Are serum thrombomodulin and interleukin-8 levels associated with disease severity and mortality in critically ill children with respiratory failure?

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Informed consent: Informed consent was obtained from all individual participants included in the study.

Abstract

Background/aim: Thrombomodulin (TM) is found on the endothelial cell surface and increases in response to endothelial injury of different organs. Interleukin-8 (IL-8) regulates pulmonary inflammation. They are candidates for a biological marker of acute respiratory distress syndrome (ARDS). The aim of the present study was to compare TM and IL-8 levels in pediatric patients with and without ARDS who received respiratory support and to determine its relationship with prognosis.

Materials and methods: This was a prospective observational study of 55 patients who received respiratory support at Pediatric Intensive Care Unit were examined. 18 patients without active infection were defined as the control group. Two blood samples were taken for serum IL-8 and TM levels on the first and third days of respiratory support.

Results: The patient group had significantly higher IL-8 and TM levels than the control group [IL-8: median 102.7 (IQR,180.42 - 189.47) vs. 45.4 (70.49 - 55.14) ng/L, p = 0.011, respectively. TM: median 6.9 (9.18 - 6.83) vs. 3.4 (5.05 - 3.62) ng/mL**,** p = 0.021, respectively]. Patients with ARDS had significantly higher markers levels on the first and third days than those who did not have ARDS.

The TM and IL-8 levels of the deceased patients were significantly higher than those of the survivors on the first day.

In mortality prediction, the cut-off point for IL-8 was found to be > 154.7 ng/L, which had a sensitivity of 76.9% and a specificity of 73.8%. The cut-off point for TM was found as > 8.4 ng/mL, which had a sensitivity of 76.9% and a specificity of 66.7%.

Conclusion: In our study, higher markers were correlated to impaired oxygenation and higher mortality. Higher TM and IL-8 levels in ARDS might reflect the degree of vascular injury and inflammation.

Key words: Acute Respiratory Distress Syndrome, Interleukin-8, Thrombomodulin

1. Introduction

Acute respiratory distress syndrome (ARDS) refers to acute lung injury affecting both lungs, which results from the disruption of the alveolocapillary membrane and is characterized by diffuse infiltration of the lungs [1]. Lung injury and inflammation become widespread with cytokine activation and the release of proinflammatory mediators [2]. It has been shown that the interleukin-8 (IL-8) level measured at the beginning of ARDS is correlated to a worse prognosis and increased mortality [3,4]. Thrombomodulin (TM) is found on endothelial cell surface and increases in response to endothelial injury of different organs. However, it is mostly expressed in the lungs. Increased plasma TM level reflects inflammation, endothelial injury, and a tendency to thrombosis [5]. TM is a biological candidate marker for respiratory failure and ARDS. Our primary aim in conducting the present study was to compare TM and IL-8 levels in pediatric patients with respiratory failure with or without ARDS who were provided with respiratory support with mechanical ventilation, and to determine their relationship with prognosis. Our secondary aim was to evaluate the relationship between the levels of TM, IL-8 and the oxygenation index (OI), extrapulmonary organ failure, number of days on mechanical ventilator, and the number of days spent in Pediatric Intensive Care

Unit (PICU), and also to compare IL-8 and TM levels in patient groups with or without ARDS to determine whether they are risk factors for developing ARDS.

2. Materials and methods

2.1. Study design

A total of 55 patients, including 34 patients receiving invasive mechanical ventilator (IMV) support and 21 patients receiving noninvasive mechanical ventilator (NIMV) support due to respiratory failure lasting longer than 72 hours in the Pediatric Intensive Care Unit of Health Sciences University Umraniye Training and Research Hospital between March 2022 and December 2022, were included in the single-center and prospective study.

Eighteen patients without active infection were defined as the control group. The study was approved by the local ethical committee in Health Sciences University Umraniye Training and Research Hospital (B.10.1.THK.4.34.H.GP.0.01/51) and complied with the Declaration of Helsinki and its later amendments. The Informed consents of the patients and control groups were obtained.

2.2. Data and blood sample collection

The clinical, demographic, and laboratory data of the patients were recorded.

The pediatric risk score of mortality (PRISM) of patients started on ventilator support for respiratory failure was calculated at the first 24 hours of treatment while the organ failure index (OFI) and pediatric logistic organ score (PELOD) were calculated at 24th and 72nd hours of treatment.

Saturation / FiO_2 (S/F) ratio was calculated in patients who received non-invasive respiratory support, saturation index (OSI: (FiO_2 × mean airway pressure × 100 / SpO_2) in those who received invasive mechanical ventilation support, and vasoactive inotrope

score (VIS) in those who received inotropic drug support at 24th and 72nd hours of treatment. The relationship between ARDS development and IL-8 and TM levels was evaluated on the first and third days of respiratory support. Immunosuppressed patients, patients using corticosteroids (at a dose of more than 1 mg/kg/day for longer than 1 month), and patients with missing medical records were excluded.

IL-8 and TM kits were studied at Farmasina Medical and Chemical Products Industries and Foreign Trade Ltd. Co. using a ELX800DA model Diagnostic Automation Inc. device and the KC junior program. Venous blood samples were taken for serum IL-8 and TM levels at 24th and 72nd hours of respiratory support treatment, simultaneously with the samples taken for other tests. After the samples were centrifuged at 4000 rpm for 10 minutes, their sera were separated into an Eppendorf tube and stored at -80 ° until biochemical analyses. Venous blood samples obtained from the control group were also centrifuged and stored at -80°.

2.3. Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics 22 software. Normality of distribution of the study parameters was tested using Kolmogorov-Smirnov test. Descriptive statistics included mean, standard deviation, and frequency. Non-normally distributed continuous variables were compared between the study groups using Kruskal Wallis test. Student's t test was used to compare normally distributed parameters between the two groups while Mann Whitney-U test was used to compare non-normally distributed parameters. Categorical parameters were compared using Fisher's Exact Chi-Square and Continuity (Yates) Correction. Multivariate analysis was carried out with logistic regression analysis. When the effects of NIMV/MV, sepsis, ARDS, inotrope requirement, days of PICU stay, first day IL-8 and TM levels, 1st and 3rd day PRISM,

PELOD, OFI, OSI scores, 3rd day total protein, C-reactive protein (CRP), procalcitonin (PCT) levels, 1st and 3rd day platelet (PLT) levels on mortality were evaluated by Backward stepwise logistic regression analysis; the model was found to be significant. ($p = 0.001$; $p < 0.05$). The Negelkerke R square level was 0.755 and the explanatory coefficient of the model (88.2%) was found to be at a good level. When we

The best cut-off points were determined using the ROC curve analysis. Pearson correlation analysis was used to test correlations between normally distributed parameters; Spearman's rho correlation analysis was used to test correlations between non-normally distributed parameters. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics of patients

The study was performed with a total of 55 patients, 52.7% (n = 29) females and 47.3% (n = 26) males, aged between 1 month and 17 years. The mean age of the patients was 64.16 ± 66.21 months. 38.2% (n = 21) of patients received respiratory support with NIMV and 61.8% (n = 34) of patients received respiratory support with IMV. Clinical characteristics of the patients are summarized in Table 1. Clinical signs of sepsis and ARDS were present in 54.5% (n = 30) and 29.1% (n = 16) of the patients, respectively. ARDS was mild in 12.5%, moderate in 43.8% and severe in 43.8% of patients. The etiology of patients with ARDS included respiratory failure, sepsis and bronchopneumonia, whereas patients without ARDS included MISC, cardiac diseases, neurological diseases and sepsis. An underlying disease was found in 81.8% (n = 45) of the patients. 47.3% (n = 26) of the patients were admitted to the PICU for respiratory failure. 72.7%) (n = 40) of patients underwent blood product transfusions. Failure of an organ was present in 49.1% of patients, failure of two organs in 38.2%, failure of three

organs in 10.9%, and failure of 4 organs in 1 patient. 27.3% patients needed inotropic drug infusion. The survival rate of the patients was 76.4%. The patient and control groups were compared with respect to age and sex, and no significant difference was found between the two groups.

3.2. Parameters changing between 24th and 72nd hours

Table 2 presents comparison of the patients' biochemical and blood gas parameters and scores on the first and third days. The decrease in CRP, PCT, white blood cell count (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, lactate, and partial carbon dioxide pressure ($PaCO_2$) seen on the third day compared to the first day was statistically significant. Significant differences were also found in the PRISM, PELOD, OFI, OSI scores on the third day compared with the first day.

3.3. Serum levels of IL-8 and TM

Table 3 presents comparison of the IL-8 and TM levels of the groups. IL-8 and TM levels of the patient group were significantly higher than those of the control group [IL-8: median 102.7 (IQR,180.42 - 189.47) vs. 45.4 (70.49 - 55.14) ng/L, p = 0.011, respectively. TM: median 6.9 (9.18 - 6.83) vs. 3.4 (5.05 - 3.62) ng/mL, p = 0.021, respectively]. As shown in Figure 1 and Figure 2, serum IL-8 and TM levels on the 3rd day were significantly lower than those on the 1st day. There was no significant difference between the patients who received NIMV and those who received IMV with respect to the IL-8 and TM levels on the first and third days. Again, as presented in Table 3, both IL-8 and TM levels of the patients with ARDS were significantly higher than those of patients without ARDS. IL-8 levels on the first and third days of patients with ARDS were median 176.6 (303.75 ± 223.08) - 90.2 (118 ± 76.55) ng/L, respectively and IL-8

levels on the first and third days of patients without ARDS were 61.5 (129.82 ± 149.46) - 43.2 (85.64 ± 93.62) ng/L, respectively. TM levels on the first and third days of patients with ARDS were 12.3 (13.85 ± 6.81) - 7.2 (9.42 ± 6.49) ng/mL, respectively and TM levels on the first and third days of patients without ARDS were 4.1 (7.26 ± 5.92) - 3.3 (5.4 ± 4.85) ng/mL, respectively. There was no significant difference between the IL-8 and TM levels by the presence of sepsis and the ARDS classification. No significant difference was found between the IL-8 and TM levels on the first and third days of the patients with and without sepsis.

3.4. Performance of biomarkers in predicting mortality

Table 4 presents comparison of the patients' clinical characteristics and laboratory parameters by their prognosis. There was a significant, positive relationship of moderate degree between the IL-8 level on the first day and the number of failed organs, PELOD score, and AST level. There was a moderately strong, positive correlation between the TM level on the first day and the number of failed organs, AST and activated partial thromboplastin time (aPTT). There was a weak, negative correlation between the TM level on the first day and the levels of albumin, total protein. The deceased patients had a significantly higher TM level on the first day than the survivors; no significant difference was found between the TM levels on the third day.

As compared with the surviving patients, the deceased patients had a higher number of days spent in PICU and on NIMV/IMV, PRISM, PELOD, OSI, OFI scores, and CRP and PCT levels on the third day although they had a lower total protein level on the third day and a lower PLT on the first and third days. The two groups had no significant difference with respect to other parameters. Risk factors affecting mortality are presented in Table 5. A logistic regression analysis was performed to determine the risk factors affecting

mortality. The effects of the IL-8 level on the first day, PLT on the third day, OFI score on the first day, and OSI score on the first day had statistically significant effects on the model. Mortality risk was increased by 1.017-fold by a high IL-8 on the first day, 0.972-fold by a low PLT on the third day, 11.418 folds by a high OFI score on the first day, and 2.733 folds by a high OSI score on the first day. As shown in Figure 3, according to the ROC analysis, the area under the curve (AUC) of IL-8 level was found to be 0.723 (95% CI:0.558-0.888). The cut-off point of IL-8 level for mortality prediction was found as > 154.7 ng/L. This cut-off value had a sensitivity of 76.9% and a specificity of 73.8%. As shown in Figure 4, according to the ROC analysis, the area under the curve (AUC) of TM level was found to be 0.715 (95% CI:0.542 - 0.882). The cut-off point of TM level for mortality prediction was found as > 8.4 ng/mL. This cut-off value was found to have a sensitivity of 76.9% and a specificity of 66.7%.

4. Discussion

Thrombomodulin is an endothelial and pulmonary capillary transmembrane protein, which has an active role in coagulation and inflammation. Its circulating level is normally very low but increases in inflammatory conditions such as sepsis or ARDS [6]. It is a candidate biological marker for respiratory failure and ARDS. TM plays an important role in the development of the lungs; it increases in response to endothelial injury of different organs, although it is most commonly expressed in the lungs. In a study conducted in adults with acute respiratory distress, increased TM level was shown to be correlated to a higher mortality [7].

In a study involving 432 pediatric patients treated with invasive mechanical ventilation for acute respiratory failure, Monteiro et al. [8] reported that TM level ranged between 16.6 and 670.9 ng/mL in the first 5 days of intubation, and an increased TM level was

associated with an increased 90- day mortality rate and a worse OI. They also reported that both initial TM level and TM level during follow-up were correlated to extrapulmonary multiorgan failure risk and the severity of hypoxic respiratory failure, and that increased TM level reflected increased dead space ventilation in patients with ARDS. These findings suggested that vascular injury plays a role in the pathogenesis of acute respiratory failure, and it can provide a potential contribution to the determination of treatment targets. Our study also showed that TM level measured in the first 3 days of intubation was significantly higher in patients with ARDS (12.3 (13.85 ± 6.81) vs 7.2 (9.42 ± 6.49) ng/mL) who underwent invasive mechanical ventilation compared with patients without ARDS (4.1 (7.26 ± 5.92) vs 3.3 (5.4 ± 4.85) ng/mL).

Orwoll et al. [9], in a prospective study involving 243 pediatric patients diagnosed with lung injury, reported that increased sTM level was associated with increased mortality and a greater rate of organ dysfunction. In accordance with the literature, our study found a moderately strong (44%), positive, and statistically significant correlation between increased TM level and the number of failed organs. Similarly, TM level measured at 24th hour was correlated to an increased mortality rate (Figure 2).

A study published in 2017, which was conducted in previously healthy pediatric patients admitted to PICU for septic shock, reported that TM levels measured on the first and third days were significantly higher in the patient group than the healthy control group. Similarly, the deceased patients had a significantly higher TM level than the survivors (9.9 mU/mL vs 4.4 mU/mL, $p = 0.046$). There was a positive correlation between serum thrombomodulin level and PRISM, PELOD, P-MODS, and disseminated intravascular coagulation (DIC) scores on the first day [10]. Similarly, our study found that the patient group had a significantly higher TM level on the first day than the control group (6.9

(9.18 - 6.83) vs. 3.4 (5.05 - 3.62) ng/mL, respectively, p = 0.021). However, no significant correlation was found between TM level and the PRISM, PELOD, OFI scores on the first day, and sepsis.

Previous animal experiments have shown that recombinant TM shows a protective effect in septic mice by suppressing leukocyte adhesion in the microvascular space, reducing thrombus formation, and preventing endothelial injury [11]. Data from another study in mice suggested that TM has protective properties in LPS-mediated ARDS [12].

Randomized controlled studies on adult patients with DIC have compared treatment with recombinant sTM and heparin; it has been reported that treatment with TM has provided a better improvement [13]. In a study on pediatric patients with acute respiratory failure who were intubated and provided respiratory support with mechanical ventilation, Carlton et al. reported that there was no significant correlation between functional deterioration and serum IL-8 and thrombomodulin levels on the first day of intubation, but serum thrombomodulin level was higher on the second and third days in patients with a deteriorated but serum thrombomodulin level was higher on the second and third days in patients with a deteriorated functional status than those without [14].

IL-8 secretion is induced by TNF and IL-1, which are classical proinflammatory cytokines secreted in the early stages of inflammation. IL-8 is secreted by pulmonary endothelial cells in injuries caused by toxins or infections. It was determined that IL-8 concentration in bronchoalveolar lavage was 5-10 folds higher in intubated patients compared with the control group [15]. A correlation was shown between increased IL-8 levels in both plasma and bronchoalveolar lavage fluid and death and multiorgan failure in adult ARDS patients [16]. It is considered that serially measured IL-8 levels can be used as a marker of treatment efficacy in pediatric patients with sustained inflammation,

particularly those with ARDS and respiratory failure. In a multicenter study dated 2017, which was conducted by Zinter et al. on pediatric ARDS patients, it was determined that IL-6, IL-8, IL-10, and TNF-R2 were strongly correlated to mortality, and there was a positive correlation between these biomarkers and OI and PRISM scores [17]. Our study found significantly higher IL-8 levels in the patient group than the control group (IL-8: median 102.7 (180.42 ± 189.47) – 45.4 (70.49 ± 55.14) ng/L, respectively $p = 0.001$). Serum IL-8 level measured on the first day was significantly higher in patients with ARDS than those without (176.6 (303.75 ± 223.08) - 61.5 (129.82 ± 149.46) ng/ L, respectively, $p = 0.001$).

Flori et al. conducted a prospective study on pediatric patients intubated for respiratory failure. In that study, which was conducted in 22 pediatric intensive care units on 480 patients, the authors aimed to evaluate the relationship between plasma IL-8 level measured serially in the early stage and ARDS development and the other markers of prognosis in pediatric patients mechanically ventilated for acute respiratory failure. They reported that the highest IL-8 level was determined on the first day of intubation, and IL-8 level gradually decreased during follow-up. An analysis based on patient subgroups revealed the highest levels in the sepsis group and the lowest level in the asthma group. Serum IL-6 level was highest in patients with ARDS than those without. Similarly, it was reported that serum IL-8 level was 4-12 folds higher in deceased patients compared with the surviving ones. Serum IL-8 level was significantly correlated to mortality, duration of mechanical ventilation, and the number of days spent in PICU, but not ARDS development [18]. In our study, patients with respiratory failure were provided with respiratory support by means of NIMV or IMV. No significant difference was found between patients treated with NIMV or IMV regarding the IL-8 levels on the first and

third days. Unlike other studies, IL-8 level was found to be significantly higher in patients who developed ARDS. The highest IL-8 level was observed on the first day of intubation (180.4 ng/L); a decrease occurred on the 3rd day (95.05 ng/L). There was no significant difference between patients with or without sepsis. No significant correlation was found between the number of days spent in PICU and serum IL-8 level.

The limitations of our study include its single-center design, and the lack of the evaluation the relationship between viral and bacterial pathogens detected by respiratory tract viral multiplex examination and tracheal aspirate culture proliferations and serum TM and IL-8 levels. Another limitation of our study is that the results cannot be generalized to the immunocompromised patient population because they were excluded from the study.

5. Conclusion

In conclusion, higher TM and IL-8 levels in pediatric patients who received invasive and non-invasive respiratory support for respiratory failure were found to be correlated to impaired oxygenation, higher mortality, and a higher number of failed organs. Higher TM and IL-8 levels in ARDS might reflect the degree of vascular injury and inflammation. A gradual decline in IL-8 and TM levels during the patients' follow-up suggests that these parameters can be used as biomarkers both for determining treatment objective and predicting prognosis. However, larger studies are needed to use TM and IL-8 as biomarkers.

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Table 1: Clinical characteristics of the patients

Study		**Min-Max**	**Mean ± SD**	**Median**
PICU (days)		3 - 123	24.29 ± 28.09	13
NIMV/ IMV days (n)		3 - 123	18.65 ± 25.37	8
VIS		0 - 240	9.92 ± 34.92	0
			N	**%**
Admission diagnosis	Respiratory Failure		26	47.3
	Sepsis		21	38.2
	MIS-C		3	5.5
	Status Epilepticus		2	3.6
	Postoperative		2	3.6
	Arrhythmia		1	1.8
Underlying disease	Yes		45	81.8
	No		10	18.2
Sepsis	Yes		25	45.5
	No		30	54.5
NIMV/ IMV	NIV		21	38.2
	IMV		34	61.8
ARDS	Yes		39	70.9
	No		16	29.1
ARDS severity (n=16)	Mild		2	12.5
	Moderate		7	43.8
	Severe		7	43.8
Blood product	No		15	27.3
	Yes		40	72.7
Number of failed organs	1		27	49.1
	2		21	38.2
	3		6	10.9
	4		1	1.8
Inotrope	No		40	72.7
	Yes		15	27.3
Mortality	Survived		42	76.4
	Deceased		13	23.6

PICU (days): Number of days spent at Paediatric Intensive Care Unit, NIMV/ IMV days (n): Number of days on non-invasive Mechanical Ventilation/Mechanical Ventilation, VIS: Vasoactive Inotrope Score

Table 2: Comparison of the patients' biochemical and blood gas parameters and scores on the first and third days

	1st day	3rd day	
	Mean ± SD (median)	**Mean ± SD (median)**	**P**
IL-8 (ng/L)	180.42 ± 189.47 (102.7)	95.05 ± 89.53 (70.5)	[1]0.001*
TM (ng/mL)	9.18 ± 6.83 (6.9)	6.57 ± 5.62 (4.4)	[1]0.001*
ALT (u/L)	128.51 ± 496.87 (28)	61.75 ± 126.54 (23)	[1]0.046*
AST (u/L)	239.47 ± 836.26 (48)	75.31 ± 141.27 (28)	[1]0.001*
BUN (mg/dl)	28.53 ± 28.29 (17.9)	20.57 ± 20.96 (13.6)	[1]0.002*
Creatinine (mg/dl)	0.42 ± 0.37 (0.3)	0.35 ± 0.3 (0.2)	[1]0.009*
Calcium (mg/dl)	8.76 ± 0.71 (8.8)	9.01 ± 0.67 (9)	[1]0.003*
CRP (mg/L)	64.18 ± 79.64 (33)	39.14 ± 53.63 (21)	[1]0.001*
PCT (ng/ml)	11.26 ± 24.97 (0.8)	3.25 ± 6.82 (0.5)	[1]0.001*
WBC (10^3 /uL)	11.82 ± 8.32 (11.5)	9.56 ± 6.41 (8.8)	[1]0.003*
pH	7.29 ± 0.17 (7.3)	7.39 ± 0.09 (7.4)	[2]0.001*
PCO_2 (mm/Hg)	49.92 ± 20.88 (46.7)	42 ± 11.25 (40.8)	[2]0.009*
HCO_3 (mmol/L)	21.63 ± 5.88 (22.4)	24.7 ± 4.45 (24)	[2]0.001*
Lactate (mmol/L)	3.22 ± 3.6 (1.8)	2.21 ± 3.73 (1.3)	[1]0.023*
PRISM	9.42 ± 5.14 (9)	6.44 ± 5.12 (7)	0.001*
PELOD	13.67 ± 7.81 (11)	8.89 ± 6.34 (10)	0.001*
OFI	1.6 ± 1.12 (2)	1.22 ± 1.17 (1)	0.001*
OSI	9.2 ± 3.81 (9.1)	7.79 ± 4.12 (6.8)	0.024*
S/F	197.28 ± 47.82 (169)	271.24 ± 30.60 (270)	0.001*

[1]Wilcoxon sign test *[2]Paired Samples t test* *$p < 0.05$*

ALT: Alanine Aminotransferase, AST: Aspartate amino transaminase, BUN: blood urea nitrogen, CRP: C Reactive Protein, PCT: Procalcitonin, WBC: White blood cell count, $PaCO_2$: Partial arterial carbon dioxide pressure, HCO_3: Bicarbonate PRISM: Paediatric Mortality Risk Scoring, PELOD: Paediatric Logistic Organ Dysfunction Score, OFI: Organ Failure Index, OSI: Oxygen Saturation Index, S/F: Saturation/FiO2

Table 3: Comparison of the IL-8 and TM levels of the groups

		Study		Control	
		Mean ± SD (median)		**Mean ± SD (median)**	**p**
IL-8 (ng/L)	1st day	180.42 ± 189.47 (102.7)		70.49 ± 55.14 (45.4)	0.011 *
TM (ng/mL)	1st day	9.18 ± 6.83 (6.9)		5.05 ± 3.62 (3.4)	0.021 *
		ARDS absent	**ARDS present**		
		Mean ± SD (median)	**Mean ± SD (median)**	**P**	
IL-8 (ng/L)	1st day	129.82 ±149.46 (61.5)	303.75 ± 223.08 (176.6)	0.001 *	
	3rd day	85.64 ± 93.62 (43.2)	118 ± 76.55 (90.2)	0.020 *	
TM (ng/mL)	1st day	7.26 ± 5.92 (4.1)	13.85 ± 6.81 (12.3)	0.001 *	
	3rd day	5.4 ± 4.85 (3.3)	9.42 ± 6.49 (7.2)	0.006 *	

Table 4: Comparison of the patients' clinical characteristics and laboratory parameters by their prognosis

		Survivors	**Deceased**	
		Mean ± SD (median)	**Mean ± SD (median)**	**P**
Age (months)		68.9 ± 69.03 (37)	48.85 ± 55.77 (16)	[1]0.545
Number of days on NIMV/IMV		16.12 ± 25.86 (6.5)	26.85 ± 22.75 (20)	[1]0.002*
Number of failed Organs		1.55 ± 0.71 (1)	2 ± 0.82 (2)	[1]0.055
IL-8 (ng/L)	1st day	150.53 ± 174.19 (67.9)	276.98 ±211.3 (173.3)	[1]0.016*
	3rd day	89.63 ± 93.69 (51.2)	112.56 ± 75.13 (83.1)	[1]0.191
TM (ng/mL)	1st day	7.93 ± 6.3 (5.4)	13.2 ± 7.17 (11.8)	[1]0.020*
	3rd day	6.09 ± 5.67 (3.7)	8.12 ± 5.4 (7.3)	[1]0.143
PRISM score	1st day	8.62 ± 5.22 (8)	12 ± 4.06 (12)	[1]0.013*
	3rd day	5.26 ± 4.54 (2.5)	10.23 ± 5.21 (10)	[1]0.001*
PELOD score	1st day	12.5 ± 7.77 (11)	17.46 ± 6.92 (20)	[1]0.008*
	3rd day	7.4 ± 6.13 (10)	13.69 ± 4.46 (12)	[1]0.001*
OFI score	1st day	1.36 ± 1.03 (1)	2.38 ± 1.04 (2)	[1]0.002*
	3rd day	0.93 ± 1 (1)	2.15 ± 1.21 (2)	[1]0.001*
OSI	1st day	7.7 ± 3 (8)	11.62 ± 3.82 (12)	[1]0.002*
	3rd day	6.18 ± 3.35 (6)	10.39 ± 4.04 (10.2)	[1]0.003*
Total protein (g/L)	1st day	54.22 ± 11.62 (54)	50.54 ± 8.68 (51)	[2]0.298
	3rd day	55.42 ± 8.81 (56)	47.8 ± 6.27 (48)	[2]0.006*
C Reaktif Protein (mg/L)	1st day	64.63 ± 83.14 (30.3)	62.75 ± 70.16 (44)	[1]0.866
	3rd day	28.86 ± 35.29 (15.5)	72.36 ± 84.39 (36.8)	[1]0.025*
Procalsitonin (ng/ml)	1st day	7.47 ± 19.69 (0.7)	23.48 ± 35.61 (2.2)	[1]0.061
	3rd day	2.2 ± 4.87 (0.3)	6.66 ± 10.57 (1.3)	[1]0.011*
PLT (10^3 /uL)	1st day	250.26 ± 138.96 (243)	148 ± 154.93 (82)	[2]0.028*
	3rd day	266.81 ± 160.51 (242)	106.77 ± 95.75 (80)	[2]0.001*

[1]Mann Whitney U Test *[2]Student t test* **p < 0.05*

Table 5: Evaluation of risk factors affecting mortality

		95% Confidence Interval		
	OR	**Lower limit**	**Upper limit**	**P**
IL-8 (ng/L) (1st day)	1.017	0.999	1.034	0.047*
PCT (ng/ml) (3rd day)	0.639	0.366	1.116	0.115
PLT (10^3 /uL) (3rd day)	0.972	0.946	0.999	0.044*
PELOD (1st day)	0.657	0.417	1.035	0.070
OFI (1st day)	11.418	0.624	209.042	0.021*
OSI (1st day)	2.733	0.887	8.418	0.040*

PELOD: Paediatric Logistic Organ Dysfunction Score, OFI: Organ Failure Index, OSI: Oxygen Saturation Index, IL-8: Interleukin-8. PCT: Procalcitonin, PLT: Platelet

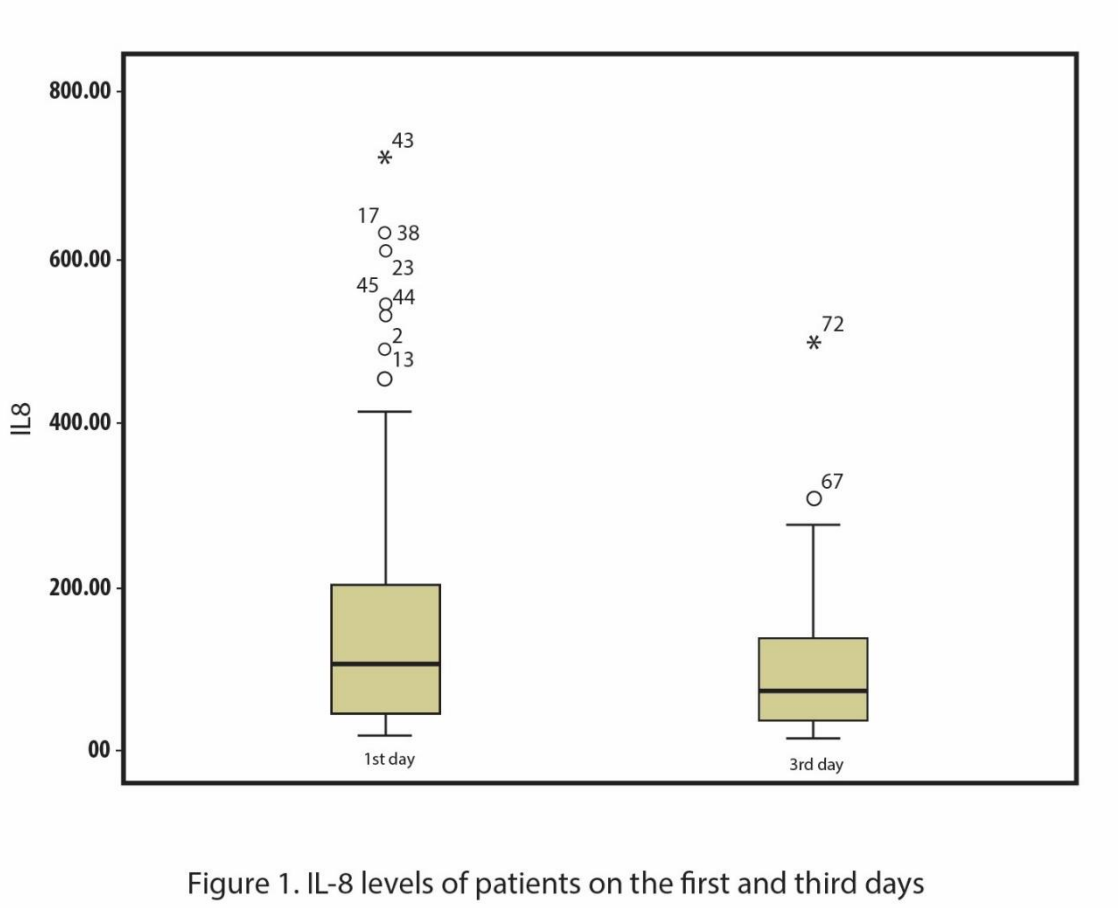

Figure 1. IL-8 levels of patients on the first and third days

1

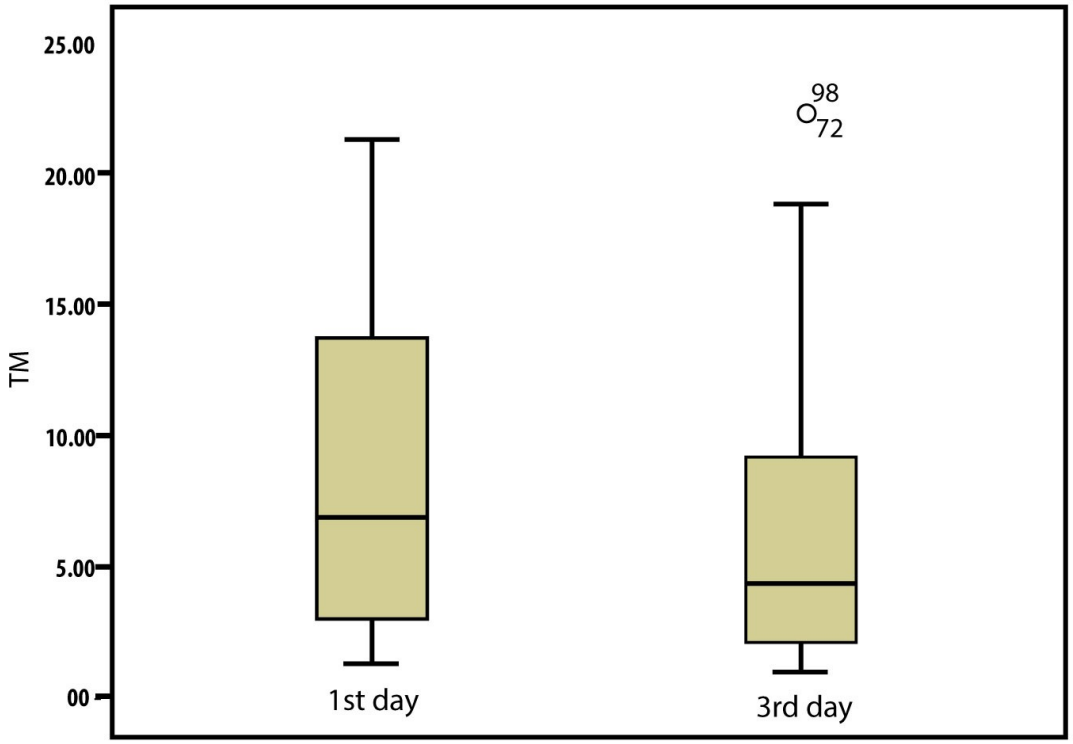

Figure 2. TM levels of patients on the first and third days

1

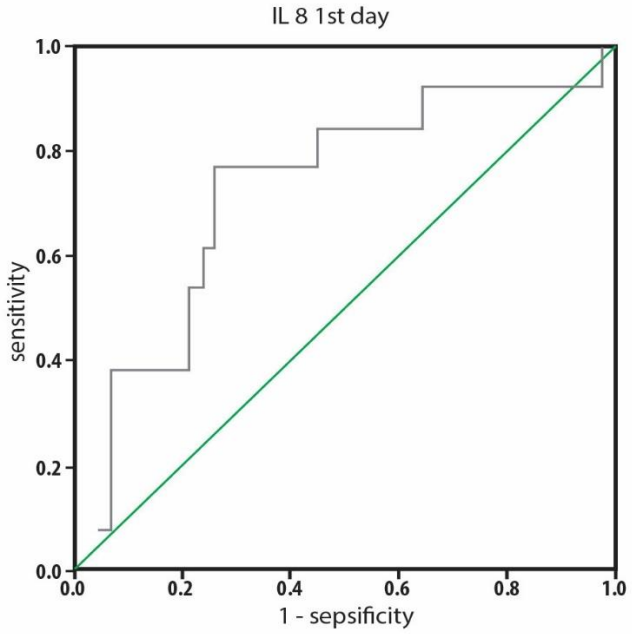

Figure 3. The cut-off point determined for IL-8 level on the first day for mortality prediction was > 154.7 nG/L. This level had a sensitivity of 76.9% and a sprecificity of 73.8%

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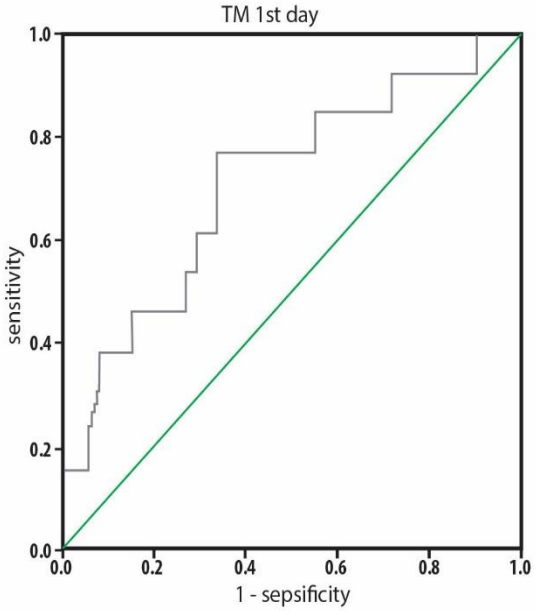

Figure 4. The cut-off determined for TM on the first day for mortality prediction was > 8.4 ng/mL. This level had a sensitivity of 76.9% and a sprecificity of 66.7%

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