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STUDY ON THE PROGNOSTIC VALUE OF THROMBOMODULIN IN ACUTE KIDNEY INJURY AND MORTALITY IN PATIENTS WITH SEPSIS

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INTRODUCTION

1. RATIONALE FOR THE STUDY

Sepsis has been identified by the World Health Organization as a top priority in global healthcare. Acute kidney injury (AKI) is a common complication of sepsis, with an incidence ranging from 14% to 87% and a mortality rate between 11% and 77%.

Thrombomodulin (TM) is considered an early biomarker reflecting endothelial injury in septic patients. It plays a crucial role in homeostasis regulation, emerging early in the local inflammatory response upon vascular or epithelial damage, and is involved in anti-inflammatory, anticoagulant, cell proliferation, and angiogenesis processes. Thrombomodulin is an independent predictor of AKI, demonstrating superior prognostic value compared to other coagulation and inflammatory markers in septic patients. Elevated thrombomodulin levels are associated with AKI and serve as a prognostic factor for 28-day mortality in critically ill patients admitted to the intensive care unit (ICU). Increased thrombomodulin levels are particularly significant in septic patients, showing a positive correlation with the Sequential Organ Failure Assessment (SOFA) score, indicating the severity of multiple organ dysfunction syndrome and predicting the likelihood of septic shock and mortality. Serum thrombomodulin levels provide a better predictive value for AKI in critically ill ICU patients compared to biomarkers such as protein C, serum neutrophil gelatinase-associated lipocalin (NGAL), urinary NGAL, serum cystatin C, urinary cystatin C, urinary kidney injury molecule-1 (KIM-1), and urinary liver-type fatty acid-binding protein (L-FABP).

This research, titled "**Study on the Prognostic Value of Thrombomodulin in Acute Kidney Injury and Mortality in Patients with Sepsis**," aims to achieve the following objectives:

1. To determine the serum thrombomodulin levels and their association with selected clinical and laboratory parameters in septic patients.

2. To investigate the prognostic value of serum thrombomodulin in predicting the development of acute kidney injury and mortality in patients with sepsis.

2. SCIENTIFIC AND PRACTICAL SIGNIFICANCE

- Serum thrombomodulin serves as a biomarker for predicting acute kidney injury (AKI) and mortality in septic patients in intensive

care units (ICUs). This study aims to contribute to existing research on serum thrombomodulin in both healthy individuals and septic patients, further clarifying and establishing its clinical significance.

- Elevated serum thrombomodulin levels facilitate early prognostication of AKI and mortality in sepsis, enabling timely interventions to reduce complications and improve survival rates.

3. CONTRIBUTIONS OF THE DISSERTATION

- Establishes reference values for serum thrombomodulin levels in healthy Vietnamese individuals.
- Determines serum thrombomodulin levels in various patient groups, including those with sepsis, septic shock, sepsis with and without AKI, and survivors versus non-survivors of sepsis.
- Demonstrates the correlation between serum thrombomodulin levels and selected clinical and laboratory parameters in septic patients.
- Provides sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic (ROC) curve, cutoff values, odds ratio (OR), and hazard ratio (HR) for serum thrombomodulin, aiding clinicians in the early prediction of AKI, septic shock, and mortality in sepsis.

Chapter 1
LITERATURE REVIEW

1.1. SEPSIS

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. This definition underscores the significance of an imbalanced immune response to infection, which is associated with a markedly higher mortality risk compared to other common infections. It also highlights the urgency of early detection and intervention in sepsis [139].

1.2. ACUTE KIDNEY INJURY IN SEPSIS PATIENTS

1.2.1. General Overview

1.2.2. Pathophysiology

The predominant pathophysiological model of sepsis-associated AKI involves reduced glomerular perfusion and secondary tubular epithelial cell death or acute tubular necrosis. However, recent evidence suggests that ischemia-reperfusion injury is not the sole mechanism. Sepsis-associated AKI may develop in the absence of overt renal hypoperfusion or with normal or even increased renal blood flow. The exact pathogenesis of

sepsis-associated AKI remains controversial [129]. Nevertheless, three primary mechanisms are widely accepted: inflammation, circulatory dysfunction, and metabolic reprogramming [103, 128].

1.2.3. Diagnosis

The diagnosis of sepsis-associated AKI requires fulfillment of the following two criteria:

1. Sepsis, as defined by the Sepsis-3 criteria.
2. Acute kidney injury, as defined by the KDIGO 2012 criteria, occurring within seven days of sepsis diagnosis [162].

1.2.4. Treatment

Severe sepsis often leads to multiple organ dysfunction syndrome (MODS), and there is currently no standardized treatment strategy. Most therapeutic approaches focus on supportive care, including timely administration of nephroprotective antibiotics, hemodynamic stabilization, fluid balance management, acid-base and electrolyte homeostasis, respiratory support, nutritional supplementation, renal replacement therapy, glycemic control, and, when necessary, blood or plasma transfusion [56, 103, 128].

1.3. THROMBOMODULIN

1.3.1. Structure and function

1.3.1.1. Structure

Thrombomodulin (TM) is a type 1 transmembrane glycoprotein first identified on endothelial cells by Esmon and Oven in 1981 [25, 39]. The human TM gene was isolated from a human DNA library by Wen and Suzuki. It is encoded by an intronless gene located on chromosome 20 [105, 143]. The mature TM protein consists of a single polypeptide chain with 557 amino acid residues and a molecular weight ranging from 70 to 100 kDa. Structurally, it comprises five distinct domains.

1.3.1.2. Function

- Anticoagulant function
- Anti-inflammatory function
- Angiogenesis regulation

1.3.2. Thrombomodulin in Sepsis-Associated Acute Kidney Injury

1.3.2.1. Elevated Thrombomodulin Levels in Sepsis-Associated AKI

Severe sepsis leads to upregulation of pro-inflammatory adhesion molecules and the release of inflammatory mediators, including cytokines and lipid-derived products, which contribute to coagulation disturbances and endothelial barrier disruption. Endothelial damage and coagulation abnormalities play crucial roles in the progression of

septic shock and disseminated intravascular coagulation (DIC) [73, 164]. An uncontrolled systemic inflammatory response to infection is a key factor driving sepsis-associated AKI. Microcirculatory alterations, increased vascular permeability, interstitial edema, and tubular epithelial hypoxia are hallmark pathophysiological features of sepsis-associated AKI. Recent studies highlight the critical role of endothelial dysfunction in the pathogenesis of sepsis-associated AKI [20]. When endothelial integrity is compromised, thrombomodulin is released into the bloodstream and tubular fluid. Thrombomodulin is regarded as an early biomarker of endothelial injury in sepsis patients [66, 164]. Soluble thrombomodulin levels are utilized for diagnosing sepsis, assessing prognosis, and predicting mortality risk [25, 112].

1.3.2.2. Mechanisms of Thrombomodulin Release

1.3.3. Thrombomodulin Quantification

1.4. RELEVANT STUDIES

In Vietnam, no studies have been identified that specifically investigate the prognostic value of thrombomodulin in sepsis patients with or without AKI, nor its predictive utility for AKI and mortality in sepsis.

1.4.1. Thrombomodulin in Sepsis Patients

Numerous studies have demonstrated a positive correlation between soluble thrombomodulin levels and sepsis severity in both adult and pediatric populations [51, 112]. Soluble thrombomodulin has been shown to outperform established prognostic scoring systems such as SOFA and APACHE II in predicting MODS-related complications [112]. Additionally, sepsis patients with fatal outcomes exhibit significantly higher plasma thrombomodulin levels compared to non-sepsis patients, with thrombomodulin levels strongly associated with disease severity and mortality risk [93]. Notable studies on this topic include those by Zhang et al. (2021), Lin et al. (2008), Rodrigues et al. (2020), and Zhou et al. (2022).

1.4.2. Thrombomodulin in Sepsis-Associated AKI

- Hergesell et al. reported that renal secretion of soluble thrombomodulin influences its serum and urinary levels in patients. In renal failure cases unrelated to endothelial injury, serum thrombomodulin levels remain elevated. Furthermore, a positive correlation exists between serum thrombomodulin and serum creatinine, while an inverse correlation is observed with estimated glomerular filtration rate (eGFR).

- Katayama et al. (2017) demonstrated that soluble thrombomodulin serves as an independent biomarker for predicting AKI and organ dysfunction, surpassing other coagulation and inflammatory biomarkers. Receiver operating characteristic (ROC) curve analysis indicated that soluble thrombomodulin is an independent predictor of AKI, with an area under the curve (AUC) of 0.758 and $p < 0.001$ [73].

- Bouchard et al. (2015) found that thrombomodulin provides superior prognostic value for AKI in critically ill ICU patients compared to NGAL, KIM-1, L-FABP, cystatin C, protein C, and the APACHE II score.

- Other studies, including those by Zhou et al. (2020), Rodrigues et al. (2020), Inkinen et al. (2019), Mihajlovic et al. (2015), Atreya et al. (2023), and Mahmoud et al. (2021), further support the prognostic significance of thrombomodulin in predicting AKI and mortality.

Chapter 2
STUDY SUBJECTS AND METHODOLOGY

2.1. STUDY SUBJECTS

2.1.1. Inclusion Criteria

- Control group:

+ 80 healthy volunteers with no underlying medical conditions, undergoing routine health examinations at the Outpatient Department, International Medical Center, Hue Central Hospital, with normal blood urea and creatinine levels.

- Study group:

+ 79 patients admitted to the Intensive Care Unit of Hue Central Hospital, diagnosed with sepsis according to the Sepsis-3 (2016) criteria [139].

+ Patients aged 18 years or older.

+ Patients and/or their legal representatives provided informed consent for study participation.

2.1.2. Exclusion Criteria

- Patients with pre-existing acute kidney injury or chronic kidney disease.

- Patients who had undergone organ transplantation or had malignancies.

- Pregnant women.

- Patients with multiple trauma or those undergoing surgical interventions.

- Patients with urinary tract obstruction.
- Patients hospitalized for less than 48 hours.

2.1.3. Diagnostic Criteria

2.1.4. Scoring Systems Used in the Study

2.2. STUDY METHODOLOGY

2.2.1. Study Design

The study was designed as a descriptive, cross-sectional, prospective, and longitudinal follow-up study.

2.2.2. Sample Size Estimation

- Estimated sample size for Objective 1: 40 patients
- Estimated sample size for Objective 2: 62 patients

2.2.3. Research Instruments

2.2.4. Study Procedures

2.2.5. Definitions and Measurement of Study Variables

Thrombomodulin (TM) quantification technique: Thrombomodulin levels were measured using the ELISA (Enzyme-Linked Immunosorbent Assay) method. The principle of this method involves the use of two monoclonal antibodies specific to thrombomodulin. The ELISA kit employs anti-thrombomodulin antibodies labeled with biotin and horseradish peroxidase (HRP) to detect soluble thrombomodulin in serum samples.

2.2.6. Data Processing

Statistical analysis was performed using SPSS 22.0 and MedCalc 14.8.1.0 software.

2.3. RESEARCH ETHICS

Chapter 3
RESEARCH RESULTS

3.1. GENERAL CHARACTERISTICS OF THE STUDY GROUP

3.1.1. Demographic Characteristics

- The mean age in the control group and the study group were 63.31 ± 6.06 years and 64.22 ± 16.09 years, respectively. There were no significant differences in age and gender between the two groups, with $p > 0.05$.

3.1.2. Characteristics of Comorbidities

- The majority of patients with sepsis had comorbidities such as hypertension and type 2 diabetes. There was no significant difference in the prevalence of comorbidities between the septic patients with acute kidney injury (AKI) and those without AKI, with $p > 0.05$, except for heart failure, which showed a significant difference.

3.1.3. Characteristics of Infection Sources

- The primary infectious foci in sepsis were predominantly the gastrointestinal and respiratory tracts**.** There was no statistically significant difference in the distribution of infection foci between the septic patients with acute kidney injury (AKI) and those without AKI**,** with $p > 0.05$.

3.1.4. Blood Culture Results

- In our study, positive blood cultures accounted for 20.3%, while negative blood cultures were observed in 79.7% of cases. Among the isolated bacterial strains, Gram-negative bacteria accounted for the highest proportion.

3.2.THROMBOMODULIN SERUM LEVELS AND CORRELATION WITH CLINICALAND LABORATORY PARAMETERS

Table 3.14. Acute Kidney Injury Classification According to KDIGO 2012 in Survivors and Non-Survivors with Sepsis

Group / Stage	Overall group (n = 79)		Survivor group (n = 57)		Non-survivor group (n = 22)		p
	n	%	n	%	n	%	
AKI	44	55.7	24	42.1	20	90.9	0.046
Stage 1	11	25.0	8	33.3	3	15.0	
Stage 2	21	47.7	13	54.2	8	40.0	
Stage 3	12	27.3	3	12.5	9	45.0	

The incidence of acute kidney injury (AKI) in septic patients was 55.7%. There was a statistically significant difference in AKI stages according to the KDIGO 2012 classification between the survivor and non-survivor groups, with $p < 0.05$.

3.2.4. Evaluating several severity scores at T0

Table 3.16. Severity Scores in the Survivor and Non-Survivor Sepsis Groups

Groups / Scores	Overall group (n = 79)	Survivor group (n = 57)	Non-survivor group (n = 22)	p
SOFA score	7 (3 - 13)	6 (3 - 12)	8 (6 - 13)	< 0.001
APACHE II score	16.54 ± 6.13	15.4 ± 6.14	20.27 ± 5.81	0.001
SIC score	3.94 ± 1.24	3.72 ± 1.25	4.50 ± 1.06	0.011
DIC score	2 (0 - 7)	2 (0 - 7)	3 (0 - 7)	0.114

The SOFA score, APACHE II score, and SIC score at T0 showed a statistically significant difference between the survivor and non-survivor sepsis groups, with $p < 0.05$.

3.2.5. Characteristics of Treatment Outcomes

Table 3.17. Treatment Outcomes in Septic Patients with and without Acute Kidney Injury (AKI)

Characteristics	Overall group (n = 79)	Non-AKI group (n = 35)	AKI group (n = 44)	p
ICU length of stay (days)	9 (3 - 27)	8 (3 - 23)	9 (3 - 27)	0.354
Continuous renal replacement therapy (CRRT), n (%)	23 (29.1%)	5 (14.3%)	18 (40.9%)	0.011
CRRT duration (hours)	26.82 ± 5.56	16.4 ± 7.39	35.11 ± 7.93	0.028
Mechanical ventilation, n (%)	26 (32.9%)	2 (5.7%)	24 (54.5%)	< 0.001
Mechanical ventilation duration (days)	0 (0 - 13)	0 (0 - 7)	1.5 (0 - 13)	< 0.001
28-day mortality, n (%)	22 (27.8)	2 (5.7%)	20 (45.5%)	< 0.001

There was no statistically significant difference in ICU length of stay between the AKI and Non-AKI groups, with $p > 0.05$. The proportion of patients requiring continuous renal replacement therapy (CRRT), CRRT duration, mechanical ventilation rate, mechanical ventilation duration, and 28-day mortality showed a statistically significant difference between the AKI and non-AKI groups, with $p < 0.05$.

3.2.6. Serum Thrombomodulin Levels in the Control and Study Groups

Table 3.19. Serum Thrombomodulin Levels in the Control and Study Groups

Group / TM (ng/mL)	Control group (n = 80)			Study group (n = 79)		p
	Male (n = 41)	Female (n = 39)	p	Male (n = 49)	Female (n = 30)	
Median (Min - Max)	1,10 (0,76-1,42)	1,07 (0,81-1,53)	0,874	3,78 (3,21-5,02)	3,9 (3,71-4,64)	0,739
	1,09 (0,78 - 1,46)			3,88 (3,49 - 4,84)		< 0,001

The median serum thrombomodulin (TM) level in the control group was 1.09 ng/mL, while in the study group, it was 3.88 ng/mL. The difference between the two groups was statistically significant, with $p < 0.05$.

There was no statistically significant difference in the median serum thrombomodulin levels between male and female patients in each group, with $p > 0.05$.

3.2.7. Serum Thrombomodulin Levels by Age group

Table 3.20. Serum Thrombomodulin Levels by Age Group in the Control and Patient Groups

Group / Age group	Thrombomodulin (ng/mL)					
	Control group			Study group		
	n	Median (Min - Max)	p	n	Median (Min - Max)	p
< 60	26	1.26 (0.60 - 1.82)	0.63	24	3.81 (2.32 - 6.44)	0.34
60 - 69	43	1.06 (0.50 - 1.93)		25	3.76 (2.64 - 6.46)	
≥ 70	11	1.16 (0.45 - 1.77)		30	4.18 (2.32 - 6.46)	

There was no statistically significant difference in the median serum thrombomodulin levels among different age groups in both the control group and the study group, with $p > 0.05$.

3.2.8. Relationship Between Thrombomodulin and Clinical and Laboratory Variables

3.2.8.1. Correlation between Thrombomodulin and clinical parameters at T0

Table 3.21. Correlation between Thrombomodulin and clinical Parameters

Clinical Parameter	n	Correlation Coefficient (r*)	p	95% Confidence Interval (CI)	
Systolic Blood Pressure (SBP) (mmHg)	79	- 0.353	0.001	- 0.537	-0.136
Diastolic Blood Pressure (DBP) (mmHg)	79	- 0.173	0.128	- 0.385	0.057
Mean Arterial Pressure (MAP) (mmHg)	79	- 0.290	0.01	- 0.485	-0.067
Central Venous Pressure (CVP) (cmH_2O)	79	- 0.326	0.003	- 0.515	-0.106
Glasgow Coma Scale (GCS) (points)	79	- 0.164	0.148	- 0.378	0.066
Continuous Renal Replacement Therapy (CRRT) Duration (hours)	23	0.233	0.038	0.006	0.438
Mechanical Ventilation Duration (days)	26	0.425	< 0.001	- 0.488	0.298
SOFA Score	79	0.255	0.023	0.029	0.456
APACHE II Score	79	0.320	0.004	0.100	0.510
SIC Score	79	0.256	0.023	0.030	0.457

*Spearman Correlation Analysis

A moderate positive correlation was observed between serum thrombomodulin levels and both mechanical ventilation duration and APACHE II score, with $p < 0.05$. A moderate negative correlation was found between serum thrombomodulin levels and both systolic blood pressure (SBP) and central venous pressure (CVP), with $p < 0.05$.

3.2.8.2. Correlation Between Thrombomodulin and Laboratory Parameters at T0

Table 3.22. Correlation Between Thrombomodulin and Laboratory Parameters (n = 79)

Laboratory Parameter	Correlation Coefficient (r*)	p	95% Confidence Interval (CI)	
White Blood Cell Count (G/L)	0.221	0.05	- 0.007	0.427
Platelet Count (G/L)	- 0.164	0.149	- 0.377	0.066
Prothrombin Ratio (%)	- 0.149	0.191	- 0.364	0.082
D-dimer (ng/mL)	0.128	0.262	- 0.103	0.345
Total Bilirubin (µmol/L)	- 0.088	0.442	- 0.309	0.143
AST (U/L)	0.022	0.847	- 0.206	0.248
ALT (U/L)	- 0.068	0.554	- 0.291	0.162
Ionized Calcium (mmol/L)	- 0.116	0.307	- 0.335	0.114
Blood Urea (mmol/L)	0.223	0.048	- 0.005	0.429
Lactate (mmol/L)	0.231	0.040	0.004	0.436
IL-6 (pg/mL)	0.103	0.368	- 0.128	0.322
Procalcitonin PCT (ng/mL)	0.046	0.685	- 0.183	0.271

*Spearman Correlation Analysis

There was a weak positive correlation between serum thrombomodulin levels and blood urea and lactate levels, with $p < 0.05$.

There was no correlation between serum thrombomodulin levels and white blood cell count, platelet count, prothrombin ratio, D-dimer, total bilirubin, AST, ALT, IL-6, or procalcitonin, with $p > 0.05$.

3.2.8.3. Correlation Between Thrombomodulin and Serum Creatinine at T0, T2, and T7

Table 3.23. Correlation Between Thrombomodulin and Serum Creatinine at T0, T2, and T7

Creatinine Parameter	N	Correlation Coefficient (r*)	p	95% Confidence Interval (CI)	
Creatinine at Day 0 (T0)	79	0.180	0.112	- 0.049	0.392
Creatinine at Day 2 (T2)	***79***	***0.455***	***< 0.001***	***0.254***	***0.618***
Creatinine at Day 7 (T7)	***66***	***0.523***	***< 0.001***	***0.313***	***0.684***

*Spearman Correlation Analysis

There was a relatively strong positive correlation between serum thrombomodulin levels and serum creatinine levels at T2 and T7, with $p < 0.05$.

3.3.PROGNOSTIC VALUE OF SERUM THROMBOMODULIN FOR ACUTE KIDNEY INJURY AND MORTALITY

3.3.1. Serum Thrombomodulin Levels in Patient Groups

Table 3.24. Serum Thrombomodulin Levels in Patient Groups

TM (ng/ml) / Groups	%	n	Median (Min - Max)	p
Non-AKI	44,3	35	3,56 (2,75 - 3,87)	< 0,001
AKI	55,7	44	4,56 (3,54 - 5,43)	
Sepsis	63,3	50	3,75 (3,05 - 4,16)	< 0,001
Septic shock	36,7	29	4,75 (3,94 - 5,53)	
Survivor group	72,2	57	3,78 (3,17 - 4,23)	< 0,001
Non-survivor group	27,8	22	5,41 (4,18 - 5,91)	

The median serum thrombomodulin level in the Non-AKI group was 3.56 ng/mL, while in the AKI group, it was 4.56 ng/mL. The difference between the two groups was statistically significant, with $p < 0.05$.

The median serum thrombomodulin level in the Sepsis group was 3.75 ng/mL, while in the Septic Shock group, it was 4.75 ng/mL. This difference was statistically significant, with $p < 0.05$.

The median serum thrombomodulin level in the Survivor group was 3.78 ng/mL, while in the Non-Survivor group, it was 5.41 ng/mL. This difference was statistically significant, with $p < 0.05$.

Table 3.25. Serum Thrombomodulin Levels by AKI Stage in Survivors and Non-Survivors with Sepsis

Group / AKI	Thrombomodulin (ng/mL)			
	Overall group (n = 79)	**Survivor group (n = 57)**	**Non-survivor group (n = 22)**	**p**
	Median (Min - Max)	**Median (Min - Max)**	**Median (Min - Max)**	
Stage 1	4.74 (3.58 - 6.21)	4.28 (3.58 - 5.47)	5.9 (4.84 - 6.21)	0.025
Stage 2	4.50 (3.39 - 6.46)	4.24 (3.57 - 5.63)	5.8 (3.39 - 6.46)	0.020
Stage 3	4.63 (3.0 - 5.94)	4.52 (4.10 - 4.85)	4.75 (3.0 - 5.94)	0.926
p	0.837	0.718	0.123	

There was a statistically significant difference in serum thrombomodulin levels among patients with AKI stages 1 and 2 between the survivor and non-survivor groups, with $p < 0.05$.

3.3.2. Prognostic Value of Thrombomodulin for Acute Kidney Injury

Table 3.26. Prognostic Value of Serum Thrombomodulin for AKI compared to Other Factors at T0

Variable	Optimal Cutoff	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC	95% CI		p
MAP (mmHg)	≤ 64	63.6	65.7	70.0	59.0	0.658	0.543	0.761	0.010
SOFA Score	> 4	79.5	42.9	63.6	62.5	0.612	0.487	0.737	0.088
APACHE II Score	> 16	59.1	68.6	70.3	57.1	0.614	0.488	0.740	0.083
SIC Score	> 3	75.0	48.6	64.7	60.7	0.639	0.513	0.764	0.035
WBC Count (G/L)	> 14.7	59.1	74.3	74.3	59.1	0.689	0.572	0.806	0.004
Prothrombin Ratio (%)	≤ 65	75.0	57.1	68.7	64.5	0.665	0.550	0.768	0.009
Blood Urea (mmol/L)	***> 8.7***	***65.9***	***82.9***	***82.9***	***65.9***	***0.753***	***0.644***	***0.862***	***< 0.001***
Ionized Calcium (mmol/L)	< 0.96	56.8	77.1	75.8	58.7	0.653	0.537	0.757	0.014
Lactate (mmol/L)	***> 2.31***	***81.8***	***65.7***	***75.0***	***74.2***	***0.713***	***0.597***	***0.830***	***0.001***
IL-6 (pg/mL)	> 108.4	77.3	51.4	66.7	64.3	0.682	0.564	0.800	0.006
PCT (ng/mL)	> 44.3	34.1	88.6	78.9	51.7	0.619	0.496	0.743	0.070
Thrombomodulin (ng/mL)	***> 4.14***	***65.9***	***91.4***	***90.6***	***68.1***	***0.844***	***0.754***	***0.933***	***< 0.001***

- The optimal cutoff value for predicting acute kidney injury (AKI) using serum thrombomodulin was > 4.14 ng/mL, with an area under the curve (AUC) of 0.844 (95% CI: 0.754 - 0.933, $p < 0.001$), a sensitivity of 65.9%, a specificity of 91.4%, a positive predictive value (PPV) of 91.4%, and a negative predictive value (NPV) of 68.1%.

- The optimal cutoff value for blood urea in predicting AKI was > 8.7 mmol/L, with an AUC of 0.753 (95% CI: 0.644 - 0.862, $p < 0.001$), a sensitivity of 65.9%, a specificity of 82.9%, a PPV of 82.9%, and an NPV of 65.9%.

- The optimal cutoff value for lactate in predicting AKI was > 2.31 mmol/L, with an AUC of 0.713 (95% CI: 0.597 - 0.830, $p = 0.001$), a sensitivity of 81.8%, a specificity of 65.7%, a PPV of 75.0%, and an NPV of 74.2%.

- Mean arterial pressure (MAP), SIC score, white blood cell count, prothrombin ratio, ionized calcium, and IL-6 had AUC values ranging from 0.60 to 0.70 with $p < 0.05$, indicating limited prognostic value for predicting AKI in septic patients.

Table 3.27. Multivariate Logistic Regression Model for Predicting Acute Kidney Injury (AKI)

	Regression Coefficient (β)	Odds ratio (OR, 95%)	p
Full Model*			
Mean Arterial Pressure (mmHg)	0.022	1.02 (0.96 - 1.1)	0.524
SOFA score	0.395	1.49 (0.91 - 2.44)	0.117
APACHE II score	- 0.088	0.92 (0.77 - 1.09)	0.312
SIC score	- 0.280	0.76 (0.27 - 2.14)	0.597
White Blood Cell (G/L)	0.084	1.09 (0.96 - 1.23)	0.185
Prothrombin Ratio (%)	- 0.006	0.99 (0.95 - 1.04)	0.811
Blood Urea (mmol/L)	***0.228***	***1.26 (1.02 - 1.54)***	***0.029***
Ionized Calcium (mmol/L)	0.736	2.09 (0.06 - 74.47)	0.687
Lactate (mmol/L)	0.201	1.2 (0.88 - 1.69)	0.228
IL-6 (pg/mL)	0.001	1.001 (1.000 - 1.002)	0.169
PCT (ng/mL)	0.017	1.02 (0.99 - 1.04)	0.167
Thrombomodulin (ng/mL)	***1.900***	***6.69 (2.21 - 20.23)***	***0.001***
Reduced Model**			
Thrombomodulin (ng/mL)	***1.830***	***6.24 (2.42 - 16.13)***	***< 0.001***
Blood Urea (mmol/L)	***0.247***	***1.28 (1.10 - 1.49)***	***0.001***
IL-6 (pg/mL)	0.001	1.001 (1.000 -1.001)	0.055

* *Full model: Includes all variables*

** *Reduced model: Based on the Backward Stepwise method.*

The multivariate logistic regression analysis using the reduced model identified serum urea and serum thrombomodulin as independent predictors of acute kidney injury (AKI), with odds ratios (ORs) of 1.28 (95% CI: 1.10 - 1.49, p = 0.001) and 6.24 (95% CI: 2.42 - 16.13, p < 0.001), respectively

3.3.3. Prognostic Value of Thrombomodulin for Septic Shock

Table 3.28. Prognostic Value of Serum Thrombomodulin for septic shock compared to Other Factors at T0

Variable	Optimal Cutoff	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC	95% CI		p
SOFA score	***> 4***	***100***	***48.0***	***52.7***	***100***	***0.798***	***0.702***	***0.894***	***< 0.001***
APACHE II score	***> 16***	***75.9***	***70.0***	***59.5***	***83.3***	***0.703***	***0.583***	***0.824***	***0.003***
SIC score	> 3	86.2	48.0	49.0	85.7	0.686	0.569	0.803	0.006
White Blood Cell (G/L)	> 8.5	69.0	14.0	31.7	43.8	0.508	0.369	0.646	0.911
Platelet count (G/L)	≤ 116	55.2	72.0	53.3	73.5	0.327	0.207	0.447	0.011
Prothrombin ratio (%)	≤ 67	79.3	46.0	46.0	79.3	0.363	0.233	0.493	0.043
Blood urea (mmol/L)	> 11.54	58.6	84.0	68.0	77.8	0.645	0.507	0.783	0.032
Lactate (mmol/L)	***> 2.43***	***100***	***70.0***	***65.9***	***100***	***0.863***	***0.786***	***0.941***	***< 0.001***
IL-6 (pg/mL)	> 226.7	65.5	68.0	54.3	77.3	0.676	0.553	0.798	0.01
PCT (ng/mL)	> 99.83	27.6	96.0	80.0	69.6	0.565	0.429	0.701	0.339
Thrombomodulin (ng/mL)	***> 3.92***	***79.3***	***74.0***	***63.9***	***86.0***	***0.761***	***0.652***	***0.871***	***< 0.001***

The optimal cutoff value for predicting septic shock (SS) using the SOFA score was > 4 points, with an area under the curve (AUC) of 0.798 (95% CI: 0.702 - 0.894, p < 0.001), a sensitivity of 100%, a specificity of 48%, a positive predictive value (PPV) of 52.7%, and a negative predictive value (NPV) of 100%.

The optimal cutoff value for APACHE II in predicting SS was > 16 points, with an AUC of 0.703 (95% CI: 0.583 - 0.824, p = 0.003), a sensitivity of 75.9%, a specificity of 70%, a PPV of 59.5%, and an NPV of 83.3%.

The optimal cutoff value for serum lactate in predicting SS was > 2.43 mmol/L, with an AUC of 0.863 (95% CI: 0.786 - 0.941, p < 0.001), a sensitivity of 100%, a specificity of 70%, a PPV of 65.9%, and an NPV of 100%.

The optimal cutoff value for serum thrombomodulin (TM) levels in predicting SS was > 3.92 ng/mL, with an AUC of 0.761 (95% CI: 0.652 - 0.871, p < 0.001), a sensitivity of 79.3%, a specificity of 74.0%, a PPV of 63.9%, and an NPV of 86.0%.

SIC score, platelet count, prothrombin ratio, blood urea, and IL-6 had AUC values ranging from 0.3 to 0.7, with p < 0.05, indicating limited prognostic value for septic shock in these patients.

Table 3.29. Multivariate Logistic Regression Model Identifying Prognostic Factors for Septic Shock

	Regression Coefficient (β)	**Odds ratio (OR, 95%)**	**p**
Full Model*			
SOFA score	***0.929***	***2.53 (1.28 - 4.99)***	***0.007***
APACHE II score	- 0.035	0.97 (0.81 - 1.15)	0.702
White Blood Cell (G/L)	- 0.009	0.99 (0.88 - 1.12)	0.880
Platelet count (G/L)	- 0.001	0.999 (0.989 - 1.009)	0.809
Prothrombin ratio (%)	0.007	1.01 (0.96 - 1.06)	0.791
Total Bilirubin (µmol/L)	- 0.004	0.996 (0.985 - 1.007)	0.498
Lactate (mmol/L)	***0.793***	***2.21 (1.31 - 3.73)***	***0.003***
IL-6 (pg/mL)	0.0005	1.000 (0.999 - 1.001)	0.899
PCT (ng/mL)	0.011	1.01(0.99 - 1.04)	0.377
Thrombomodulin (ng/mL)	***0.836***	***2.31 (1.02 - 5.23)***	***0.045***
Reduced Model**			
Thrombomodulin (ng/mL)	***0.765***	***2.15 (1.11 - 4.15)***	***0.023***
Lactate (mmol/L)	***0.760***	***2.14 (1.35 - 3.39)***	***0.001***
SOFA score	***0.791***	***2.21 (1.39 - 3.50)***	***0.001***

* *Full model: Includes all variables*

*** Reduced model: Based on the Backward Stepwise method.*

The multivariate logistic regression analysis using the reduced model identified SOFA score, serum lactate, and serum thrombomodulin as independent predictors of septic shock, with odds ratios (ORs) of 2.21 (95% CI: 1.39 - 3.50, p = 0.001), 2.14 (95% CI: 1.35 - 3.39, p = 0.001), and 2.15 (95% CI: 1.11 - 4.15, p = 0.023), respectively.

3.3.4. Prognostic Value of Serum Thrombomodulin for Mortality

Table 3.30. Prognostic Value of Serum Thrombomodulin for Mortality Compared to Other Factors at T0

Variable	Optimal Cutoff	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC	95% CI		p
MAP (mmHg)	≤ 64	86.4	63.2	47.5	92.3	0.183	0.088	0.279	< 0.001
SOFA score	***> 5***	***100***	***45.6***	***41.5***	***100***	***0.787***	***0.683***	***0.892***	***< 0.001***
APACHE II score	***> 17***	***72.7***	***71.9***	***50.0***	***87.2***	***0.732***	***0.607***	***0.856***	***0.001***
SIC score	> 3	86.4	43.9	37.3	89.3	0.686	0.562	0.811	0.011
Platelet count (G/L)	≤ 250	100	29.8	35.5	100	0.672	0.557	0.774	0.007
Prothrombin ratio (%)	≤ 67	81.8	43.9	36.0	86.2	0.585	0.469	0.695	0.218
Ionized Calcium (mmol/L)	≤ 0.85	45.5	87.7	58.8	80.6	0.671	0.556	0.773	0.022
Blood urea ((mmol/L))	***> 11.3***	***63.6***	***78.9***	***53.8***	***84.9***	***0.722***	***0.609***	***0.817***	***0.002***
Lactate (mmol/L)	***> 2.43***	***86.4***	***56.1***	***43.2***	***91.4***	***0.738***	***0.615***	***0.860***	***0.001***
IL-6 (pg/mL)	> 226.7	72.7	66.7	45.7	86.4	0.654	0.519	0.788	0.035
Thrombomodulin (ng/mL)	***> 4.74***	***72.7***	***89.5***	***72.7***	***89.5***	***0.823***	***0.702***	***0.944***	***< 0.001***

The optimal cutoff value for predicting mortality using serum thrombomodulin (TM) levels was > 4.74 ng/mL, with an AUC of 0.823 (95% CI: 0.702 - 0.944, p < 0.001), a sensitivity of 72.7%, a specificity of 89.5%, a positive predictive value (PPV) of 72.7%, and a negative predictive value (NPV) of 89.5%.

The optimal cutoff value for SOFA score in predicting mortality was > 5 points, with an AUC of 0.787 (95% CI: 0.683 - 0.892, p < 0.001), a sensitivity of 100%, a specificity of 45.6%, a PPV of 41.5%, and an NPV of 100%.

The optimal cutoff value for APACHE II score in predicting mortality was > 17 points, with an AUC of 0.732 (95% CI: 0.607 - 0.856, p = 0.001), a sensitivity of 72.7%, a specificity of 71.9%, a PPV of 50.0%, and an NPV of 87.2%.

Blood urea (> 11.3 mmol/L, AUC = 0.722, p < 0.05) and lactate (> 2.43 mmol/L, AUC = 0.738, p < 0.05) were good predictors of mortality in septic patients.

SIC score, platelet count, ionized calcium, and IL-6 had AUC values between 0.6 and 0.7, with p < 0.05, indicating limited prognostic value for mortality in these patients.

Table 3.31. Multivariate Cox Regression Model Identifying Prognostic Factors for Mortality

	Regression Coefficient (β)	**Hazard Ratio (HR, 95% CI)**	**p**
Full model*			
Age (years)	- 0.013	0.99 (0.95 - 1.02)	0.478
MAP (mmHg)	- 0.047	0.95 (0.83 - 1.10)	0.509
Mechanical Ventilation (%)	1.087	2.96 (0.50 - 17.67)	0.233
CRRT (%)	***1.854***	***6.39 (1.57 - 26.01)***	***0.01***
SOFA score	0.388	1.47 (0.98 - 2.22)	0.064
APACHE II score	- 0.007	0.99 (0.87 – 1.14)	0.918
SIC score	- 0.772	0.46 (0.19 - 1.10)	0.081
Platelet count (G/L)	- 0.006	0.99 (0.98 - 1.01)	0.504
Prothrombin ratio (%)	- 0.027	0.97 (0.94 - 1.01)	0.111
Ionized calcium (mmol/L)	- 2.275	0.10 (0.01 - 1.79)	0.118
Blood urea ((mmol/L))	***0.085***	***1.09 (1.00 - 1.19)***	***0.049***
Lactate (mmol/L)	- 0.039	0.96 (0.86 - 1.08)	0.503
IL-6 (pg/mL)	0.0007	1.000 (0.999 - 1.000)	0.775
Thrombomodulin (ng/mL)	***0.957***	***2.60 (1.15 - 5.87)***	***0.022***
Reduced model**			
Thrombomodulin (ng/mL)	0.678	1.97 (1.17 - 3.32)	0.011
Mechanical Ventilation (%)	1.644	5.17 (1.36 - 19.65)	0.016
CRRT (%)	1.345	3.84 (1.32 - 11.15)	0.013
SOFA score	0.316	1.37 (1.11 - 1.69)	0.003

* *Full model: Includes all variables*

** *Reduced model: Based on the Backward Stepwise method.*

The multivariate Cox regression analysis using the reduced model identified serum thrombomodulin, mechanical ventilation, continuous renal replacement therapy (CRRT), and SOFA score as independent predictors of 28-day mortality in septic patients, with hazard ratios (HRs) of 1.97 (95% CI: 1.17 - 3.32, p = 0.011), 5.17 (95% CI: 1.36 - 19.65, p = 0.016), 3.84 (95% CI: 1.32 - 11.15, p = 0.013), and 1.37 (95% CI: 1.11 - 1.69, p = 0.003), respectively.

Chapter 4
DISCUSSION

4.1. GENERAL CHARACTERISTICS OF THE STUDY POPULATION

4.1.1. Demographic Characteristics

The mean age in the control group and the septic group in our study was 63.31 ± 6.06 years and 64.22 ± 16.09 years, respectively, with no statistically significant difference between the two groups ($p > 0.05$). Studies have shown that the majority of sepsis patients admitted to the ICU are elderly. In our study, 62% of patients were male and 38% were female. Several studies have reported a higher incidence of sepsis and septic shock in males compared to females, but mortality rates did not significantly differ between genders.

4.1.2. Comorbidities

Our study found that hypertension was present in 39.2% of septic patients, followed by diabetes mellitus (29.1%), coronary artery disease (13.9%), chronic obstructive pulmonary disease (COPD) (13.9%), liver cirrhosis (10.1%), and heart failure (10.1%). Several studies have demonstrated that hypertension, diabetes, cardiovascular diseases, and COPD are common underlying conditions among ICU-admitted septic patients. Effective management, care, and prevention of these comorbidities can help reduce the risk of sepsis and improve hospital and ICU survival rates.

4.1.3. Infection Sources

In our study, respiratory tract infections accounted for 38.0%, gastrointestinal infections for 35.4%, and urinary tract infections for 17.7%. Multiple studies have indicated that respiratory, gastrointestinal, and urinary tract infections are the most common sources of sepsis. Furthermore, research has highlighted that the site of infection is a critical factor in predicting mortality in septic patients.

4.1.4. Blood Culture Results

In our study, positive blood cultures were identified in 20.3% of patients, with Gram-negative bacteria being the predominant pathogens. Other studies have reported negative blood culture rates ranging from 28% to 89% in sepsis patients. A study by Li et al. (2021) found that hospital stay and mechanical ventilation duration were longer in septic patients with positive blood cultures compared to those with negative cultures [91]. A trial assessing the sensitivity of

blood cultures before and after antibiotic administration in emergency departments demonstrated that collecting blood samples 30 - 240 minutes after antibiotic administration resulted in a 50% reduction in blood culture sensitivity [144].

4.2. SERUM THROMBOMODULIN LEVELS AND ITS CORRELATION WITH CLINICAL AND LABORATORY FACTORS

In our study, the incidence of acute kidney injury (AKI) in septic patients was 55.7%, with stage 1 AKI accounting for 25.0%, stage 2 for 47.7%, and stage 3 for 27.3%. A study by Nguyen Hai Ghi et al. reported that the incidence of AKI related to sepsis and septic shock at the 108 Military Central Hospital was 64.7% [5]. A multicenter study conducted in 24 European countries reported an AKI incidence of 51% in septic patients [128]. Similarly, Wang et al. studied 2,175 septic patients in 18 ICUs across China and found an AKI incidence of 61.7% [149]. A study by Inkinen et al. reported that 51.1% of septic patients developed AKI, with stage 1 accounting for 19.7%, stage 2 for 8.7%, and stage 3 for 22.6% [66]. These studies demonstrate that AKI is highly prevalent in septic patients, though the reported incidence varies, likely due to differences in diagnostic criteria for sepsis, AKI, and patient selection methods.

4.2.6. Serum Thrombomodulin Levels in Control Group and Sepsis Patient Group

Our study found that the median serum thrombomodulin (TM) level in control group, with a mean age of 63.31 ± 6.06 years, was 1.09 ng/mL. Similarly, Keshk et al. investigated thrombomodulin levels in control group with normal body weight and reported an average plasma TM level of 1.56 ± 0.29 ng/mL [75]. Minakami et al. examined control group, showing that serum TM levels were 1.8 ± 0.2 ng/mL in females and 1.9 ± 0.4 ng/mL in males [113].

In our study, the median serum TM level in sepsis patient group was 3.88 ng/mL. This finding is in line with Inkinen et al. (2019), who reported a median TM level of 5.30 ng/mL in sepsis patient group [65].

Furthermore, Mihajlovic et al. (2015) reported that sepsis patient group with multiple organ dysfunction syndrome (MODS) had significantly higher TM levels (10.40 ± 4.58 ng/mL) compared to those without MODS (7.6 ± 3.10 ng/mL, $p < 0.05$) [111]. A study by Yue et al. (2021) found that the mean serum TM level in sepsis patient group was 9.27 ± 3.19 ng/mL [160]. Zhou et al. (2022) reported a median TM level of 6.82 ng/mL in sepsis patient group [164].

These studies consistently show that serum TM levels are markedly elevated in sepsis patient group, supporting its role as a biomarker of endothelial injury. When the endothelium is damaged due to inflammation, hypoxia, or microvascular dysfunction, thrombomodulin is released into the bloodstream, where it exerts anticoagulant, anti-inflammatory, and anti-apoptotic effects.

4.2.8. Correlation Between Thrombomodulin and Clinical and Laboratory Variables at T0

4.2.8.1. Correlation Between Thrombomodulin and Clinical Variables

In our study, serum thrombomodulin (TM) levels showed a moderate negative correlation with systolic arterial pressure (SAP) ($r = -0.353$, $p = 0.001$) and central venous pressure (CVP) ($r = -0.326$, $p = 0.003$), as well as a weak negative correlation with mean arterial pressure (MAP) ($r = -0.290$, $p = 0.01$). Additionally, serum TM levels demonstrated a moderate positive correlation with mechanical ventilation duration ($r = 0.425$, $p < 0.001$) and weak positive correlations with continuous renal replacement therapy (CRRT) duration ($r = 0.233$, $p = 0.038$), APACHE II score ($r = 0.320$, $p = 0.004$), SOFA score ($r = 0.255$, $p = 0.023$), and SIC score ($r = 0.256$, $p = 0.023$). Our findings are consistent with previous studies by Johansen et al. (2015), Yue et al. (2021), Zhou et al. (2022), Ostrowski et al. (2013), Lin et al. (2017), Rodrigues et al. (2020), Mei et al. (2019), Zhang et al. (2021), Intenov et al. (2017), Khattab et al. (2021), and Schønemann-Lund et al. (2022).

These studies indicate that higher serum TM levels are associated with increased disease severity. Thrombomodulin levels in endothelial cells and circulation are tightly regulated to maintain homeostasis and rapidly respond to coagulation and localized inflammation during endothelial injury [32]. In vascular injury-related conditions such as infections, sepsis, and inflammation, elevated soluble TM levels result from proteolytic cleavage by neutrophil-derived enzymes and membrane-bound proteases [35].

4.2.8.2. Correlation Between Thrombomodulin and Laboratory Variables

Our study found a weak positive correlation between serum TM levels and blood lactate levels ($r = 0.231$, $p = 0.04$). In contrast, studies by Zhou et al. (2022) and Ostrowski et al. (2013) reported stronger positive correlations between serum TM and blood lactate levels ($r = 0.458$, $p < 0.001$ and $r = 0.58$, $p = 0.008$, respectively). These findings suggest a strong association between endothelial injury and tissue

perfusion. In critically ill patients, particularly those with sepsis and septic shock, elevated lactate levels are commonly observed and strongly correlate with sepsis severity and mortality. Lactate is a widely used biomarker for tissue hypoxia, serving as an essential prognostic indicator in sepsis management. Our study also found a weak positive correlation between serum TM and blood urea levels ($r = 0.223$, $p = 0.048$) but a stronger positive correlation between TM and serum creatinine on days 2 and 7 ($r = 0.455$ and $r = 0.513$, respectively, $p < 0.001$). These findings align with studies by Ho et al. (2003), Mota et al. (2018), Lin et al. (2017), Yamazaki et al. (2023), and Drożdż et al. (2018).

The majority of studies confirm a significant correlation between serum TM and blood urea/creatinine levels, supporting TM's role as a biomarker for acute kidney injury (AKI). According to KDIGO 2012 guidelines, serum creatinine is a key biomarker for AKI assessment, but it typically rises late in the course of AKI. In contrast, serum TM increases earlier, making it a promising early biomarker for AKI detection. Early identification of AKI using TM could guide timely interventions, potentially reducing complications and mortality in septic ICU patients.

4.3. PROGNOSTIC VALUE OF SERUM THROMBOMODULIN FOR ACUTE KIDNEY INJURY AND MORTALITY

4.3.2. Prognostic Value of Serum Thrombomodulin for Acute Kidney Injury

In our study, the median serum thrombomodulin (TM) level in septic patients with acute kidney injury (AKI) was 4.56 ng/mL, which was significantly higher than that in septic patients without AKI (3.56 ng/mL, $p < 0.001$). These findings are consistent with previous studies by Inkinen et al. (2019), Lin et al. (2022), Katayama et al. (2017), Bouchard et al. (2015), Mota et al. (2018), Hatton et al. (2021), and Atreya et al. (2023).

Our study demonstrated that serum thrombomodulin has excellent predictive receiver operating characteristic (ROC) curve (AUC) of 0.844 ($p < 0.001$). Multivariate logistic regression analysis (reduced model) identified serum TM as an independent predictor of AKI, with an odds ratio (OR) of 6.24 (95% CI: 2.42 - 16.13, $p < 0.001$). The optimal cutoff value for predicting AKI was 4.14 ng/mL.

Elevated serum TM levels indicate ongoing endothelial injury and dysfunction, which is associated with disease severity and prolonged

multi-organ dysfunction, particularly affecting the kidneys. Endothelial-stabilizing therapies may represent a promising approach for the management of AKI in septic patients.

4.3.3. Prognostic Value of Thrombomodulin for Septic Shock

The results of our study indicate that the median serum thrombomodulin (TM) level in patients with sepsis without shock was 3.75 ng/mL (range: 2.32 - 6.46 ng/mL), which was significantly lower compared to patients with septic shock (4.75 ng/mL, range: 3.00 - 6.44 ng/mL, $p < 0.001$). Serum TM exhibited a good predictive value for septic shock, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.761 (95% confidence interval [CI]: 0.652 - 0.871, $p < 0.001$). The optimal cutoff value for predicting septic shock was 3.92 ng/mL. Multivariate logistic regression analysis (reduced model) confirmed that serum thrombomodulin is a strong predictor of septic shock, with an odds ratio (OR) of 2.15 (95% CI: 1.11 - 4.15, $p = 0.023$). Our findings are consistent with previous studies by Yin et al. (2013), Lin et al. (2017), Khattab et al. (2021), Mahmoud et al. (2021), Zhou et al. (2022), and Zhang et al. (2021), which also highlight the prognostic significance of serum TM levels in sepsis-related shock.

Moreover, prior research has established that serum thrombomodulin levels are markedly elevated in patients with multiple organ dysfunction syndrome (MODS), with higher TM concentrations correlating with increased severity of organ damage. Recent studies have also highlighted serum TM as an independent predictor of adverse outcomes in septic patients. These findings emphasize the critical role of endothelial dysfunction in the pathogenesis of sepsis and underscore the necessity of early identification and intervention for disseminated intravascular coagulation (DIC) and septic shock in this patient population.

4.3.4. Prognostic Value of Thrombomodulin for Mortality

In our study, the 28-day mortality rate was 27.8% (22 cases). The findings demonstrated that the median serum thrombomodulin levels in the survivor and non-survivor sepsis patients were 3.78 ng/mL and 5.41 ng/mL, respectively, with a statistically significant difference ($p < 0.001$). Serum thrombomodulin demonstrated a strong prognostic value for mortality in septic patients, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.823 (95% confidence interval [CI]: 0.702 - 0.944, $p < 0.001$). The optimal cutoff

value for predicting mortality was 4.74 ng/mL. Multivariate Cox regression analysis (reduced model) identified serum thrombomodulin as an independent predictor of mortality, with a hazard ratio (HR) of 1.97 (95% CI: 1.17 - 3.32, p = 0.011). Several previous studies have also demonstrated the significant prognostic value of serum TM in sepsis-related mortality, including research by Lin et al. (2017), Mahmoud et al. (2022), Monteiro et al. (2021), Li et al. (2022), Yin et al. (2013), Inkinen et al. (2019), and Zhang et al. (2021).

These findings provide substantial evidence that most septic patients experience severe endothelial cell injury early in the disease course. This is supported by abnormalities in endothelial biomarkers and their strong correlation with adverse clinical outcomes, including the progression to septic shock, disseminated intravascular coagulation (DIC), multiple organ dysfunction syndrome (MODS), and sepsis-related mortality.

CONCLUSION

Based on the study investigating the prognostic value of serum thrombomodulin in acute kidney injury (AKI) and mortality among 79 patients with sepsis admitted to the Intensive Care Unit of Hue Central Hospital, we have drawn the following conclusions:

1. Serum Thrombomodulin Levels and Their Correlation with clinical and laboratory parameters in Patients with Sepsis

- The serum thrombomodulin level in septic patients was 3.88 ng/mL, with 3.78 ng/mL in males and 3.90 ng/mL in females, significantly higher than in the control group (1.09 ng/mL, $p < 0.05$).
- A moderate negative correlation was observed between serum thrombomodulin levels and systolic blood pressure (SBP) ($r = -0.353$, $p = 0.001$) and central venous pressure (CVP) ($r = -0.326$, $p = 0.003$), while a weak negative correlation was found with mean arterial pressure (MAP) ($r = -0.290$, $p = 0.01$).
- A moderate positive correlation was identified between serum thrombomodulin levels and duration of mechanical ventilation ($r = 0.425$, $p < 0.001$).
- Weak positive correlations were noted between serum thrombomodulin levels and continuous renal replacement therapy (CRRT) duration ($r = 0.233$, $p = 0.038$), APACHE II score ($r = 0.320$, $p = 0.004$), SOFA score ($r = 0.255$, $p = 0.023$), and SIC score ($r = 0.256$, $p = 0.023$).

- Weak positive correlations were also observed with serum lactate levels ($r = 0.231$, $p < 0.05$) and serum urea levels ($r = 0.223$, $p < 0.05$).

- A relatively strong positive correlation was found between serum thrombomodulin levels and serum creatinine levels on day 2 ($r = 0.455$, $p < 0.05$) and serum creatinine levels on day 7 ($r = 0.523$, $p < 0.05$).

2. Prognostic Value of Serum Thrombomodulin for Acute Kidney Injury and Mortality in Patients with Sepsis

- The serum thrombomodulin level in septic patients with acute kidney injury was 4.56 ng/mL, significantly higher than in those without AKI (3.56 ng/mL, $p < 0.05$).

- The serum thrombomodulin level in survivors was 3.78 ng/mL, significantly lower than in non-survivors (5.41 ng/mL, $p < 0.05$).

- The optimal cutoff value for predicting acute kidney injury was > 4.14 ng/mL, with an area under the curve (AUC) of 0.844 (95% CI: 0.754 - 0.933, $p < 0.001$). Multivariate logistic regression analysis (reduced model) demonstrated that serum thrombomodulin is an independent predictor of AKI with an odds ratio (OR) of 6.24 (95% CI: 2.42 - 16.13, $p < 0.05$).

- The optimal cutoff value for predicting mortality was > 4.74 ng/mL, with an AUC of 0.823 (95% CI: 0.702 - 0.944, $p < 0.05$). Multivariate Cox regression analysis (reduced model) showed serum thrombomodulin as an independent predictor of mortality, with a hazard ratio (HR) of 1.97 (95% CI: 1.17 - 3.32, $p < 0.05$).

RECOMMENDATIONS

Based on the study findings, we propose the following recommendations:

1. Serum thrombomodulin testing should be integrated into clinical practice as a prognostic biomarker for acute kidney injury and mortality in septic patients, particularly in intensive care units.

2. The application of serum thrombomodulin cutoff values for clinical prognosis:

- Septic shock: > 3.92 ng/mL
- Acute kidney injury: > 4.14 ng/mL
- 28-day mortality: > 4.74 ng/mL

3. Further studies on the value of serum thrombomodulin in patients with sepsis are needed, with larger sample sizes and multicenter designs.

LIST OF RELATED PUBLISHED SCIENTIFIC WORKS OF THE AUTHOR

1. Van Tri Nguyen, Hong Ngoc Nguyen-Phan, That Ngoc Ton, Bui Bao Hoang (2023), "Value of Serum Thrombomodulin as a Marker and Predictor in Patients with Sepsis-Associated Acute Kidney Injury", International Journal of General Medicine. 10 (16), pp.2933-2941. doi: 10.2147/IJGM.S417410
2. Van Tri Nguyen, Hong Ngoc Nguyen-Phan, Bui Bao Hoang (2023), "Serum Thrombomodulin Level Can Predict Mortality in Patients With Sepsis?", Medical Archives. 77(6), pp.433-439. doi: 10.5455/medarh.2023.77.433-439
3. Nguyen Van Tri, Nguyen Tat Dung, Hoang Bui Bao (2024), "Characteristics of acute kidney injury and mortality in patients with sepsis and septic shock", Hue Journal of Medicine and Pharmacy - Hue University of Medicine and Pharmacy, Vol. 14, No. 1 (2024), pp. 71-77. doi: 10.34071/jmp.2024.1.10.