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Original Article

Diagnostic value of macrophage inflammatory protein-1α, plasma thrombomodulin, and interleukin 12 in stroke-associated infections

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Abstract: Objective: To investigate the levels of macrophage inflammatory protein-1α (MIP-1α), plasma thrombomodulin (PTM), and interleukin-12 (IL-12) in the peripheral blood of patients with stroke-associated infections (SAIs) and clarify their correlation with secondary nosocomial infection. Methods: Clinical data from 75 patients with acute ischemic stroke (AIS) complicated by SAIs admitted between January 2022 and October 2024 were retrospectively analyzed as the infected group. Another 60 AIS patients without infection during the same period were selected as the uninfected group. Peripheral blood levels of MIP-1α, PTM, and IL-12 were measured, and their correlation with secondary nosocomial infection was evaluated. Results: Pearson correlation analysis showed that serum MIP-1α, PTM, and IL-12 levels were positively correlated with inflammatory cytokines, including high-sensitivity C-reactive protein (hs-CRP), procalcitonin, and IL-6 in the infected group (all $P < 0.001$). Logistic regression analysis indicated that elevated serum MIP-1α, PTM, and IL-12 levels were independent risk factors for AIS-associated infection ($P < 0.05$). Receiver operating characteristic (ROC) curve analysis showed that the combined prediction of serum MIP-1α, PTM, and IL-12 yielded a larger area under the curve for predicting SAIs compared with any individual marker. Conclusion: Patients with SAIs exhibited elevated serum levels of MIP-1α, IL-12, and PTM, demonstrating significant diagnostic value for stroke-associated infection.

Keywords: Stroke, infection, MIP-1α, IL-12, PTM

Introduction

Stroke-associated infections (SAIs) refer to infections that neither occur during the stroke event itself nor within the latent period of infection, but typically develop within one week after stroke onset, primarily involving pulmonary and urinary tract infections [1, 2]. Studies [3] have shown that immune-inflammatory responses play a crucial role throughout the course of stroke. Severe ischemia following stroke disrupts cerebral energy metabolism and rapidly triggers immune-inflammatory response characterized by microglial activation, pro-inflammatory factor release, and neutrophil infiltration. These early immune responses, occurring within hours after ischemia, damage the blood-brain barrier and exacerbate cerebral edema and inflammatory injury. Such inflammatory response precedes overt neurological dysfunction and further contributes to neuronal death and functional deterioration through a sustained inflammatory cascade. Therefore, it is of great clinical significance to elucidate the immune-inflammatory mechanisms underlying stroke-associated infection and identify therapeutic targets.

In recent years, serum macrophage inflammatory protein-1α (MIP-1α), plasma thrombomodulin (PTM), and interleukin-12 (IL-12) have emerged as potential biomarkers of infection [4]. MIP-1α, a key chemokine, promotes the recruitment of monocytes and macrophages at the site of infection, amplifying local inflammatory responses. Elevated MIP-1α levels have been reported to correlate closely with infection severity [5]. PTM, a thrombin-binding glycoprotein with anticoagulant and anti-inflammatory effects, also plays an important role in infec-

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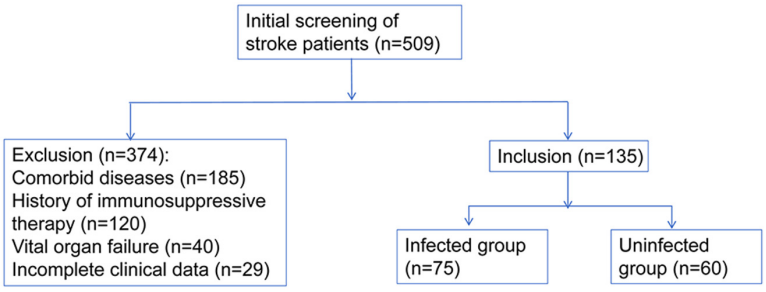

Figure 1. Flow diagram for patient selection.

tion-related thrombosis and inflammation, and its dysregulation may aggravate disease progression [6]. Additionally, IL-12 activates natural killer (NK) cells and T lymphocytes, enhancing cell-mediated immune responses, but its excessive expression may lead to hyperinflammation and tissue injury [7]. Although these molecules have been implicated in various infectious diseases, their roles in post-stroke immune dysregulation and the early diagnosis of SAIs remain unclear.

Therefore, this study postulates that MIP-1α, PTM, and IL-12 levels are elevated in patients with SAIs and are closely associated with post-stroke immunosuppression and infection risk. We investigated the expression levels of MIP-1α, PTM, and IL-12 in the peripheral blood of stroke patients and analyzed their relationship with the occurrence of SAIs, aiming to provide clinical evidence for early diagnosis, differentiation, and targeted intervention.

Materials and methods

Case selection

This single-center, retrospective, case-control study included patients with acute ischemic stroke (AIS) who were hospitalized at our institution between January 2022 and October 2024. All subjects were consecutively enrolled from the hospital's electronic medical record system. Routine blood tests were performed during hospitalization, and patients presenting with significantly decreased white blood cell counts were further evaluated after excluding malignancies and other confounding conditions. Given that stroke patients in the acute phase or during hospitalization are prone to infection, immune dysfunction, or excessive immune activation, immunological factor testing, including MIP-1α, PTM, IL-12, was conducted to assess immune status. All test data were archived in the hospital's electronic medical record system. The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Gannan Medical University. The study adhered to the ethical principles of the Declaration of Helsinki and followed the TRIPOD reporting guidelines [8]. Due to the retrospective nature of study design, informed consent from patients was waived.

Inclusion criteria: (1) meeting the diagnostic criteria outlined in the *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (2021 edition)*; (2) confirmed diagnosis of stroke via cranial magnetic resonance imaging (MRI) or computed tomography (CT); (3) first onset of stroke, with symptom onset within 24 hours prior to admission; (4) no history of infectious diseases within one month prior to admission; (5) complete clinical data, including laboratory tests (MIP-1α, PTM, IL-12, T cell, and NK cells assessments for diagnostic purposes) and infection monitoring records.

Exclusion criteria: (1) patients with concomitant cerebrovascular diseases or a history of brain injury; (2) patients with concomitant autoimmune diseases, malignancy, or severe cardiovascular diseases; (3) patients with psychiatric disorders; (4) use of corticosteroids, immunosuppressants, or other medications affecting immune function within the past month; (5) presence of functional failure of vital organs; (6) incomplete clinical data.

A total of 509 patients who met the diagnostic criteria were preliminarily screened, and eligible cases were identified according to strict inclusion and exclusion criteria (**Figure 1**). Specifically, 374 patients were excluded for the following reasons: comorbid diseases (n = 185), history of immunosuppressive therapy (n = 120), vital organ failure (n = 40), and incomplete clinical data (n = 29). A total of 135 eligible patients were ultimately included and divided into two groups according to the occurrence of hospital-acquired infection (HAI) dur-

Table 1. Univariate analysis of factors associated with SAIs

Item	Infected group (n = 75)	Uninfected group (n = 60)	t/χ^2	*P*
Sex (n)				
Male	45	32	0.605	0.437
Female	30	28		
Age (years)				
< 60	32	43	11.354	0.001
≥ 60	43	17		
BMI (kg/m^2)				
< 24	50	41	0.042	0.837
≥ 24	25	19		
Alcohol consumption history				
Yes	17	15	0.129	0.720
No	58	45		
Smoking history				
Yes	28	21	0.079	0.779
No	47	39		
History of pulmonary disease				
Yes	32	14	5.546	0.019
No	43	46		
Diabetes				
Yes	43	21	6.668	0.010
No	32	39		
Hypertension				
Yes	23	19	0.016	0.901
No	52	41		
NIHSS score upon admission (points)				
< 14	29	42	13.126	0.001
≥ 14	46	18		
Invasive procedures				
Yes	34	14	7.041	0.008
No	41	46		
Dysphagia				
Yes	32	15	4.584	0.032
No	43	45		
Length of hospital stay (d)				
< 14	24	23	11.845	0.001
≥ 14	51	37		

Note: SAI: stroke-associated infection; BMI: body mass index; NIHSS: National Institutes of Health Stroke Scale.

ing hospitalization: the infected group (n = 75) and the uninfected group (n = 60).

Research methods

Data collection: Demographic and clinical characteristics of patients were collected from the hospital's medical record system, including sex, age, body mass index (BMI), alcohol consumption history, smoking history, pulmonary diseases (chronic obstructive pulmonary disease or asthma), diabetes mellitus, hypertension, National Institutes of Health Stroke Scale (NIHSS) score, invasive procedures (e.g., endotracheal intubation, central venous catheterization, urethral catheter placement, nasogastric tube placement, and surgical procedures), dysphagia, and length of hospital stay. Upon admission, NIHSS and Glasgow Coma Scale (GCS) scores were assessed by trained neurologists using standardized procedures.

Imaging evaluation: All enrolled patients underwent routine cranial MRI upon admission to confirm the diagnosis of AIS. Chest CT was performed when necessary to evaluate pulmonary infection. The diagnosis of stroke was based on characteristic MRI findings of acute cerebral infarction, including hyperintense signals on diffusion weighted imaging (DWI) and hypointense areas on apparent diffusion coefficient (ADC) maps. Pulmonary infection was diagnosed by typical radiologic features - such as patchy infiltrates or ground-glass opacities on chest CT - combined with clinical symptoms and laboratory values.

Clinical evaluation: Laboratory values related to inflammation and immune status in patients with AIS were comprehensively evaluated, regarding their systemic inflammatory response and immune alterations.

First, all patients exhibited significant leukopenia during hospitalization, and peripheral blood

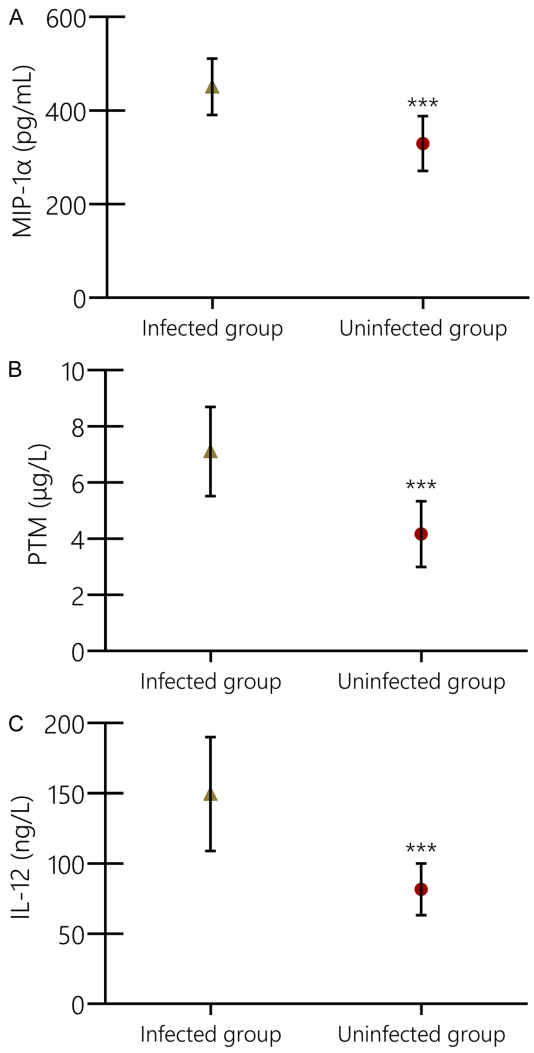

Figure 2. Comparison of peripheral blood levels of MIP-1α, PTM, and IL-12 between patients with and without SAIs. Note: (A) MIP-1α; (B) PTM; (C) IL-12. ***P < 0.001 vs. infected group. MIP-1α: macrophage inflammatory protein-1α; PTM: plasma thrombomodulin; IL-12: interleukin-12; SAI: stroke-associated infection.

samples was collected for further analysis. The serum levels of MIP-1α, PTM, and IL-12 were detected using enzyme-linked immunosorbent assay (ELISA). All kits were provided by Wuhan Cloud-Clone Corp, (catalog numbers: SEA092Hu, SEA529Hu, and SEA111Hu, respectively).

Second, to comprehensively assess disease severity, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score system was used. Parameters included age, GCS score, presence of immune deficiency or severe organ dysfunction, and several key physiological indicators such as heart rate, body temperature, mean arterial pressure, arterial oxygen partial pressure, and respiratory rate. The APACHE II score ranges from 0 to 71, with higher scores indicating more severe illness. This scoring system was used to quantify systemic stress responses and estimate prognostic risk in stroke patients.

In addition, a series of serum inflammatory cytokines and humoral immune markers were measured, including procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), and calcitonin gene-related peptide (CGRP). Among these, PCT levels were determined using immunofluorescence assay, hs-CRP was assessed by immunoturbidimetry, and IL-6 was detected by ELISA (kit catalog number: SEA079Hu, Wuhan Cloud-Clone Corp.). T lymphocyte subsets and NK cells were detected using flow cytometry (EPICS-XL flow cytometer). The labeled antibodies used included PE-CY5-labeled CD3 and $CD16^+CD56^+$, which were used to quantify the proportions of T cells and NK cells in peripheral blood, thereby reflecting the cellular immune status of patients.

The primary indicators in this study were peripheral blood MIP-1α, plasma PTM, and IL-12, which served as the key biomarkers for evaluating their predictive and clinical value in SAIs. The secondary indicators included T cells ($CD3^+$), NK cells ($CD16^+CD56^+$), immunoglobulins (IgA, IgG, IgM), and conventional inflammatory markers (hs-CRP, PCT, IL-6). These indicators comprehensively reflected patient's immune function and aided in analyzing systemic inflammatory responses related to infection.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS) 20.0 software (IBM Corp., Armonk, NY, USA). Categorical data were expressed as counts and percentages [n (%)], and intergroup comparisons were conducted using the χ^2 test. Normally distributed continuous variables were presented as mean ± standard deviation (mean ± SD), and intergroup comparisons were conducted using the independent samples t-tests. Variables significantly associated with SAIs in univariate analysis (e.g., χ^2

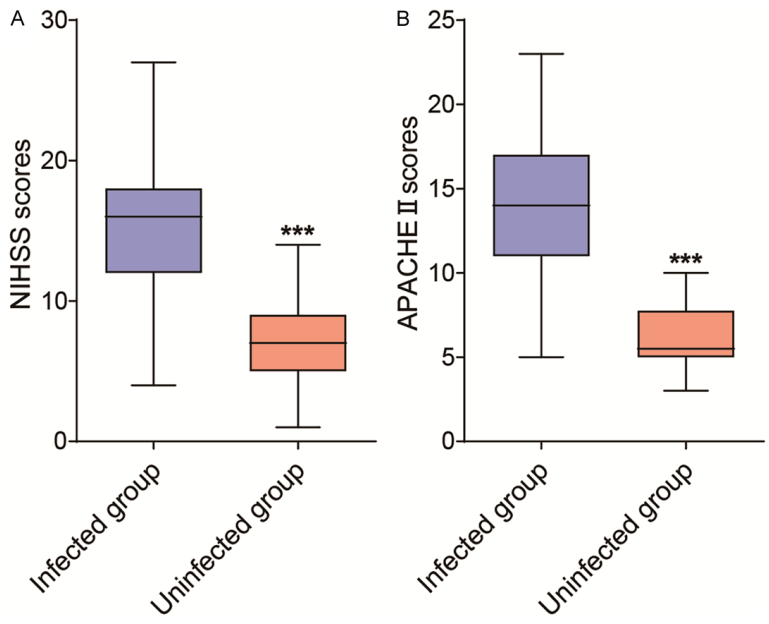

Figure 3. Comparison of NIHSS and APACHE II scores between patients with and without SAIs. Note: (A) NIHSS scores; (B) APACHE II scores. ***P < 0.001 vs. infected group. NIHSS: National Institutes of Health Stroke Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; SAI: stroke-associated infection.

test, t-test) were subsequently entered into a multivariable logistic regression model. Clinically relevant covariates were adjusted to identify independent risk factors associated with SAI occurrence. Finally, binary logistic regression analysis was used to identify the independent correlation between MIP-1α, PTM, and IL-12 levels and the risk of SAIs. The receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to evaluate the predictive value of peripheral blood MIP-1α, PTM, and IL-12 expression levels for diagnosing SAIs. The significance level was set at α = 0.05, and P < 0.05 was considered significant.

Results

Patient characteristics

A total of 135 patients with AIS were included, comprising 75 in the infected group and 60 in the uninfected group. Baseline demographic and clinical characteristics of both groups are summarized in **Table 1**. There were no statistically significant differences between groups in terms of sex, BMI, smoking history, alcohol consumption history, or hypertension prevalence (P > 0.05). However, the infected group had a higher proportion of patients aged ≥ 60 years, a higher prevalence of pulmonary disease and diabetes, higher NIHSS scores at admission, higher rates of invasive procedures and dysphagia, and longer hospital stays compared to the uninfected group (P < 0.05).

Peripheral blood levels of MIP-1α, PTM, and IL-12

The infected group exhibited significantly higher peripheral blood levels of MIP-1α, PTM, and IL-12 compared to the uninfected group (P < 0.05) (**Figure 2**).

Infection and APACHE II scores

The infected group demonstrated significantly higher infection and APACHE II scores compared to the uninfected group (P < 0.05) (**Figure 3**).

T cells and NK cells

Patients in the infected group exhibited significantly lower levels of $CD3^+$ and $CD16^+CD56^+$ NK cells compared to the uninfected group (P < 0.05) (**Figure 4**).

Immune function

The infected group exhibited significantly lower IgG levels compared to the uninfected group (P < 0.05). However, no significant differences were observed in IgA and IgM levels between the two groups (P > 0.05) (**Figure 5**).

Serum inflammatory markers

Serum levels of hs-CRP, PCT, and IL-6 were significantly higher in the infected group than in the uninfected group (P < 0.05) (**Figure 6**).

Correlation analysis between MIP-1α, PTM, IL-12 and inflammatory cytokines in the infected group

Pearson correlation analysis revealed positive correlations between serum levels of MIP-1α,

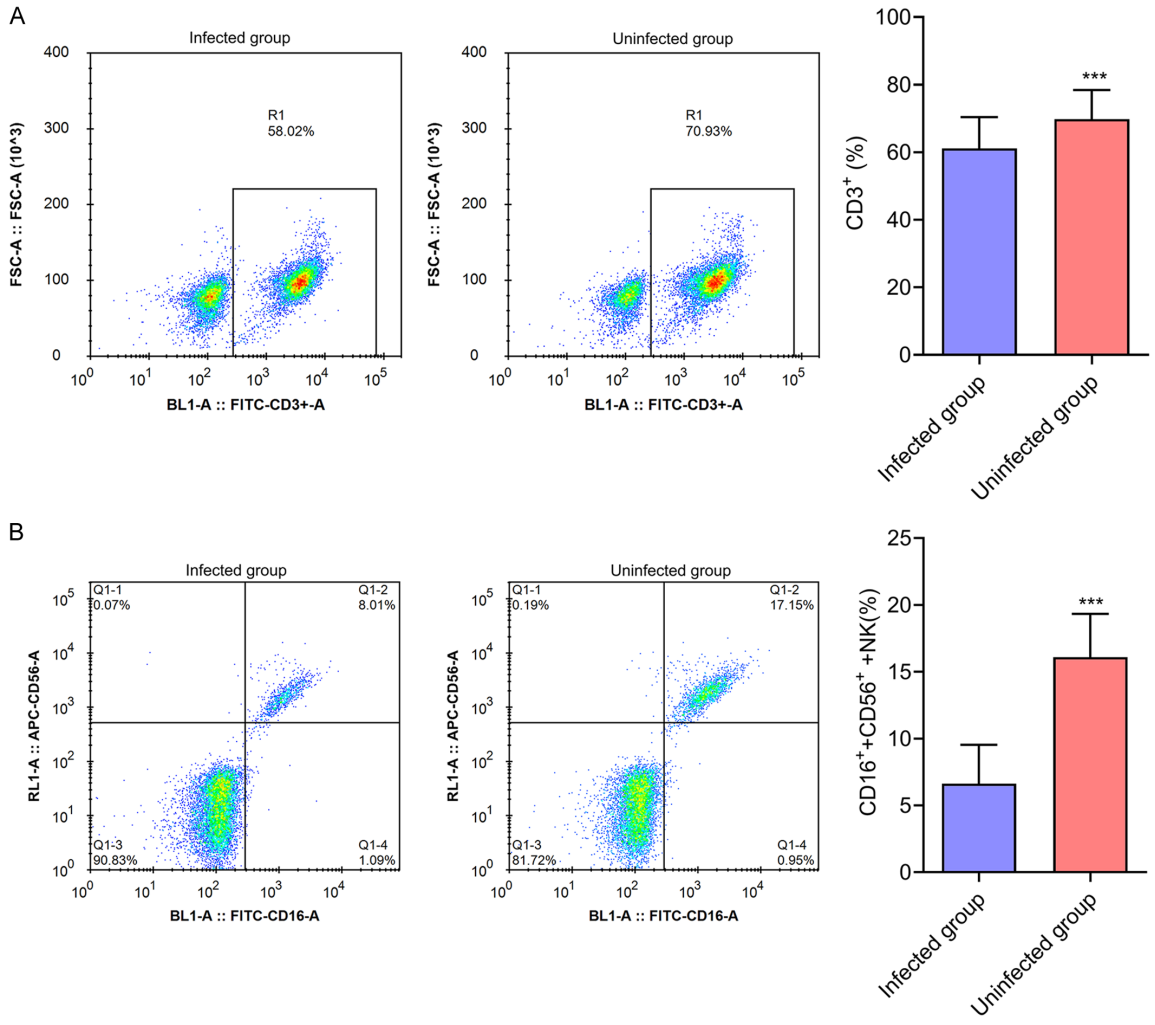

Figure 4. Comparison of immune cell levels between patients with and without SAIs. Note: (A) $CD3^+$; (B) $CD16^+CD56^+$ NK cells. ***$P < 0.001$ vs. infected group. SAI: stroke-associated infection.

PTM, IL-12 levels and the inflammatory cytokines hs-CRP, PCT, IL-6 in the infected group (all $P < 0.001$), suggesting that these biomarkers are closely associated with infection-related inflammatory responses (**Figure 7**).

Correlation analysis among MIP-1α, PTM, and IL-12 in the infected group

Pearson correlation analysis also revealed a positive correlation among the serum MIP-1α, PTM, and IL-12 levels in the infected group (all $P < 0.001$) (**Figure 8**).

Univariate analysis of factors influencing SAI

Univariate analysis identified several factors significantly associated with SAI, including age, history of pulmonary diseases, diabetes mellitus, NIHSS score upon admission, invasive procedures, dysphagia, and length of hospital stay ($P < 0.05$) (**Table 1**).

Predictive value of peripheral blood levels of MIP-1α, PTM, and IL-12

The occurrence of SAIs was defined as the dependent variable (infection = 1, absence of infection = 0), and serum MIP-1α, PTM, and IL-12 levels were used as the main independent variables. Statistically significant clinical factors screened in the univariable analysis (e.g., age, history of pulmonary diseases, diabetes mellitus, NIHSS score, invasive procedures, dysphagia, length of hospital stay, and the levels of hs-CRP, PCT, and IL-6) were incorporated

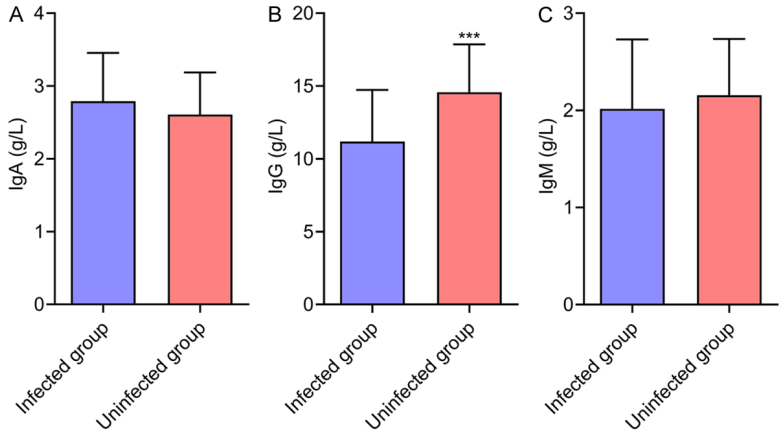

Figure 5. Comparison of peripheral blood immunoglobulin levels between patients with and without SAIs. Note: (A) IgA; (B) IgG; (C) IgM. ***P < 0.001 vs. infected group. SAI: stroke-associated infection.

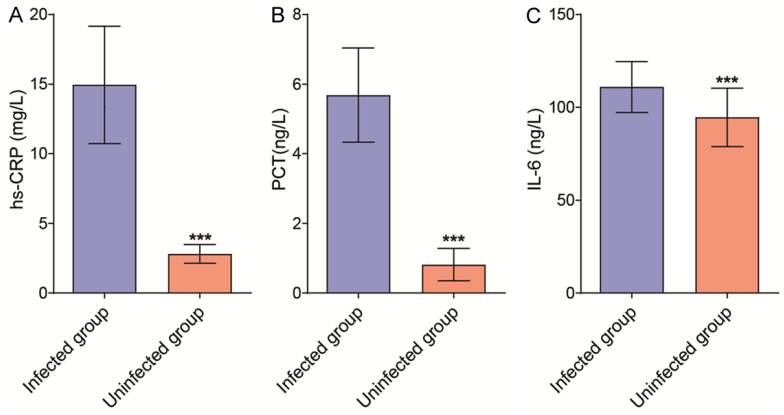

Figure 6. Comparison of inflammatory response makers between patients with and without SAIs. Note: (A) hs-CRP; (B) PCT; (C) IL-6. ***P < 0.001 vs. infected group. hs-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; SAI: stroke-associated infection.

as covariates in a multivariate logistic regression analysis. After adjusting for confounding factors, serum MIP-1α, PTM, and IL-12 levels remained independent risk factors for AIS-associated infections (P < 0.05) (**Table 2**). ROC curve analysis showed that the AUCs for MIP-1α, PTM, and IL-12 were 0.925, 0.926, and 0.928, respectively, significantly higher than those for conventional inflammatory markers such as CRP (AUC = 0.908) and PCT (AUC = 0.900). Additionally, IL-6 exhibited relatively weaker performance with an AUC of 0.785, making it suitable as an auxiliary indicator. The combined detection model incorporating MIP-1α, PTM, and IL-12 achieved an AUC of 0.997, markedly improving the accuracy of early infection diagnosis in patients with AIS (**Figure 8**).

Discussion

Stroke accompanied by SAIs not only exacerbates disease severity but also compromises treatment efficacy and prognosis. This study revealed that the combined detection of peripheral serum MIP-1α, PTM, and IL-12 has significant predictive value for SAIs, providing an important basis for their early diagnosis and clinical assessment.

Biomarkers play a crucial role in the early diagnosis and evaluation of infections. MIP-1α, a member of the CC chemokine subfamily, is markedly upregulated during inflammatory responses. By binding to its receptors, MIP-1α promotes inflammatory responses, regulates immune activity, and enhances intercellular adhesion [9, 10]. IL-12 is a multifunctional cytokine involved in mediating immune-inflammatory responses [11, 12]. PTM is a membrane-bound glycoprotein expressed on vascular endothelial cells. During infection, neutrophil activation and cytokine release disrupt vascular endothelial integrity, leading to increased PTM release into the circulation and further endothelial injury [13, 14]. In this study, patients in the infected group exhibited significantly higher serum MIP-1α, IL-12, and PTM levels compared with those in the uninfected group. These markers were also positively correlated with conventional inflammatory cytokines hs-CRP, PCT, and IL-6, indicating that they may reflect the systemic inflammatory status associated with stroke-related infection. Furthermore, ROC curve analysis showed that the combined detection of these three biomarkers achieved the highest diagnostic accuracy for predicting SAIs.

Additionally, changes in immune cell [15] and immunoglobulin [16] levels also reflect the impact of infection on the host immune system.

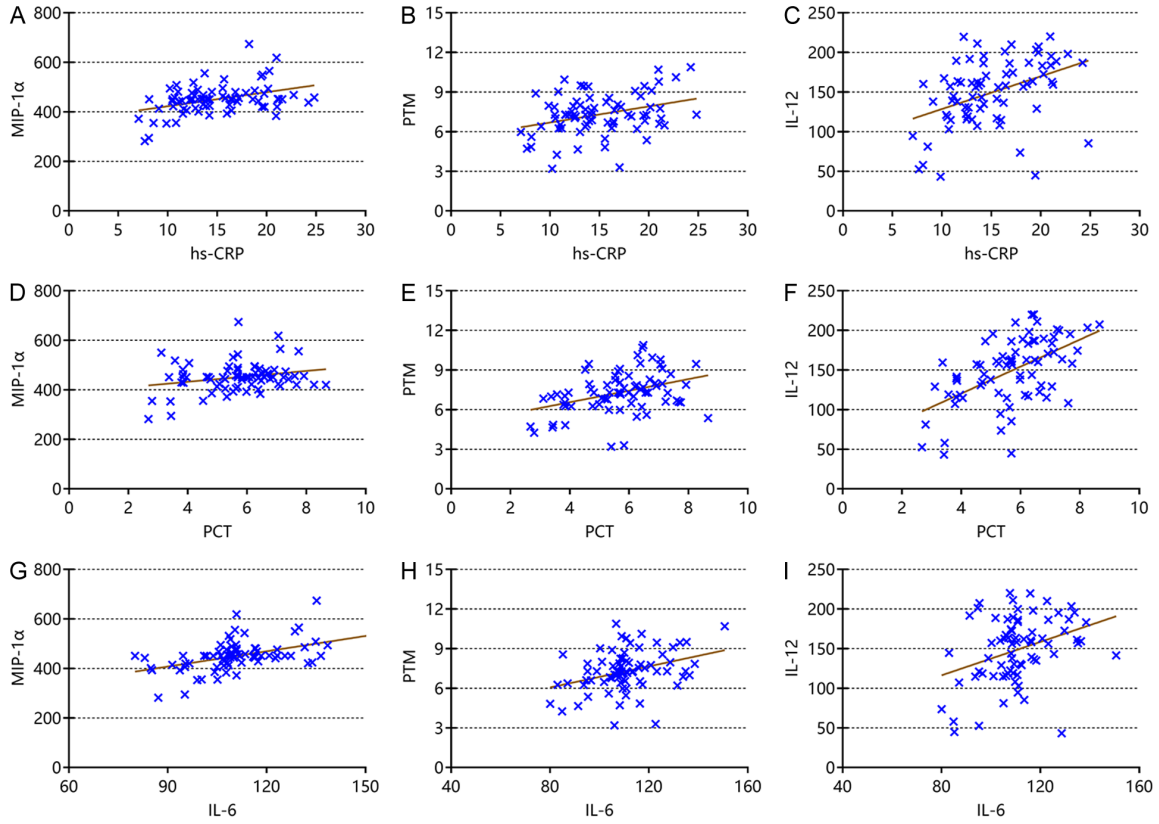

Figure 7. Correlation analysis of MIP-1α, PTM, and IL-12 with inflammatory cytokines. Pearson correlation analysis revealed that serum levels of MIP-1α, PTM, and IL-12 in the infected group were positively correlated with inflammatory markers (A-C) hs-CRP, (D-F) PCT, and (G-I) IL-6. Note: MIP-1α: macrophage inflammatory protein-1α; PTM: plasma thrombomodulin; IL-12: interleukin-12; hs-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6.

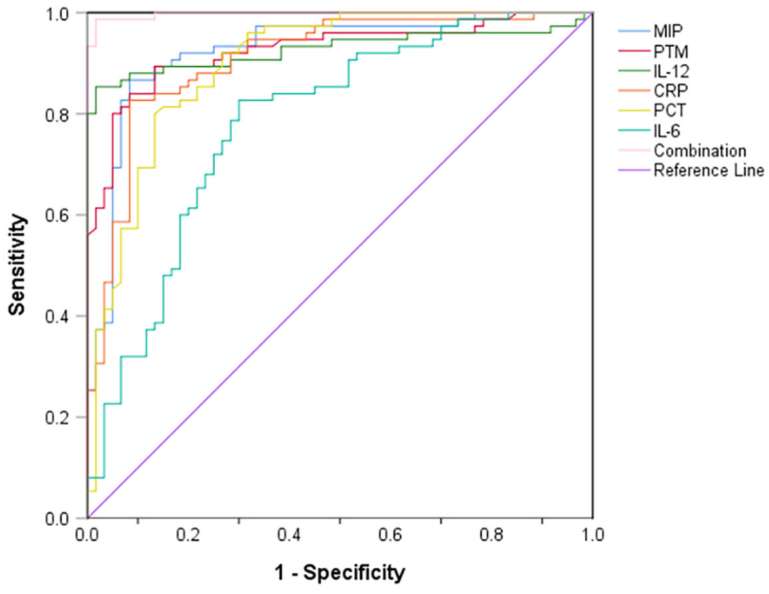

Figure 8. Predictive value of serum MIP-1α, PTM, and IL-12 levels for SAIs. Note: MIP-1α: macrophage inflammatory protein-1α; PTM: plasma thrombomodulin; IL-12: interleukin-12; SAI: stroke-associated infection.

During infection, the levels of T lymphocytes [17], NK cells [18, 19], and immunoglobulins typically decline, leading to suppression of both humoral and cellular immune responses. This immunosuppressed state increases patients' susceptibility to infection and worsens disease severity [20]. The findings of this study showed that patients in the infected group exhibited significantly lower levels of $CD3^+$ and $CD16^+CD56^+$ NK cells than those in the uninfected group. Additionally, IgG levels were significantly lower in the infected group, suggesting that the immune function of patients with SAI was decreased to varying degrees.

Table 2. ROC analysis for MIP-1α, PTM, IL-12, and their combined detection for diagnosing SAIs

Indicators	AUC	95% CI	*P*	Sensitivity (%)	Specificity (%)
MIP-1α	0.925	1.065-1.113	0.005	85.22	72.09
PTM	0.926	1.400-33.608	0.018	72.67	90.77
IL-12	0.928	1.028-1.203	0.008	80.17	65.14
Combined detection	0.997	0.993-1.000	< 0.001	91.09	93.44

Note: ROC: receiver operating characteristic; MIP-1α: macrophage inflammatory protein-1α; PTM: plasma thrombomodulin; IL-12: interleukin-12; SAI: stroke-associated infection; AUC: area under the curve; 95% CI: 95% confidence interval.

Furthermore, univariate analysis identified age, history of pulmonary diseases, diabetes mellitus, NIHSS score upon admission, invasive procedures, dysphagia, and length of hospital stay as significant factors associated with SAI. These findings indicate that, for preventing SAI, the aforementioned factors should be incorporated into comprehensive risk assessment models to improve the reliability of early identification and targeted intervention.

This study has several limitations. First, as a retrospective analysis, it was subject to data selection bias, which may affect the generalizability of the findings. This issue has been acknowledged as a methodologic shortcoming and will be addressed in future studies through improved data collection and more robust analytical design. Second, the 95% confidence interval (CI) for the PTM variable was relatively wide (1.400-33.608), which may be attributable to the limited sample size. A smaller sample size may increase the standard error of parameter estimates, leading to wider CI and, thereby affecting the stability of statistical inference. Despite this limitation, the present study provides important insight into the potential clinical significance of PTM in stroke-associated infections. Future research should further expand sample sizes, incorporate multicenter data, and include prospective validation to enhance the stability and generalizability of the findings.

Conclusions

Elevated peripheral blood levels of MIP-1α, IL-12, and PTM in patients with SAIs demonstrate significant clinical diagnostic value. These markers may serve as useful indicators for the early diagnosis, differentiation, and timely intervention of SAIs. In addition, clinicians should comprehensively evaluate immune function, age, and medical history when assessing patients with acute ischemic stroke to improve infection risk stratification and optimize clinical management.

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Disclosure of conflict of interest

None.

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