostic assessment.

CaMK II is a key signal transduction molecule closely associated with intracellular calcium ion channels and is widely involved in various biological processes, including cell proliferation, differentiation, metabolic regulation, and apoptosis.[21] In the pathophysiological mechanism of AP, the role of CaMK II is particularly prominent.[22] Recent studies[23] have shown that abnormally high expression of CaMK II can induce necrosis of pancreatic acinar cells, thereby playing a role in the onset and progression of AP. In this study, we found that the expression level of CaMK II in Group B was higher than in Group A ($P<0.05$). This finding suggests that high expression of CaMK II is associated with the severity of AP, indicating that it may play a promoting role in the development of AP. Further ROC curve analysis showed that the AUC of serum CaMK II in predicting mild AP patients was 0.773, indicating that CaMK II can serve as an effective serological marker for assessing the severity of AP. Moreover, this study further explored the relationship between CaMK II and the prognosis of AP patients. The results showed that the expression level of CaMK II in the systemic group and death group was higher than in the local group, and the death group was higher than the systemic group ($P<0.05$). This result suggests that high expression of CaMK II may not only be a result of AP exacerbation but could also be an important factor contributing to the worsening of AP. Through ROC curve analysis, we found that the

AUC of serum CaMK II in predicting local complications, systemic complications, and death in AP patients was 0.673, 0.689, and 0.716, respectively, further supporting the potential of CaMK II as a prognostic marker for AP patients. In addition, this study also explored the predictive efficacy of the combined use of HAPS scores and CaMK II in AP patients. The results showed that the AUC of the combined prediction of mild AP by HAPS scores and serum CaMK II reached 0.902, while the AUCs for predicting local complications, systemic complications, and death in AP patients were 0.737, 0.765, and 0.791, respectively. Compared to using the HAPS score or CaMK II alone, the combined use of both significantly improved predictive efficacy. This finding suggests that the combined detection of HAPS scores and serum CaMK II can more accurately assess the severity and prognosis of AP patients, providing more reliable guidance for early clinical intervention. Overall, as a key molecule in the pathological process of AP, the high expression of CaMK II is not only closely related to the exacerbation of the condition but can also serve as an important serological marker for predicting the prognosis of AP patients. When combined with the HAPS score, the joint detection can more comprehensively reflect the patient's condition, guiding clinicians in formulating more precise treatment plans, thereby helping to improve the overall prognosis of the patients. Future research can further explore the potential target value of CaMK II in AP treatment, with the aim of bringing more effective treatment strategies to patients.

It is important to note that despite the clinically meaningful conclusions drawn from this study, there are still some limitations that need to be improved and further explored in future research: ① Sample size limitation: This study only included 103 AP patients, which is relatively small, potentially limiting the generalizability and representativeness of the research findings. ② Single-center study: This study was conducted in a single medical center, and the results may be influenced by the specific medical environment and patient population. ③ Short follow-up period: The follow-up period in this study was 3 months, which, although sufficient to observe short-term prognosis, is still insufficient for assessing long-term prognosis. ④ Research on other potential markers: While this study focused on HAPS scores and CaMK II, the pathogenesis of AP is complex, involving multiple signaling pathways and biomarkers. ⑤ Diagnostic validation methodology: Our study analyzed CaMK II as a prognostic biomarker through retrospective correlation, but did not prospectively evaluate its diagnostic utility using blinded methods. Future studies should employ a blinded design where CaMK II levels are measured independently prior to clinical severity classification. This approach could calculate the accuracy (eg, sensitivity/specificity) of CaMK II in distinguishing mild vs severe AP, thereby informing real-time clinical decision-making for treatment stratification.

In summary, although this study provides a basis for the clinical application of HAPS scores and CaMK II expression levels in the prognostic assessment of AP patients, further research is needed to overcome the above limitations in order to optimize and improve AP diagnosis and treatment strategies.

Conclusion

As the condition worsens, the HAPS scores and CaMK II expression levels in AP patients significantly increase. HAPS scores and CaMK II not only demonstrate high efficacy in predicting the severity of mild and severe AP but also hold significant clinical value in predicting local complications, systemic complications, and death in patients, particularly through the application of their combined detection, which further enhances the ability to predict the severity and prognosis of AP patients. Therefore, the combined detection of HAPS scores and CaMK II can serve as an important tool for early prognostic assessment in AP patients, providing strong support for the formulation of early clinical intervention measures.

Disclosure

The authors report no conflicts of interest in this work.

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