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ORIGINAL ARTICLE

Soluble Thrombomodulin can Predict In-Hospital Mortality of Community-Acquired Pneumonia Patients in Intensive Care Unit

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SUMMARY

Background: **Community-acquired pneumonia (CAP) patients admitted to ICU face high mortality rates, necessitating prognostic biomarkers to risk stratify patients. Soluble thrombomodulin (sTM) is a biomarker of endothelial injury. This retrospective study aimed to investigate sTM's association with disease severity and in-hospital mortality in ICU-admitted CAP patients.**

Methods: **From June 2024 to September 2025, 115 ICU CAP patients in Shanghai Jian District Shibei Hospital were analyzed retrospectively. sTM levels were measured together with other laboratory tests at ICU admission. Demographic data, clinical characteristics, APACHE II scores and laboratory test results were obtained from medical records. The difference between 97 survivors and 18 non-survivors were compared. ROC analysis and multivariable logistic regression were used to evaluate sTM's value in predicting in-hospital mortality. Spearman's correlation and multiple linear regression assessed the association of sTM with other blood biomarkers and APECH II scores.**

Results: **Non-survivors had significantly higher sTM than survivors. sTM correlated with APACHE II scores and disease severity, as well as blood biomarkers of kidney function, inflammation and coagulation. ROC analysis showed that sTM predicted in-hospital mortality with an AUC of 0.747 ($p < 0.001$), higher than that of APACHE II score. The optimal cutoff of sTM was 12.9 TU/mL with sensitivity of 88.9% and specificity of 53.6%. Elevated sTM levels remained independently associated with the risk of in-hospital mortality even after adjusted with APACHE II scores or kidney dysfunction.**

Conclusions: **sTM levels were significantly higher in non-survivors and correlates to APACHE II scores, suggesting its potential as a prognostic biomarker, aiding early risk stratification and tailored ICU management for CAP patients.**

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KEYWORDS

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INTRODUCTION

Community-acquired pneumonia (CAP) remains a significant cause of mortality, particularly in severe cases, despite advancements in diagnostic and therapeutic approaches. Among CAP patients in intensive care units (ICUs), the morality rates during hospitalization and at 30 days are 17% and 27%, respectively [1]. Thus, there is a need for improved methods of risk stratification and

prognostication to guide clinical management and improve outcomes. Prognostic biomarkers are useful to help clinicians identify high-risk patients and mitigate adverse outcomes. Previous studies suggested C-reactive protein (CRP), procalcitonin (PCT), proadrenomedullin as prognostic biomarkers of pneumonia [2], and clinical scores (Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA)) as prognostic biomarkers of ICU pneumonia patients [3,4]. The areas under the curve (AUCs) of those suggested biomarkers for discriminating non-survivors are approximately 0.70 - 0.80. Continuous efforts are being made to identify new prognostic markers to further improve the prediction accuracy.

Thrombomodulin (TM), localized primarily to the vascular endothelium, is a key component of a multimolecular system that integrates crucial biological processes including coagulation, innate immunity, inflammation, and cell proliferation [5,6]. It can activate protein C (APC), playing anti-coagulation and anti-inflammatory role. TM may also exhibit anti-inflammatory activity independent of APC, mediated through its lectin-like domain to suppress complements, pathogen-associated molecular patterns and damage-associated molecular patterns. Both inflammation and coagulation are important to the pathogenesis of pneumonia and progression to severe cases [7]. Soluble thrombomodulins (sTM) are cleaved extracellular fragments of TM with various lengths upon endothelia injury [8]. sTM can be measured in blood samples and is recognized as a biomarker of endothelia injury. Elevated sTM levels are observed in disseminated intravascular coagulation (DIC), sepsis, multiple organ dysfunction syndrome, acute respiratory distress syndrome (ARDS), and kidney diseases [9]. It is of interest to investigate the role of sTM in CAP patients, especially those in ICU. In this retrospective study, it is aimed to investigate the association of sTM with disease severity and its prognostic value in predicting in-hospital mortality in CAP patients admitted to ICU.

MATERIALS AND METHODS

Subjects

A total of 115 patients with CAP admitted to ICU of Shanghai Jingan District Shibei Hospital between June 2024 to September 2025 were retrospectively analyzed in this observational study. The inclusion criteria were: 1) CAP diagnosis per Chinese guidelines for diagnosis and treatment of CAP in adults [10], 2) age > 18 years old, 3) ICU stay > 72 hours, and 4) available sTM measurements at ICU admission. The exclusion criteria were patients with 1) cancer, 2) coagulation disorders (hemophilia, thrombocytopenia, antiphospholipid syndrome), 3) autoimmune diseases, 4) pregnancy or lactation, and 5) incomplete laboratory test results. This study was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shanghai Jingan District Shibei Hospital (Ethics No.: YL-2025-224-07).

Methods

Data of included patients were obtained from medical records, including demographic characteristics, clinical parameters and APACHE II scores (calculated within 24 hours of ICU admission). Laboratory tests including sTM, CRP, PCT, D-dimer (DD), white blood cells (WBC), hemoglobin (HGB), platelet counts (PLT), lymphocyte counts (LYM), neutrophil counts (NEU), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), lactate dehydrogenase (LD), creatinine (CREA), and uric acid (UA) were also collected. sTM and PCT were measured by fluorescent immunoassays on Pylon 3D immunoassay analyzer from ET Healthcare Inc. CRP and DD were measured by turbidimetric immunoassays using the instruments and reagents from Shanghai Upper BioTech Pharma Ltd. and Sekisui Medical Ltd., respectively. Complete blood counts were acquired by XN-20 analyzer using reagents from Sysmex Corp. All clinical biochemistry results were acquired using reagents from Fujifilm Wako Pure Chemical Corp. or Sekisui Medical Ltd. on TBA-FX8 analyzer (Toshiba Medical Systems Corp.).

Statistical analysis

Continuous variables were presented as mean ± SD or median (interquartile range) and compared by Student's *t* test and Mann-Whitney test for normal-distribution and non-normal-distribution data, respectively. Normal distribution was assessed by Kolmogorov-Smirnov test. Categorical variables were expressed as numbers (%) and compared using Fisher's exact test or chi-squared test. Spearman's correlation was used for correlation analyses between sTM and other parameters. Multivariable linear regression identified laboratory biomarkers independently associated with sTM. The optimal cutoff value for sTM was determined by maximizing Youden's index from receiver operating characteristic (ROC) curve analysis. The AUC of ROCs were calculated to compare the predictive performance for in-hospital mortality of sTM and APACHE II scores. Multivariable logistic regression assessed the independent prognostic value of sTM after adjustment for APACHE II scores or kidney dysfunction. All statistical tests were two tailed, and a value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using MedCalc statistical software version 22.009 (MedCalc Ltd., Ostend, Belgium).

RESULTS

The study subjects were mostly elderly patients with a median age of 76 years. The demographic characteristics and clinical parameters of survivors and non-sur-

Table 1. Characteristics of survivors and non-survivors.

	Overall	Survivors	Non-survivors	p
	n = 115	n = 97	n = 18	
Age (years)	76.0 (69.3, 87.8)	76.0 (69.0, 83.3)	87.5 (70.0, 91.0)	0.080
Gender				
Female	60 (52.2%)	48 (49.5%)	12 (66.7%)	0.182
Male	55 (47.8%)	49 (50.5%)	6 (33.3%)	
In-hospital stays (days)	22.0 (15.0, 27.0)	22 (15.8, 27.3)	14.5 (5.0, 21.0)	0.013
Comorbidity				
Coronary artery diseases	57 (49.6%)	48 (49.5%)	9 (50.0%)	0.968
Acute coronary syndrome	6 (5.2%)	5 (5.2%)	1 (5.6%)	1.000
High blood pressure	76 (66.1%)	65 (67.0%)	11 (61.1%)	0.629
Diabetes	45 (39.1%)	34 (35.1%)	11 (61.1%)	0.038
Stroke	63 (54.8%)	55 (56.7%)	8 (44.4%)	0.339
Kidney dysfunction	20 (17.4%)	13 (13.4%)	7 (38.9%)	0.009
Heart failure	28 (24.4%)	21 (21.6%)	7 (38.9%)	0.126
Cardiac arrythmia	8 (7.0%)	6 (6.2%)	2 (11.1%)	0.609
Malnutrition	57 (49.6%)	49 (50.5%)	8 (44.4%)	0.638
APACHE II	16.76 ± 5.42	17.0 (12.0, 19.0)	20.0 (16.0, 21.0)	0.021
sTM (TU/mL)	13.2 (10.4, 17.1)	12.3 (10.2, 15.9)	17.5 (14.5, 23.7)	< 0.001
CRP (mg/L)	51.7 (17.7, 94.1)	46.0 (15.0, 91.1)	59.5 (45.8, 163.2)	0.035
PCT (µg/L)	0.22 (0.11, 1.21)	0.18 (0.10, 0.62)	2.23 (0.50, 8.77)	0.001
DD (µg/L FEU)	2350 (1,393, 4,682)	2,010 (1,330, 4,440)	5,490 (2,880, 10,180)	0.001
WBC (x 10^9/L)	8.8 (6.3, 12.4)	8.6 (6.2, 12.2)	9.7 (6.6, 14.1)	0.444
HGB (g/L)	96.4 ± 22.6	98.0 ± 20.8	98.2 ± 21.4	0.084
PLT (x 10^9/L)	205.5 (148.0, 257.0)	206.0 (147.8, 270.0)	205.0 (160.0, 235.0)	0.911
LYM (x 10^9/L)	1.14 (0.77, 1.54)	1.19 (0.84, 1.72)	0.74 (0.45, 1.01)	< 0.001
NEU (x 10^9/L)	6.9 (4.4, 10.1)	7.2 (4.9, 14.1)	8.1 (4.4, 12.3)	0.993
TBIL (µmol/L)	7.3 (4.8, 13.2)	8.0 (5.0, 11.0)	6.0 (4.0, 7.0)	0.012
ALT (U/L)	15.0 (8.3, 27.0)	15.0 (9.0, 27.0)	16.0 (8.0, 26.0)	0.925
AST (U/L)	21.0 (15.3, 32.0)	20.0 (15.0, 30.0)	22.0 (20.0, 55.0)	0.092
ALB (g/L)	31.9 (28.7, 35.5)	32.5 (29.8, 35.5)	27.9 (23.9, 30.0)	0.012
LD (U/L)	231.0 (186.0, 301.25)	222.0 (182.0, 280.0)	360.0 (307.0, 449.0)	< 0.001
CREA (µmol/L)	56.0 (39.0, 81.8)	53.5 (39.0, 75.0)	80.0 (49.0, 171.0)	0.034
UA (mmol/L)	0.29 (0.20, 0.39)	0.28 (0.19, 0.37)	0.46 (0.27, 0.63)	0.003

vivors were compared in Table 1. Among 115 patients, 18 (15.7%) deceased in the hospital. The two groups showed similar age and gender distributions. Two groups exhibited similar high prevalence of chronic comorbidities including coronary heart diseases, hypertension, diabetes mellitus, strokes, and malnutrition, while acute coronary syndrome, heart failure, and cardiac arrythmia were present at lower proportions in both groups. However, diabetes (61.1% vs 35.1%, p = 0.038) and kidney dysfunction (38.9% vs 13.4%, p = 0.041) were more prevalent in non-survivors, and APACHE II scores at admission were significantly higher in non-survivors compared to survivors (20.0 [16.0, 21.0] vs. 17.0 [12.0, 19.0], p = 0.021).

Notably, non-survivors showed significantly higher sTM compared to survivors (17.50 [14.5, 23.7] vs. 12.3 [10.2, 15.9] TU/mL, p < 0.001), together with higher inflammatory biomarkers (CRP, PCT and LD), higher coagulation biomarkers (DD), and organ dysfunction indicators (TBIL, CREA and UA). Meanwhile, ALB and LYM were much lower in non-survivors than in survivors (all p < 0.05, Table 1).

Table 2. Multivariable linear regression of factors independently associated with sTM levels.

Variables	Coefficient	Std. Error	T	p
ALB	-0.0049	0.0032	-1.518	0.133
CREA	0.0008	0.0003	3.099	0.003
CRP	0.0003	0.0002	1.225	0.224
DD	0.0000	0.0000	-0.306	0.760
LD	0.0003	0.0001	2.341	0.022
HGB	-0.0021	0.0006	-3.740	0.000
NEU	0.0004	0.0005	0.807	0.422
PCT	-0.0006	0.0025	-0.236	0.814
UA	0.1885	0.0952	1.980	0.051
LYM	-0.0014	0.0022	-0.618	0.538
WBC	0.0012	0.0011	1.160	0.249

Table 3. Logistic regressions of sTM, APACHE II, and kidney dysfunction on in-hospital mortality.

	Odds ratio	95% CI	p
Model 1			
sTM	1.114	1.040 to 1.192	0.002
Model 2			
sTM	1.098	1.019 to 1.184	0.014
APACHE II Score	1.076	0.965 to 1.199	0.186
Model 3			
sTM	1.094	1.017 to 1.177	0.016
Kidney dysfunction	2.302	0.660 to 8.036	0.191

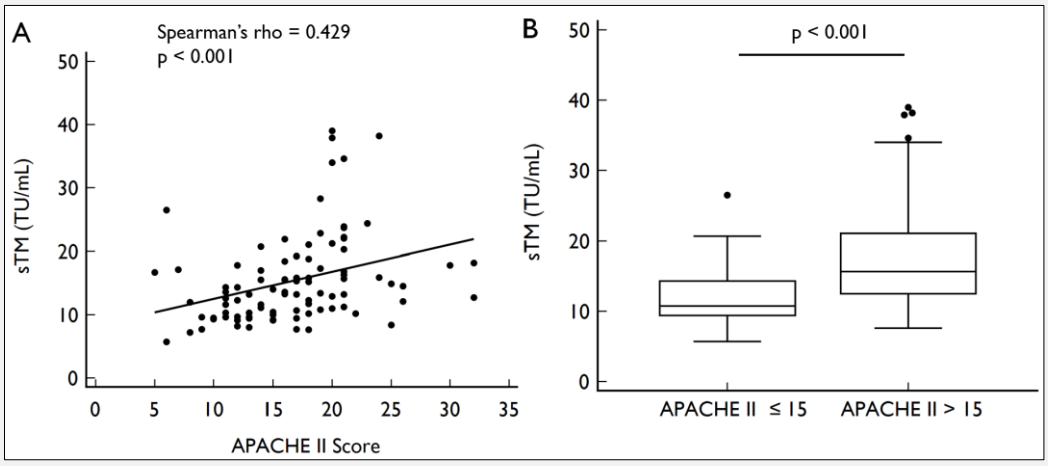

Figure 1. Association between sTM levels with disease severity in ICU admitted CAP patients: a) correlation of sTM with APACHE II scores, b) sTM between severity groups (APACHE II ≤ 15 vs. > 15).

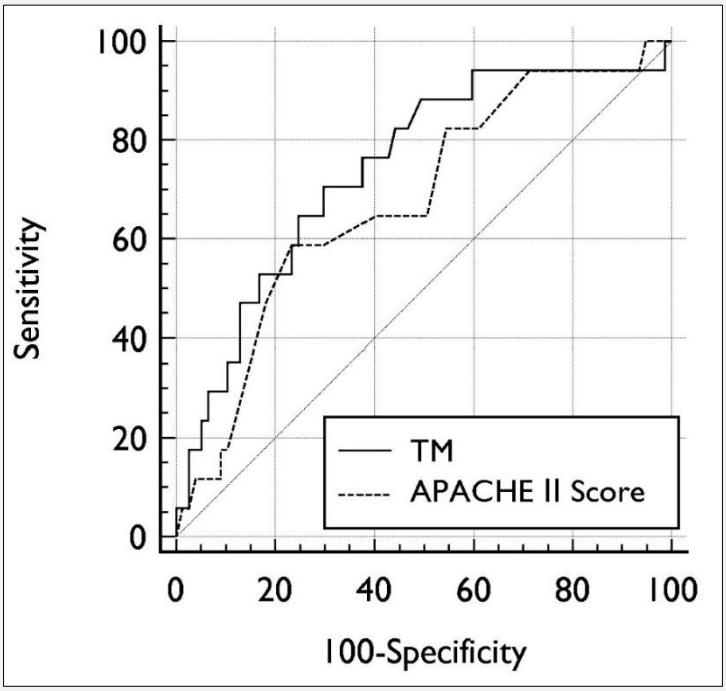

Figure 2. ROC analysis comparing predictive performances of sTM and APACE II for in-hospital mortality.

sTM levels positively correlated with APACE II scores (Spearman's rho = 0.429, p < 0.001). When stratifying patients by disease severity using an APACHE II cutoff of 15 points, sTM concentrations in severely ill patients were significantly higher compared to less severe patients (15.7 [12.5 - 21.1] vs. 10.8 [9.4 - 14.3] TU/mL, p < 0.001).

Spearman's correlation analysis revealed that sTM was positively correlated with CREA (rho = 0.551, p < 0.001), CRP (rho = 0.245, p = 0.008), DD (rho = 0.416, p < 0.001), LD (rho = 0.465, p < 0.001), NEU (rho = 0.314, p = 0.002), PCT (rho = 0.463, p < 0.001), UA (rho = 0.459, p < 0.001), WBC (rho = 0.308, p = 0.001), and age (rho = 0.219, p = 0.029), and it was negatively correlated with ALB (rho = -0.423, p < 0.001), LYM (rho = -0.206, p = 0.031), and HGB (rho = -0.373, p < 0.001). Multivariable linear regression analysis identified CREA, LD, and HGB as independent determinants of sTM after adjustment for potential confounders (Table 2).

ROC analysis showed that sTM effectively differentiated non-survivors and survivors (AUC = 0.747, 95% CI 0.658 - 0.824, p < 0.001), with an optimal cutoff of 12.9 TU/mL (sensitivity 88.9%, specificity 53.6%) determined by Youden's index. sTM showed slightly greater predictive accuracy than APACHE II scores (AUC = 0.679, 95% CI 0.575 - 0.772, p = 0.014), but the difference did not reach statistical significance (p = 0.317 for comparison) (Figure 2). Logistic regression analysis confirmed that the increase of sTM was associated with increased risk of in-hospital mortality (unadjusted OR = 1.114 per unit increase, 95% CI 1.040 - 1.192, p = 0.002). The association remained significant after adjusted for either APACHE II scores (adjusted OR = 1.098, 95% CI 1.019 - 1.184, p = 0.015) or kidney dysfunction (adjusted OR = 1.094, 95% CI 1.017 - 1.177, p = 0.016) (Table 3).

DISCUSSION

In this study, sTM was found significantly higher in non-surviving CAP patients at ICU admission compared to the survivors. It correlated with APACHE II scores and disease severity, and effectively predicted in-hospital mortality. Notably, elevated sTM levels remained independently associated with mortality risk even after adjustment for APACHE II scores or kidney dysfunction.

In CAP, acute and chronic inflammatory responses, immunologic reactions, complement activation and cytokine release can lead to endothelia injury, which resulted in increased shedding of sTM from endothelia surfaces. Thus, sTM levels reflect the degree of endothelial

injury and systemic inflammation. The findings in this study demonstrated significant positive correlations between sTM and inflammatory markers including CRP and PCT, as well as immune cell counts i.e. WBC and NEU, supporting this mechanism. Noteworthily, endothelium is a major player in the systemic response to infection, and TM plays a crucial role in regulating immunity, inflammation and coagulation. When endothelial injury and dysfunction occur, it may shift toward a proinflammatory phenotype, contributing to the characteristic imbalance between hyper-inflammation and immune suppression observed in sepsis [11]. In addition, endothelia injury activates coagulation and impairs the anticoagulant properties of endothelial cells, consistent with the observation of a positive correlation between sTM and DD levels in this study. Hypercoagulation is well-documented in ARDS [12] and sepsis [13]. Thus, rising sTM levels, increasing endothelial injury may indicate progression towards these life-threatening complications in these ICU-admitted CAP patients. Aligning with these, this study found not only a positive correlation between sTM and APACHE II scores, but also significantly higher sTM levels in both more severe patients (classified by APACHE II scores) and non-survivors. Importantly, multivariable logistical regression confirmed the additive prognostic value of sTM beyond APACHE II scores (adjusted OR: 1.098, p = 0.014), highlighting its potential for stratifying risks and predicting outcomes of CAP patients in ICU.

These findings are supported by existing literature. In emergency department patients, sTM levels were found to correlate with pneumonia severity and improved 30-day mortality prediction of CAP in addition to PSI scores [14]. In hospitalized COVID-19 patients, elevated sTM was associated with disease severity [15], mortality [16] and endothelial cell dysfunction-induced hypercoagulation state [17,18]. Collectively, these studies-along with our findings-support sTM as a biomarker for disease severity and prognosis in pneumonia, with our study specifically demonstrating its utility in ICU-admitted CAP patients.

In this study, we examined additional blood biomarkers in CAP patients. Non-survivors exhibited significantly elevated levels of PCT, CRP, WBC, DD, LYM, TBIL, ALB, LD, CREA, and UA compared to survivors (Table 1). ROC analyses revealed comparable performance for predicting in-hospital mortality among these biomarkers (Supplemental Table 1). While our small sample size precluded comprehensive multivariate analysis to identify independent mortality predictors or develop a risk model, multiple linear regression identified CREA. LD, and HGB as independent factors associated with sTM levels. Notably, hemoglobin showed an inverse relationship with sTM. Anemia, indicated by low hemoglobin levels, reduces tissue oxygen delivery [19], potentially exacerbating hypoxic endothelial injury in pneumonia. This endothelial damage may in turn promote red blood cell hemolysis through endothelial necroptosis [20], creating a vicious cycle of anemia and endothelial dysfunction. LD and CREA were positive influencers of sTM. The positive associations of LD (a marker of cellular damage) with sTM align with known pathophysiology. CREA is a biomarker of kidney function. sTM is cleared renally [8] and impaired kidney function leads to its accumulation in blood. Although the prevalences of kidney dysfunction were significantly higher in the non-survivors in this study, sTM remained independently associated with mortality even after adjusting for kidney dysfunction (adjusted OR: 1.094, p = 0.016), supporting its prognostic utility across renal function states.

Several study limitations warrant consideration. First, the retrospective design and small ICU cohort may limit generalizability. Second, sTM levels were not monitored continuously during our routine practice, which prevented assessment of dynamic changes during treatment in relation to disease development or treatment effectiveness. Further prospective studies with larger cohorts and serial measurements will be essential to validate clinical use of sTM in ICU-admitted CAP patients.

CONCLUSION

Our study revealed that elevated sTM levels at ICU admission strongly correlate with APACHE II scores and disease severity, and they predict in-hospital mortality in CAP patients. These suggest potential use of sTM as a prognostic biomarker to risk stratify ICU CAP patients and as a surrogate of APACH II scores for serial assessments. Further large-scale prospective studies are warranted to validate the clinical values of sTM in ICU-admitted CAP patients.

Declaration of Generative AI in Scientific Writing:
Deepseek V3 was used to improve language after the draft of manuscript was finished.

Declaration of Interest:
The author states no conflict of interest.

References:

1. Cavallazzi R, Furmanek S, Arnold FW, et al. The burden of community-acquired pneumonia requiring qdmission to ICU in the United States. Chest 2020;158(3):1008-16. (PMID: 32298730)

2. Viasus D, Del Rio-Pertuz G, Simonetti AF, et al. Biomarkers for predicting short-term mortality in community-acquired pneumonia: A systematic review and meta-analysis. J Infect 2016;72(3): 273-82. (PMID: 26777314)

3. Gursel G, Demirtas S. Value of APACHE II, SOFA and CPIS scores in predicting prognosis in patients with ventilator-associated pneumonia. Respiration 2006;73(4):503-8. (PMID: 16205047)

4. Beigmohammadi MT, Amoozadeh L, Rezaei Motlagh F, et al. Mortality predictive value of APACHE II and SOFA scores in COVID-19 patients in the intensive care unit. Can Respir J 2022; 2022:5129314. (PMID: 35356088)

5. Loghmani H, Conway EM. Exploring traditional and nontradetional roles for thrombomodulin. Blood 2018;132(2):148-58. (PMID: 29866818)

6. Watanabe-Kusunoki K, Nakazawa D, Ishizu A, Atsumi T. Thrombomodulin as a physiological modulator of intravascular injury. Front Immunol 2020;11:575890. (PMID: 33042158)

7. Yang Y, Tang H. Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia. Cell Mol Immunol 2016;13(4):432-42. (PMID: 27041635)

8. Boron M, Hauzer-Martin T, Keil J, Sun XL. Circulating thrombomodulin: release mechanisms, measurements, and levels in diseases and medical procedures. TH Open 2022;6(3):e194-e212. (PMID: 36046203)

9. Califano F, Giovanniello T, Pantone P, et al. Clinical importance of thrombomodulin serum levels. Eur Rev Med Pharmacol Sci 2000;4(3):59-66. (PMID: 11558626)

10. Cao B, Huang Y, She DY, et al. Diagnosis and treatment of community-acquired pneumonia in adults: 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association. Clin Respir J 2018;12(4):1320-60. (PMID: 28756639)

11. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial responses in sepsis. Am J Respir Crit Care Med 2020;202(3):361-70. (PMID: 32101446)

12. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia - a review. Crit Care Med 2006;34(3):871-7. (PMID: 16521285)

13. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392(10141):75-87. (PMID: 29937192)

14. Yin Q, Liu B, Chen Y, Zhao Y, Li C. Soluble thrombomodulin to evaluate the severity and outcome of community-acquired pneumonia. Inflammation 2014;37(4):1271-9. (PMID: 24573987)

15. S B MJ, Chacko B, Selvarajan S, et al. Biomarkers of coagulation, endothelial, platelet function, and fibrinolysis in patients with COVID-19: A prospective study. Sci Rep 2024;14(1):2011. (PMID: 38263377)

16. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: Evidence from a single-centre, cross-sectional study. Lancet Haematol 2020;7(8):e575-e582. (PMID: 32619411)

17. Norooznezhad AH, Mansouri K. Endothelial cell dysfunction, coagulation, and angiogenesis in coronavirus disease 2019 (COVID-19). Microvasc Res 2021;137:104188. (PMID: 34022205)

18. Padilla S, Andreo M, Marco P, et al. Enhanced prediction of thrombotic events in hospitalized COVID-19 patients with soluble thrombomodulin. PLoS One 2025;20(3):e0319666. (PMID: 40106444)

19. Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev 2021;12(12):CD002042 (PMID: 34932836)

20. Wu MCL, Italiano E, Jarvis-Child R, et al. Ischaemic endothelial necroptosis induces haemolysis and COVID-19 angiopathy. Nature 2025;643(8070):182-91. (PMID: 40468079)

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