

Study on the Predictive Value of MASP-1 Combined with Four Thrombotic Molecular Markers for Disseminated Intravascular Coagulation in Patients with Severe Infection

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Objective: To investigate the predictive value of mannose-binding lectin-associated serine protease-1 (MASP-1) combined with four thrombotic molecular markers [thrombin-antithrombin complex (TAT), thrombomodulin (TM), plasmin- α 2-plasmin inhibitor complex (PIC), and tissue-type plasminogen activator inhibitor complex (t-PAIC)] for disseminated intravascular coagulation (DIC) in patients with severe infection.

Methods: Clinical data of 114 patients with severe infection admitted between January and December 2024 were retrospectively analyzed. Patients were divided into DIC (n=25) and non-DIC (n=89) groups per ISTH criteria. Serum MASP-1 (ELISA) and TAT, TM, PIC, t-PAIC (chemiluminescent immunoassay) levels were compared. Pearson correlation assessed relationships between MASP-1 and thrombotic markers. ROC curves evaluated diagnostic performance.

Results: The expression levels of MASP-1, TAT, TM, PIC, and t-PAIC in Group A (with DIC) were significantly higher than those in Group B (without DIC) ($P < 0.05$). Pearson correlation analysis showed that MASP-1 levels in patients with severe infection and DIC were positively correlated with TAT, TM, PIC, and t-PAIC levels ($P < 0.05$). ROC curves showed that the area under the curve (AUC) for MASP-1, TAT, TM, PIC, t-PAIC, combined detection of thrombotic molecular markers, and MASP-1 combined with thrombotic molecular markers were 0.714, 0.739, 0.692, 0.684, 0.776, and 0.835, respectively. The diagnostic efficacy of MASP-1 combined with thrombotic molecular markers was superior to MASP-1, TAT, TM, PIC, t-PAIC alone or thrombotic molecular markers combined alone (Z MASP-1+thrombotic markers combined-MASP-1, TAT, TM, PIC, t-PAIC and thrombotic markers combined = 3.637, 3.152, 4.126, 3.974, 4.383, and 2.975, $P < 0.05$).

Conclusion: This retrospective study suggests that MASP-1 correlates with thrombotic marker expression in severe infection. The combination of MASP-1 and thrombotic markers shows promise for improving early DIC diagnosis, but its clinical utility warrants confirmation by larger, prospective studies.

Keywords: MASP-1, thrombotic molecular markers, severe infection, disseminated intravascular coagulation, predictive value

Introduction

Disseminated intravascular coagulation (DIC) is a life-threatening complication of severe infection, characterized by systemic activation of coagulation leading to microvascular thrombosis and consumption of platelets and coagulation factors, which can progress to organ failure and high mortality.^{1,2} Early diagnosis is critical for improving outcomes. The International Society on Thrombosis and Haemostasis (ISTH) scoring system, relying on conventional tests like platelet

count and prothrombin time, remains the diagnostic cornerstone but has limitations in sensitivity for early-stage DIC.^{3,4} Consequently, there is a pressing need for biomarkers that more directly reflect the underlying hypercoagulable state and endothelial injury before overt clinical deterioration.

In this context, molecular markers indicative of specific pathophysiological pathways have gained prominence. The thrombin-antithrombin complex (TAT) is a direct marker of thrombin generation, providing a sensitive measure of coagulation system activation often preceding abnormalities in conventional tests.⁵ Thrombomodulin (TM), a transmembrane glycoprotein expressed on endothelial cells, plays a key role in the protein C anticoagulant pathway. Soluble TM levels in plasma reflect the extent of endothelial cell injury, a central event in DIC pathogenesis.⁶ The plasmin- α 2-plasmin inhibitor complex (PIC) is a reliable indicator of plasmin generation and hyperfibrinolysis, while the tissue-type plasminogen activator-inhibitor complex (t-PAIC) reflects the balance between fibrinolysis and its inhibition, aiding in identifying different DIC phenotypes.⁷ Thus, the combined detection of TAT, TM, PIC, and t-PAIC offers a comprehensive profile of the coagulation, endothelial, and fibrinolytic systems, potentially enhancing early DIC detection.

Mannose-binding lectin-associated serine protease-1 (MASP-1), a key enzyme in the lectin complement pathway, has emerged as a potential link between innate immunity and coagulation. Beyond its role in complement activation, MASP-1 can interact directly with the coagulation cascade by cleaving procoagulant factors such as fibrinogen and prothrombin, and it may promote endothelial activation.^{8–10} Elevated MASP-1 levels have been reported in sepsis and systemic inflammatory response syndrome (SIRS), correlating with disease severity.^{11,12} However, the relationship between MASP-1 and established thrombotic molecular markers in the context of DIC complicating severe infection remains underexplored.

Therefore, this study aimed to investigate the expression levels of MASP-1 alongside TAT, TM, PIC, and t-PAIC in patients with severe infection, with or without DIC. We sought to analyze their correlations and evaluate whether the combination of MASP-1 with these thrombotic markers could provide superior value for the early identification of DIC, thereby offering new insights for risk stratification and timely intervention.

Materials and Methods

Study Subjects

This study is a retrospective analysis that included a total of 114 patients with severe infections who were hospitalized in our hospital from January 2024 to December 2024. (1) Inclusion Criteria: ① Age ≥ 18 years, regardless of gender; ② Meeting the clinical diagnostic criteria for “severe infection”,¹³ including severe community-acquired pneumonia, septic shock, complicated intra-abdominal infections, and enterogenic infections; ③ Laboratory tests completed within 24 hours of admission, with complete plasma specimens retained; ④ Detection items included five indicators: MASP-1, TAT, TM, PIC, and t-PAIC; ⑤ Complete clinical data with all indicators required for ISTH scoring available. (2) Exclusion Criteria: ① Patients with underlying diseases that could affect coagulation function, such as active tumors, cirrhosis, or systemic lupus erythematosus; ② Past or current use of anticoagulant/antifibrinolytic drugs; ③ Recent history of major surgery or trauma; ④ Pregnant or lactating women; ⑤ Incomplete detection data or clinical information. This study was approved by the Medical Ethics Committee of the First Hospital of Zhangjiakou City (Approval No.: ZZJY202412), and the research was conducted in strict accordance with the ethical norms of the Declaration of Helsinki. Informed consent was voluntarily signed by the patients themselves or their guardians after being informed of the research content.

Grouping and Sample Collection

All included patients were grouped according to the DIC scoring criteria issued by the ISTH.¹⁴ Patients with scores ≥ 5 were defined as clinically diagnosed with DIC and assigned to Group A ($n=25$), while those with scores < 5 were categorized as non-DIC and placed in Group B ($n=89$). Fasting venous blood samples (2.7 mL) were collected upon enrollment into vacuum tubes containing 3.2% sodium citrate. Tubes were gently inverted immediately after collection. The samples were centrifuged at $3,000 \times g$ for 10 minutes at room temperature to obtain platelet-poor plasma. The supernatant plasma was aliquoted into sterile cryogenic vials. To preserve the stability of the protein biomarkers, all aliquots were promptly stored at -80°C until batch analysis. This standardized protocol aimed to minimize pre-analytical variability.

Detection Methods

The biomarker testing involved in this study included five indicators: MASP-1, TAT, TM, PIC, and t-PAIC. All tests were conducted in the Department of Laboratory Medicine of our hospital in strict accordance with standard operating procedures. All laboratory personnel underwent unified training, and a double-blind principle was rigorously implemented throughout the experimental process. MASP-1 levels were quantitatively analyzed using enzyme-linked immunosorbent assay (ELISA), employing a commercial MASP-1-specific ELISA kit (Manufacturer: Jianglai Bio, Catalog No.: JL16890-48T). The detection platform used was the E1080 fully automated ELISA analyzer from Shandong Laibo Bio. A standard curve was prepared according to the kit instructions, with blank controls and positive quality controls set up. Each sample was tested in duplicate, and the average value was recorded. TAT, TM, PIC, and t-PAIC levels were quantitatively detected using chemiluminescence immunoassay (CLIA) on the MT80 fully automated chemiluminescence analyzer from Shenzhen Jinrui Bio, along with its proprietary reagent kits. The assays strictly followed the instructions provided with the reagents and adhered to equipment operation specifications. Calibration was performed for each indicator using standard substances, and the detection range and sensitivity met clinical diagnostic requirements. Throughout the entire experimental process, all steps—from sample collection, preservation, thawing, to testing—were standardized in accordance with SOP protocols. This minimized inter-batch variation and human error, ensuring the stability and reproducibility of the data.

Statistical Analysis

All data were statistically analyzed using SPSS 26.0 software, and GraphPad Prism 8 was used for plotting. Measurement data with normal distribution were expressed as ($\bar{x} \pm s$), and comparisons between groups were performed using *t*-test. Count data were described as n (%) and compared between groups using the chi-square test. Pearson correlation analysis was used to analyze the correlations between MASP-1 and thrombotic molecular markers TAT, TM, PIC, and t-PAIC. Receiver Operating Characteristic (ROC) curves were plotted to evaluate the early diagnostic value of each marker for severe infection combined with DIC. A P-value <0.05 was considered statistically significant.

Results

Comparison of Basic Information

A total of 114 patients with severe infection were included in this retrospective study and stratified into two groups based on the ISTH criteria: an overt DIC group (Group A, n=25) and a non-DIC group (Group B, n=89). As summarized in Table 1, the baseline characteristics, including gender, age, BMI, comorbidities, infection site, and education level, were well-balanced between the two groups (all *P* > 0.05). This comparability enhances the reliability of subsequent analyses focused on biomarker differences.

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

	Group A (n=25)	Group B (n=89)	<i>t</i> / χ^2	<i>P</i>
Sex	–	–	0.542	0.461
Male	15 (60.00)	46 (51.69)	–	–
Female	10 (40.00)	43 (48.31)	–	–
Age (years)	66.82±10.94	65.79±11.28	0.406	0.685
BMI (kg/m ²)	22.76±2.25	22.51±2.39	0.467	0.640
Comorbidities	–	–	–	–
Diabetes	5 (20.00)	12 (13.48)	0.240	0.623
Hypertension	11 (44.00)	32 (35.96)	0.537	0.463
CHD	8 (32.00)	27 (30.34)	0.025	0.873

(Continued)

Table 1 (Continued).

	Group A (n=25)	Group B (n=89)	<i>t/x</i> ²	<i>P</i>
Infection site	–	–	0.033	0.854
Pulmonary	14 (56.00)	48 (53.93)	–	–
Abdominal	6 (24.00)	26 (29.21)	–	–
Others	5 (20.00)	15 (16.85)	–	–
Education level	–	–	0.110	0.739
Primary or below	18 (72.00)	67 (75.28)	–	–
Secondary or above	7 (28.00)	22 (24.72)	–	–

Abbreviation: BMI, Body Mass Index.

Plasma Levels of MASP-1 and Thrombotic Molecular Markers

To investigate their potential roles in DIC pathogenesis, we first compared the plasma levels of MASP-1 and four thrombotic markers between the groups. The plasma concentration of MASP-1 was significantly higher in the DIC group ($35.37 \pm 8.74 \mu\text{g/mL}$) than in the non-DIC group ($28.65 \pm 8.92 \mu\text{g/mL}$; $P < 0.05$; [Figure 1](#)).

Consistently, the DIC group also exhibited markedly elevated levels of all four thrombotic molecular markers, reflecting a state of heightened coagulation activation (TAT: $11.67 \pm 6.32 \text{ ng/mL}$ vs $5.14 \pm 2.05 \text{ ng/mL}$), endothelial injury (TM: $19.28 \pm 6.96 \text{ TU/mL}$ vs $14.05 \pm 4.13 \text{ TU/mL}$), and fibrinolysis imbalance (PIC: $4.36 \pm 2.05 \mu\text{g/mL}$ vs $1.72 \pm 0.84 \mu\text{g/mL}$; t-PAIC: $21.16 \pm 7.85 \text{ ng/mL}$ vs $13.19 \pm 5.27 \text{ ng/mL}$) (all $P < 0.05$; [Figure 2](#)).

Correlations Between MASP-1 and Thrombotic Markers

Given the concurrent elevation of MASP-1 and the thrombotic markers in DIC patients, we next assessed their interrelationships. Pearson correlation analysis revealed significant positive correlations between plasma MASP-1 levels and each of the four thrombotic markers (TAT: $r = 0.747$; TM: $r = 0.643$; PIC: $r = 0.685$; t-PAIC: $r = 0.626$; all $P < 0.05$; [Table 2](#) and [Figure 3](#)). These correlations reinforce the postulated biological link between lectin pathway activation (represented by MASP-1) and the dysregulation of coagulation and endothelial function in severe infection.

Diagnostic Performance of Biomarkers for DIC

The central objective of this study was to evaluate the diagnostic potential of these biomarkers, both individually and in combination, for identifying DIC in severely infected patients. Receiver operating characteristic (ROC) curve analysis

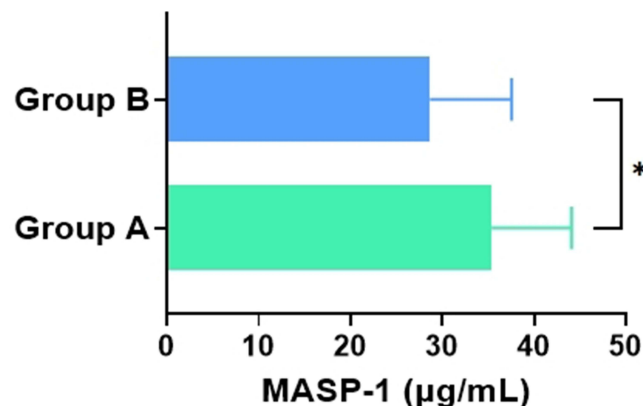


Figure 1 Comparison of MASP-1 expression levels in plasma between two groups ($\bar{x} \pm s$).

Notes: * indicates $P < 0.05$ between groups.

Abbreviation: MASP-1, Mannan-binding lectin-associated serine protease-1.

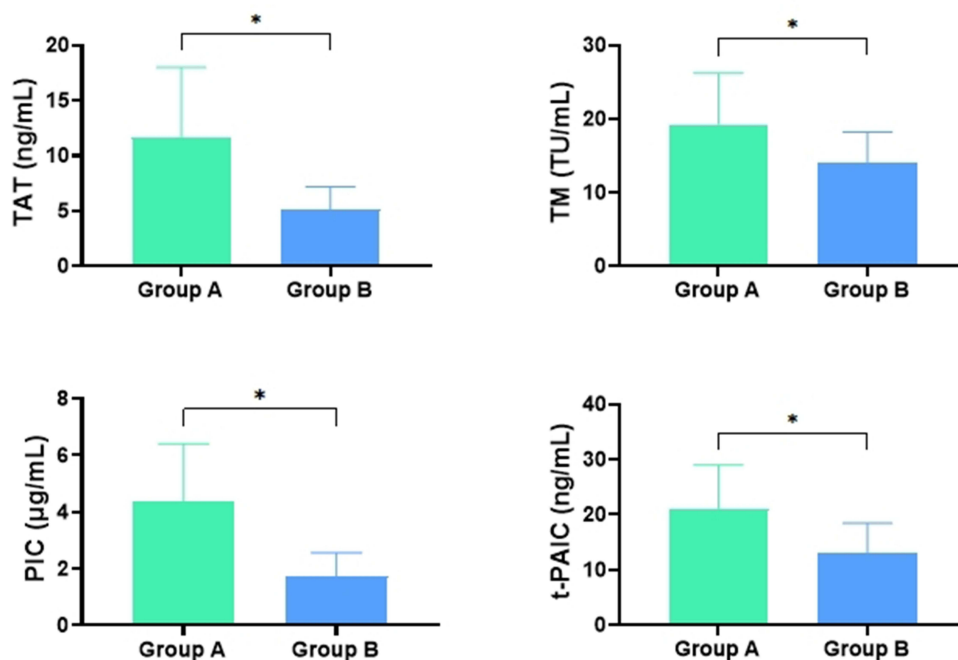


Figure 2 Comparison of thrombotic molecular marker levels in plasma between two groups ($\bar{x} \pm s$).

Notes: * indicates $P < 0.05$ between groups.

Abbreviations: TAT, Thrombin-Antithrombin Complex; TM, Thrombomodulin; PIC, Plasmin- $\alpha 2$ Plasmin Inhibitor Complex; t-PAIC, Tissue Plasminogen Activator-Inhibitor Complex.

was performed (Figure 4, Table 3). The area under the curve (AUC) for individual markers ranged from 0.684 (PIC) to 0.739 (TAT). MASP-1 alone showed an AUC of 0.714. The combination of the four thrombotic markers (CTMM) yielded an improved AUC of 0.776.

Most importantly, the combination of MASP-1 with the panel of thrombotic markers achieved the highest diagnostic efficacy, with an AUC of 0.835, a sensitivity of 86.42%, and a specificity of 84.27%. This combined model demonstrated statistically superior performance compared to the use of MASP-1 alone, any single thrombotic marker alone, or the

Table 2 Correlation Between MASP-1 Expression and TAT, TM, PIC, t-PAIC Expression Levels

Item	MASP-1	
	<i>r</i>	<i>P</i>
TAT	0.747	<0.05
TM	0.643	<0.05
PIC	0.685	<0.05
T-PAIC	0.626	<0.05

Abbreviations: MASP-1, Mannan-binding lectin-associated serine protease-1; TAT, Thrombin-Antithrombin Complex; TM, Thrombomodulin; PIC, Plasmin- $\alpha 2$ Plasmin Inhibitor Complex; t-PAIC, Tissue Plasminogen Activator-Inhibitor Complex.

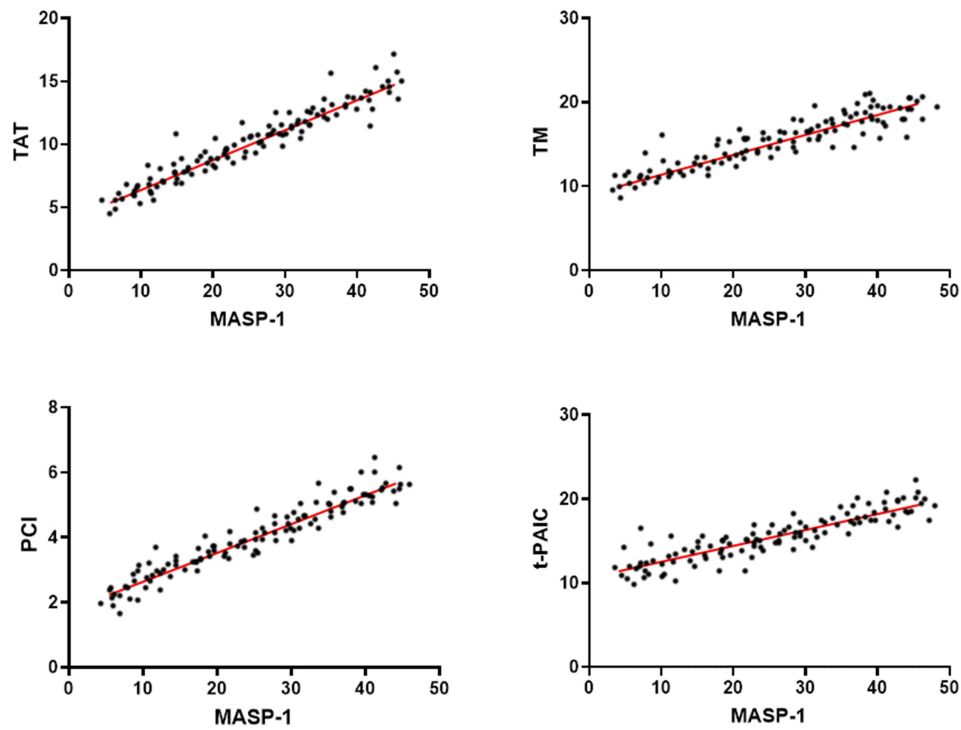


Figure 3 Scatter plots showing correlation between MASP-1 expression and TAT, TM, PIC, t-PAIC expression levels.
Abbreviations: MASP-1, Mannan-binding lectin-associated serine protease-1; TAT, Thrombin-Antithrombin Complex; TM, Thrombomodulin; PIC, Plasmin- α 2 Plasmin Inhibitor Complex; t-PAIC, Tissue Plasminogen Activator-Inhibitor Complex.

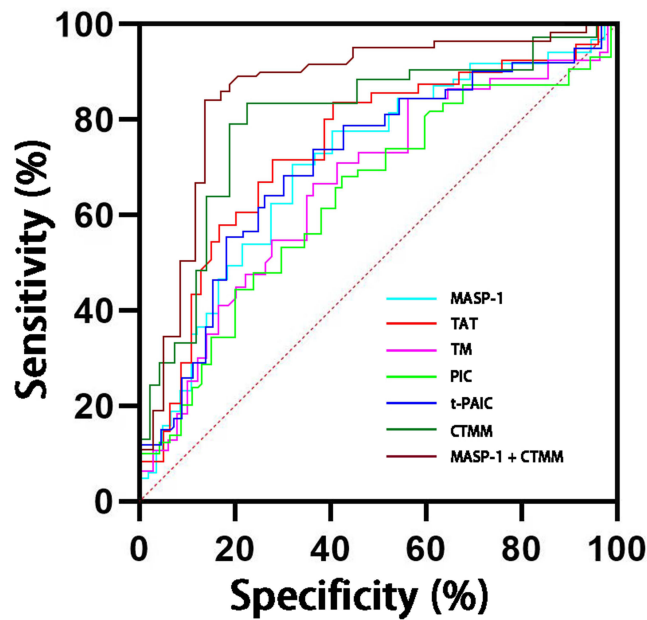


Figure 4 ROC curves for the diagnostic value of each marker for severe infection with DIC.
Abbreviations: MASP-1, Mannan-binding lectin-associated serine protease-1; TAT, Thrombin-Antithrombin Complex; TM, Thrombomodulin; PIC, Plasmin- α 2 Plasmin Inhibitor Complex; t-PAIC, Tissue Plasminogen Activator-Inhibitor Complex; CTMM, Combined Thrombotic Molecular Markers.

Table 3 Diagnostic Value of Each Marker for Severe Infection with DIC

Marker	Cut-Off value	AUC	95% CI	P	Sensitivity (%)	Specificity (%)
MASP-1	31.25 µg/mL	0.714	0.637–0.785	<0.05	72.41	69.23
TAT	8.40 ng/mL	0.739	0.672–0.798	<0.05	76.84	65.19
TM	16.55 TU/mL	0.692	0.564–0.743	<0.05	63.95	72.78
PIC	3.10 µg/mL	0.684	0.549–0.737	<0.05	57.39	73.44
t-PAIC	17.20 ng/mL	0.727	0.659–0.789	<0.05	69.05	75.16
CTMM	-	0.776	0.701–0.834	<0.05	79.39	77.86
MASP-1+CTMM	-	0.835	0.784–0.911	<0.05	86.42	84.27

Abbreviations: MASP-1, Mannan-binding lectin-associated serine protease-1; TAT, Thrombin-Antithrombin Complex; TM, Thrombomodulin; PIC, Plasmin- α 2 Plasmin Inhibitor Complex; t-PAIC, Tissue Plasminogen Activator-Inhibitor Complex; CTMM, Combined Thrombotic Molecular Markers.

combination of thrombotic markers without MASP-1 (all $Z > 2.975$, $P < 0.05$). This finding suggests that MASP-1 provides complementary diagnostic information that is not fully captured by the traditional thrombotic markers alone.

Discussion

DIC is a critical pathological condition characterized by systemic activation of coagulation, widespread microthrombi formation, and secondary fibrinolytic disorders. It is often secondary to severe infections, trauma, malignancies, and other underlying conditions, with particularly high incidence and mortality rates among critically ill patients with infections.^{15,16} Therefore, early identification and timely intervention of DIC have long been a focus of clinical attention. This study focuses on the predictive value of MASP-1 combined with four thrombotic molecular markers in the early diagnosis of DIC in patients with severe infections, aiming to provide a more reliable laboratory assessment tool for clinical practice.

MASP-1, a key serine protease in the MBL pathway, plays a central role in complement activation and immune responses. Previous studies¹⁷ have shown that MASP-1 not only cleaves C4 and C2 to initiate the classical complement cascade but also acts directly on coagulation factors, including the activation of fibrinogen, prothrombin, and the protein C pathway, thereby mediating the initiation and maintenance of the coagulation cascade. The results of this study showed that MASP-1 was significantly elevated in critically ill patients with infections complicated by DIC and was positively correlated with the levels of TAT, TM, PIC, and t-PAIC, suggesting that MASP-1 may activate the coagulation system, affect endothelial function, and participate in fibrinolytic disorders, acting as a key mediator in the progression from severe infection to DIC. This result is consistent with the experimental observations by Kristensen et al, who reported that elevated MASP-1 in a sepsis model promoted DIC development,¹⁸ further supporting the dual role of MASP-1 as a “bridge molecule” between the complement and coagulation systems.

This study further analyzed the combined diagnostic value of four thrombotic molecular markers—TAT, TM, PIC, and t-PAIC—and found that all were significantly elevated in DIC patients and were highly correlated with MASP-1. This finding aligns with the current understanding of DIC as a disorder involving multidimensional dysregulation.^{19,20} TAT is an early and sensitive indicator of thrombin generation and reflects the degree of coagulation system activation.²¹ In this study, TAT was significantly elevated in DIC patients, suggesting its involvement in early disease pathogenesis. Similar findings were reported by Yamakawa et al (2021) in their study on septic DIC patients, where TAT was considered a dynamic predictor of DIC development.²² TM is a membrane-bound endothelial cell protein involved in anticoagulant mechanisms; its elevated levels often indicate endothelial cell injury and apoptosis, contributing to dysfunction in the protein C pathway.²³ Chen et al pointed out that endothelial damage caused by severe infection is a critical mechanism triggering DIC, and elevated TM reflects a “stress release” in the body’s attempt to rebalance coagulation.²⁴ This study also found that TM levels were significantly elevated in the DIC group, suggesting it is a reliable marker for assessing endothelial injury. PIC is a direct product of fibrinolytic system activation and reflects changes in plasmin generation and activity. In DIC patients, secondary fibrinolytic activation leads to a dynamic process in which fibrinolytic hyperactivity and inhibition may alternate.²⁵ Ling et al found that elevated PIC levels closely tracked DIC progression and could help monitor fibrinolytic status.²⁶ t-PAIC reflects the level of complex formation

between t-PA and PAI-1 and indirectly assesses the degree of suppression following fibrinolytic activation. Early-stage DIC is often characterized by fibrinolytic hyperactivity, which transitions to inhibition in later stages.²⁷ Zhang et al reported that elevated t-PAIC is an important marker for the shift of DIC from the compensatory to the decompensated phase.²⁸ Similarly, this study found that t-PAIC levels were significantly elevated in the DIC group, indicating the involvement of the fibrinolytic system in the DIC process and its positive correlation with MASP-1.

This study further evaluated the predictive performance of individual and combined markers for DIC using ROC curves and found that the AUC of MASP-1 combined with the four thrombotic markers (0.835) was significantly higher than that of any single marker or combination of thrombotic markers alone (0.714–0.776). This result suggests that the inclusion of MASP-1 provides a gain effect in enhancing predictive sensitivity, particularly in early identification. Previous studies^{29,30} have attempted to use multi-marker combinations such as TAT and PIC to evaluate DIC, but these mainly focused on parameters within the coagulation-fibrinolysis pathway. This study is the first to introduce MASP-1 as a complement pathway-related marker, thus expanding the evaluation framework to cover the three major pathological processes—coagulation, fibrinolysis, and complement—achieving a broader mechanistic coverage and enabling earlier and more accurate understanding of the DIC pathogenesis.

This study discusses the expression characteristics and combined predictive value of MASP-1 and thrombotic molecular markers (TAT, TM, PIC, t-PAIC) in patients with severe infections complicated by DIC and preliminarily confirms the potential mediating role of MASP-1 in DIC development and its close correlation with coagulation and fibrinolytic markers. However, several limitations exist in this study: First, as a single-center retrospective analysis with a limited sample size, it may be subject to selection and information bias, limiting the generalizability and statistical robustness of the conclusions. Whether MASP-1 expression is consistent across infections caused by different pathogens (eg, bacteria, viruses, fungi) remains to be further validated. Second, both plasma MASP-1 and thrombotic markers were measured as one-time static indicators, lacking continuous monitoring of dynamic trends, which limits the ability to reveal the temporal relationship of each marker in DIC formation and progression, affecting their clinical utility as “early prediction tools.” Additionally, although this study demonstrated correlations between MASP-1 and TAT, TM, PIC, and t-PAIC, it did not explore the specific mechanisms by which MASP-1 regulates thrombin generation, endothelial injury, or fibrinolytic abnormalities at the cellular or animal model level, and lacks direct causal evidence. Future research could construct MASP-1 knockout models or simulate infectious conditions *in vitro* to further clarify its specific role within the complement-coagulation-fibrinolysis network. Moreover, there is currently no universally accepted clinical testing standard or reference range for MASP-1; varying detection methods and sensitivities limit its broad application.

Limitations and Future Perspectives

However, several limitations of this retrospective study must be acknowledged. First, the single-center design and relatively limited sample size may affect the generalizability of our findings and limit the power for more extensive subgroup analyses. Second, the measurements were taken at a single time point upon admission. The lack of dynamic monitoring of these biomarkers prevents us from understanding their temporal changes and relationship with the evolution of DIC, which is crucial for establishing their true predictive value. Third, although we observed significant correlations, the retrospective nature of this study cannot establish causality. The specific mechanistic pathways by which MASP-1 influences coagulation and fibrinolysis in human sepsis remain to be elucidated through targeted *in vitro* and *in vivo* experimental models.

Future research should focus on validating these findings in larger, multicenter prospective cohorts. Incorporating multi-timepoint measurements to track biomarker dynamics will be essential. Furthermore, mechanistic studies are needed to clarify the precise role of MASP-1 in the pathogenesis of infection-induced DIC, which could open avenues for novel therapeutic strategies.

Conclusion

In this retrospective study, we demonstrated that plasma MASP-1 levels are significantly elevated in severely infected patients with DIC compared to non-DIC controls. Furthermore, our analysis revealed significant positive correlations

between MASP-1 and the established thrombotic markers TAT, TM, PIC, and t-PAIC, supporting the hypothesized cross-talk between the complement and coagulation systems in DIC pathogenesis.

The key finding of our work is that the combination of MASP-1 with the four thrombotic markers provided a significantly higher diagnostic value for DIC than the assessment of MASP-1 alone or the panel of thrombotic markers without MASP-1. This indicates that MASP-1 contributes complementary information, enhancing the early identification of DIC in the context of severe infection.

Therefore, our results suggest that integrating MASP-1 into a multi-marker diagnostic approach could improve the early detection of DIC. However, the clinical utility of this strategy needs to be validated in future large-scale, prospective studies.

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Disclosure

The authors declare no conflict of interest.

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