ORIGINAL RESEARCH

Prognostic value of ADAMTS13 in patients with severe sepsis and septic shock

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Abstract

Purpose: ADAMTS13 level was evaluated as a predictor of mortality in patients with severe sepsis and septic shock, and compared with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.

Methods: This prospective observational study was conducted in the Medical and Surgical Intensive Care Units of King Khalid University Hospital. Detailed clinical evaluations were performed on 84 patients (56.08±18.18 years of age) with severe sepsis and septic shock. ADAMTS13 levels were determined (three blood samples at 24 hours intervals) and APACHE II scores, hematological profiles, indices of organ hypo-perfusion, renal functions and coagulation profiles were recorded. Primary outcome was 30 days ICU mortality and secondary outcomes were its comparison with APACHE II score, length of ICU stay and use of vasopressor agents.

Results: Hypertension (53.6%) and diabetic mellitus (45.2%) were the commonest comorbidities. The median ADAMTS13 levels were 336.65, 339.35 and 313.9, respectively. ROC analysis showed maximum area under the curve for second ADAMTS13 (AUC=0.760) compared with first (AUC=0.660) and third samples (AUC=0.707) and APACHE II scores (AUC=0.662). Patients were divided into low and high ADAMTS13 groups according to the best cut-off point. Mortality was high in the low ADAMTS13 level group [OR=4.5]and was significantly associated with age, DBP, ADAMTS13, APACHE II score, DIC score and platelet count. ADAMTS13 (OR=5.3), APACHE II (OR=4.13) and DIC scores (OR=7.32) were significant risk factors for mortality.

Conclusions: Low ADAMTS13 was associated with increased mortality in patients with severe sepsis and septic shock and was comparable to APACHE II scores for predicting mortality.

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Sepsis is a syndrome of systemic inflammation in response to infection. Severe sepsis is defined as sepsis with organ dysfunction while septic shock is sepsis induced hypotension persisting despite adequate fluid resuscitation [1]. Severe sepsis and septic shock are the leading causes of death in critically ill patients [2]. Recent advances in pathophysiology of severe sepsis suggest the systemic dysregulation of inflammatory response results in hemostatic imbalance, which leads to procoagulant activity [3]. Plasma levels of von Willebrand Factor (VWF) have been found to increase in response to severe systemic inflammation, probably due to activation of endothelial cells [4-8].

A large number of endothelia cell-active molecules have been investigated as potential biomarkers for the early diagnosis, triage and prognostication of sepsis. These include regulators of endothelial activation, vWF and ADAMTS13 [9]. In 1996, a protease that was able to cleave VWF [10,11]was described and, in 2001, Zheng *et al*.[12] named this protease ADAMTS13 (the 13th member of A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 motif, member 13). Under physiological conditions, ADAMTS13 promptly cleaves and removes from circulation ultra large (UL) VWF, which is released from endothelial cells [13]. If not cleaved then ULVWF multimers activate platelet aggregation, resulting in a prothrombotic condition [14].

The role of ADAMTS13 has been studied and described in both acquired and congenital (thrombotic thrombocytopenic purpura) TTP [15]. In the past decade, the use of the ADAMTS13 activity assay has become important in the diagnosis and treatment of TTP [15,16]. The relevance of ADAMTS13 levels in severe sepsis and septic shock is still not clear but in recent years its usefulness as a biomarker has been studied [17,18].

Despite a better knowledge of ADAMTS13, there is still a paucity of data regarding the correlation between ADAMTS13 and severe sepsis and septic shock; therefore, the aim of this study was to correlate ADAMTS13 levels and mortality (outcome) in patients with severe sepsis and septic shock, and to compare the predictive value of ADAMTS13 levels with that of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Methods

This was a prospective observational study conducted in the Medical (MICU) and Surgical (SICU) Intensive Care Units of King Khalid University Hospital, King Saud University Medical City and the Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia. This project was approved by the Institutional Review Board of the King Saud University Medical City (Project Number E-11-348). Informed consent was obtained from next of kin of all patients. The study was conducted over a period of three years, from January 2011 to December 2013, during which time 587 patients were screened, 243 cases were selected and 84 patients were finally included in the study. Criteria for screening and selection of all patients in the study are summarized in Figure 1.

Adult patients (>18 years) admitted to MICU or SICU with the diagnosis of severe sepsis and septic shock and who fit the criteria of the study were included. Severe sepsis and septic shock were defined according to the definitions laid down by "Surviving Sepsis Campaign, International Guidelines for Management of Severe Sepsis and Septic Shock 2008". Patients with known thrombotic or bleeding disorders, who had received blood or blood products within seven days of enrolment, who had end-stage renal or liver disease, were pregnant or were on anticoagulants were excluded from the study. The end point in this study was 30 day ICU mortality.

Blood samples were collected from all patients at three time points: within 24 hours of admission; between 24 – 48

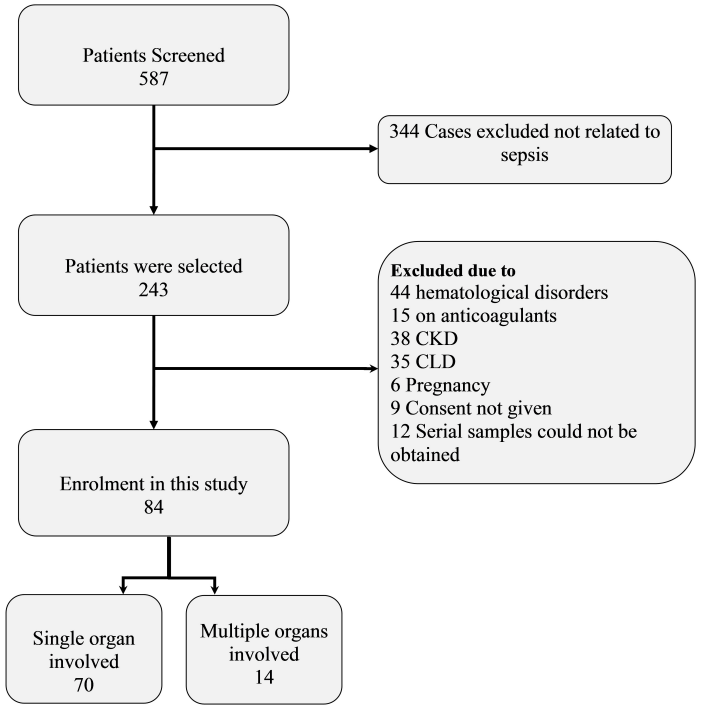

FIGURE 1: Screening and selection of all patients in the study.

TABLE 1. Demographic, baseline hemodynamic and hematological parameters of the study patients (n=84)

Variables	Mean ±SD	Range /[IQR]
Age (years)	56.08±18.18	15-96
Weight (kg)	75.51±15.23	35-120
Height (cm)	162.92±7.85	140-178
Heart rate (beat/min)	92.56±16.54	62-138
MAP (mmHg)	78.87±12.24	53-124
Hemoglobin (g/dl)	9.80±1.59	6.8-14.8
Hematocrit (%)	29.23±4.78	20-44.6
D-dimers (mcg/ml FEU)	5.44±5.62	0.44-25
INR	1.45±0.61	0.93-5.1
WBC (10^9/L)	16.57±13.25	0.30-91.8
Urea (mmol/L)	14.39±13.16	2.1-63
Creatinine (μmol/L)	159.36± 135.59	17-932
PH	7.35±0.093	7.10-7.55
PCO_2 (mmHg)	37.69±9.79	21-85.9
PO_2 (mmHg)	92.18±34.31	37-200
HCO_3 (mmol/L)	21.72±4.68	11.9-34
Platelets (count /μL) median	154	[87.75-276.75]
PT (seconds) median	18.3	[15.82-19.57]
APTT (seconds) median	43.15	[36.02-51.67]
Fibrinogen (g/dL) median	3.64	[2.14-5.21]
Lactate (g/L)	2.93±2.85	0.4-16
APACHE II Score	22.85±9.07	3-52
DIC score	2.73±1.99	0-8
LOS	13.5	[6-26.75]
Mortality	56	66.7%

Values are expressed as mean ± SD, median [IQR= Q1-Q3] and n (%)

hours of admission; and, between 48 – 72 hours of admission. Approximately 10 ml of venous blood was collected after all aseptic measures in sodium citrate-added tubes and serum tubes. Sample was then centrifuged, aliquoted and stored at −80°C until assayed. All samples were analyzed for ADAMTS13 levels by sandwich ELISA technique with kits supplied by Human ADAMTS13 ELISA Kit (American Diagnostica, USA; Catalog Number 813).

In addition to ADAMTS13 levels, data were collected on a predesigned proforma, including demographic characteristics, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, hematological profiles (Hb, HCT and WBC), indices of organ hypo-perfusion (pH, HCO_3, lactate), renal function, coagulation profile (platelet, PT, aPTT, fibrinogen and D-dimer), use of mechanical ventilator, vasopressors and organ involvement, length of stay (LOS) in the MICU and SICU was also recorded. The research protocol did not interfere with any medical recommendations or prescriptions.

Statistical Analysis

Categorical data were summarized as number and percentages, whereas continuous data were summarized as mean, median and standard deviation. Comparison between groups for categorical variable was done using chi-square test or Fisher's exact test, whereas for continuous data Student's t-test or Mann Whitney U test was used for two groups and analysis of variance or Kruskal-Wallis test for more than two groups for normally and non-normally distributed data, respectively. To measure the predictive power of ADMATS13 score, area under the curve (AUC) along with 95% confidence interval were calculated using ROC analysis. Any association with P-value <0.05 was considered statistically significant and all P-values were 2-tailed.

Results

A total of 84 ICU-admitted cases were enrolled in this study; all patients were in severe sepsis as well as septic shock. Demographic, hemodynamic and hematological parameters of the patients are summarized in Table 1. Hypertension 53.6% (45/84) and diabetic mellitus 45.2% (38/84) were commonest comorbid conditions, followed by ischemic heart disease (IHD) 11.9% (10/84), chronic obstructive pulmonary disease (COPD) 8.3% (7/84). Single organs were involved in 83.3% cases (70) while 16.7% patients (14) had multiple organ involvement. Lungs were affected in 82.1% (69) cases, gastrointestinal (GIT) in 5.9% (5), kidney in 4.8% (4), soft tissue infection in 4.8% (4) and central nervous system (CNS) 2.4% (2). All patients received vasopressors agents while 94.6% (81/84) were on ventilator. The ICU mortality rate observed in this study was 66.7% (56/84) (see Table 1).

The median ADAMTS13 of the first sample (within 24 hours after ICU admission) was 336.65 [IQR: 409.45-231.75],

TABLE 2. Comparison of demographics, baseline hemodynamic measured, ADAMTS13 levels and severity indices between survivor and non-survivors of septic shock (n=84)

Variables	Non-Survivor (n=56)	Survivor (n=28)	P-Value [2-tailed]
Age (years)	60.38±16.92	47.5±17.85	0.002
Weight (kg)	75.57±14.58	75.39±16.72	0.96
Height (cm)	162.39±7.82	163.96±7.96	0.391
Male	27(48.2%)	15(53.6%)	0.643
Female	29(51.8%)	13(46.4%)	
Heart rate (beat/min)	93.21±17.51	91.25±14.62	0.611
SBP (mmHg)	119.96±18.12	123.29±19.82	0.445
DBP (mmHg)	59.68±9.36	64.71±11.85	0.037*
MAP (mmHg)	77.21±11.45	82.42±13.33	0.073
ADAMTS13 (24-48 hours samples)			
Mean ± SD	300.53±120.8	405.75±136.9	0.001*
Median (IQR)	306(375-202)	391(479-306)	
APACHE II score			
<= 20	12(21.4%)	15(53.6%)	0.003
>20	44(78.6%)	13(46.4%)	
DIC score			
≤ 3	35(62.5%)	25(89.3%)	0.01
4 to 8	21(37.5%)	3(10.7%)	
APTT on admission			
≤40	23(41.1%)	15(53.6%)	0.278
>40	33(58.9%)	13(46.4%)	
PT on admission			
≤ 16	24(42.9%)	16(57.1%)	0.217
>16	32(57.1%)	12(42.9%)	
D-dimers			
<5	40(71.4%)	20(71.4%)	0.999
>5	16(28.6%)	8(28.6%)	
Fibrinogen			
≤ 2	36(64.3%)	12(42.9%)	0.061
>2	20(35.7%)	16(57.1%)	
Platelet on admission			
≤ 150	30(53.6%)	8(28.8%)	0.03
>150	26(46.4%)	20(71.4%)	
Use of mechanical ventilation			
Yes	55(98.2%)	26(82.9%)	0.257
No	1(1.8%)	2(7.1%)	
Single organ involved (lung, kidney, CNS, GIT)	48(85.7%)	22(78.6%)	0.408
Multiple organs involved	8(14.3%)	6(21.4%)	
Vasopressor agent			
Norepinephrine	31(55.4%)	21(75%)	0.081
Norepinephrine in combination	25(44.6%)	7(25%)	

Values are expressed as mean ± SD for continuous normal and median [Q3-Q1] for non-normal data set. Number (%) for categorical and nominal variables. Independent sample t test applied for normal distributed data and Mann-Whitney U test used for non-normal data. Categorical and nominal variables were compared by chi-square test or Fisher exact test.

TABLE 3. Multivariate stepwise logistic regression, showing the factors independently associated with ICU mortality

Factors	Odd Ratio	95%CI	P-value
ADMTS13 (within 24 to 48 hours after ICU admission)			
≤365	5.3	1.73-16.17	0.003
>365	Reference		
APACHE II score			
≤20	Reference 4.13		0.017
>20		1.28-13.25	
DIC			
0-3	Reference 7.32		0.009
08-Apr		1.63-32.87	

Hosmer-Lemeshow=1.06(p=0.95), model accuracy=76.8%, area under the curve= 0.81, CI= Confidence interval.

second sample (during 24 to 48 hours) 339.35 [IQR: 408.27-242.55] and third sample (during 48 to 72 hours) was 313.9 [IQR: 434-205.6]. ROC curve (Figure 2) shows comparison of predictive value of three serial samples of ADAMTS13 antigen levels with APACHE II scores in all cases. All serial samples of ADAMTS13 had an AUC comparable with APACHE II score for mortality prediction.

AUC of ADAMTS13 by second blood sample was larger i.e. 0.76 (AUC=0.760, CI 0.643 to 0.878, p=.001) than other samples and APACHE II; therefore, the overall performance of the ADAMTS13 level taken within 24 to 48 hours (second sample) was better than the first and third samples of ADAMTS13 level (AUC=0.660 CI 0.524-0.795 p=.033, AUC=0.707 CI 0.585-0.828 p=.006) and APACHE II scores (AUC=0.662 CI 0.521-0.803, p=.030).

The cut-off point for an optimal diagnostic test was chosen to optimize the rate of true positive whilst minimizing the rate of false positives. It showed that the differences in ROC data

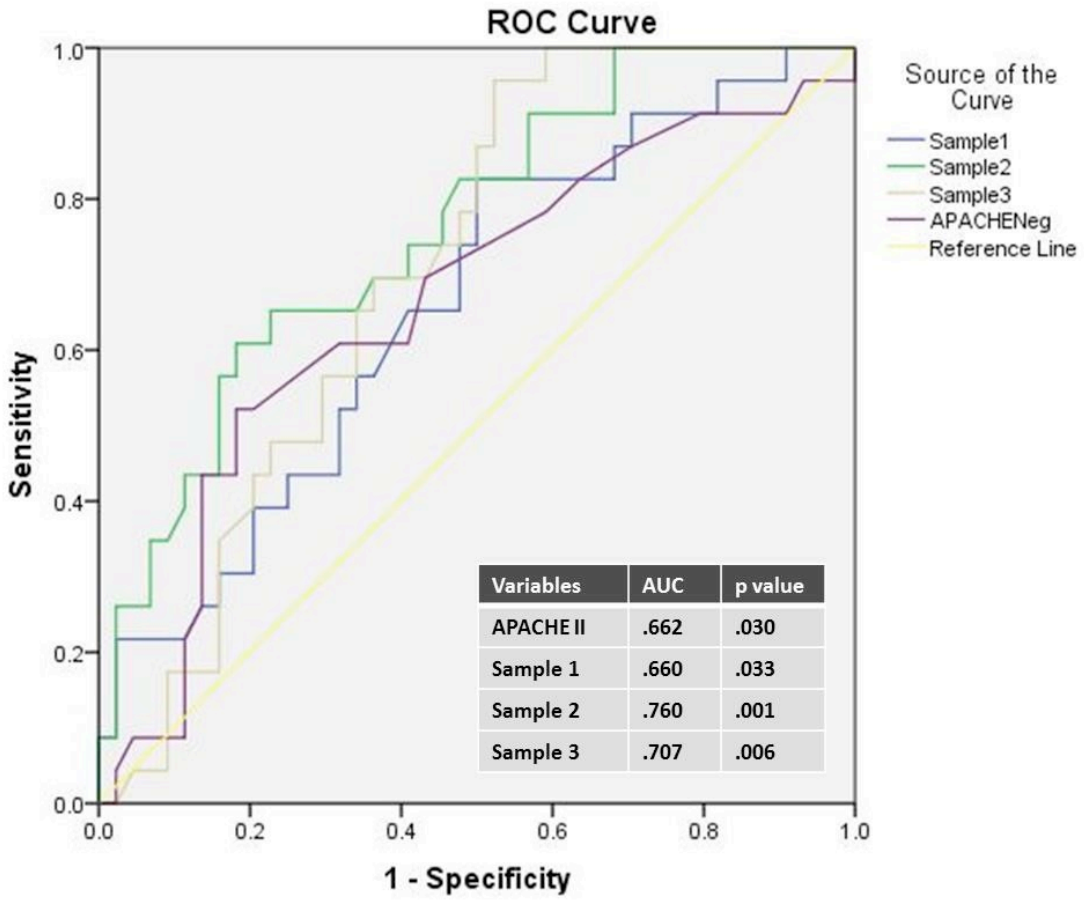

FIGURE 2. ROC curve for ADAMTS13 level of three serial samples and APACHE II scores for mortality prediction. The differences in ROC data for the three serial samples and APACHE II were statistically significant.

for the three different days were statistically significant in mortality prediction (Figure 2). As per method to find the "optimal threshold point", the ROC analysis showed sensitivity and 1-specificity for all the observed cut-off points. The minimum distance was found 0.17 with true positive (0.714) and false positive rate (0.357) so the coordinated value of ADAMTS13 was 365, which is the cut-off point for an optimal diagnostic test. According to the cut-off point, patients were divided into two groups: ADAMTS13 level ≤365 ng/ml (low); and, >365 ng/ml (high), with sensitivity and specificity of 71.4% and 64.3%, respectively.

Figure 3 shows boxplot graphs of serial ADAMTS13 levels on days 1, 2 and 3, between survivors and non-survivors. All thee serial samples showed a significant difference in ADAMTS13 levels between survivors and non-survivors (p=0.045, 0.001 and 0.006).

Mortality rate was high in cases with ADAMTS13 level ≤365 ng/ml with an odds ratio of 4.5 [95%CI: 1.71 to 11.82]. A comparison between ICU survivors and non-survivor is presented in Table 2. Univariate analysis showed that mortality was significantly associated with age, diastolic blood pressure (DBP), ADAMTS13, APACHE II score, DIC score and low platelet count. Multivariate stepwise logistic regression model was created of variables with p≤ 0.20 to find the best predictor for mortality. The final model (Table 3) identified low ADAMTS13 (≤365 ng/ml) (OR=5.3 95%CI=1.73 to 16.17), APACHE II score of >20 (OR=4.13; 95%CI=1.28 to 13.25) and DIC score 4-8 (OR=7.32; 95%CI: 7.32 95%CI=1.63 to 32.82) as significant risk factors for mortality. Figure 4 shows mortality rate at different quartiles of ADAMTS13 levels. Linear-by-linear association showed a significant trend of increased mortality at decreasing level of ADAMTS13 in patients with severe sepsis and septic shock (p=0.007).

Discussion

Prediction of mortality in patients with severe sepsis and septic shock depends on multiple factors. The purpose of this study was to confirm that ADAMTS13 levels could be used to predict mortality in patients with severe sepsis and septic shock. Two studies have reported decreased levels of ADAMTS13 level in patients with severe sepsis and septic shock and its relationship with mortality [17,18]; however, the predictive value of serial samples of ADAMTS13 in patients with severe sepsis and septic shock have not been reported. Our study also compared ADAMTS13 levels with APACHE II scores, as predictors of mortality in patients with severe sepsis and septic shock.

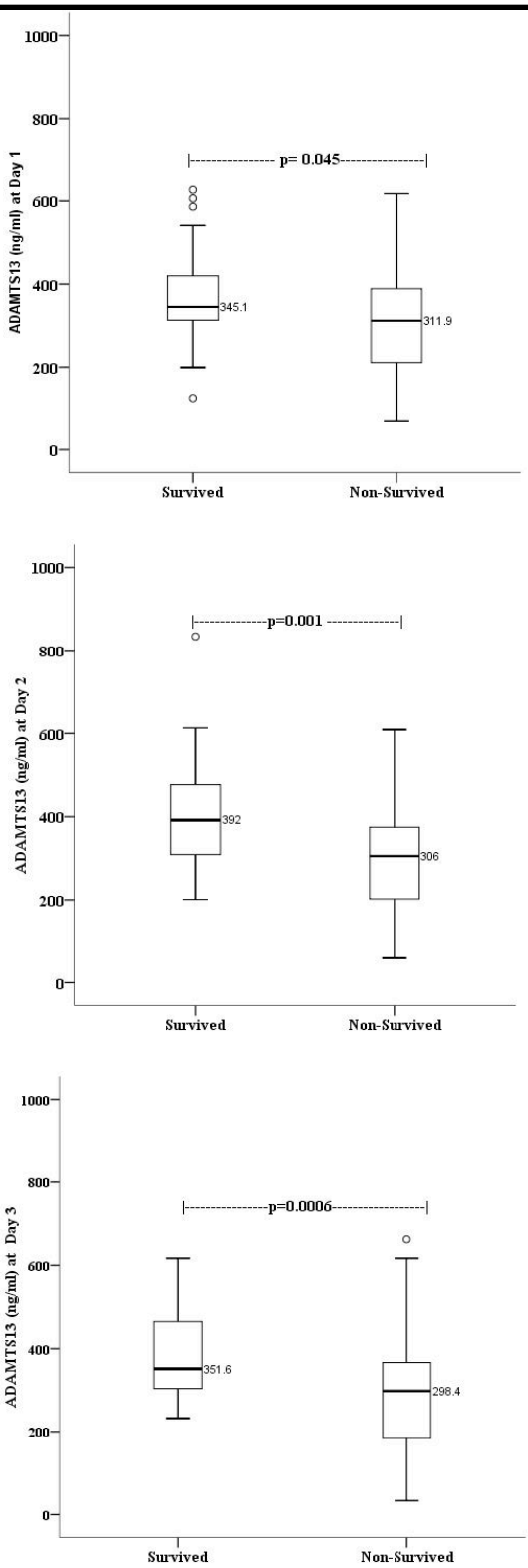

FIGURE 3. Comparison of ADAMTS13 levels between survived and non-survived at Day 1, Day 2 and Day 3.

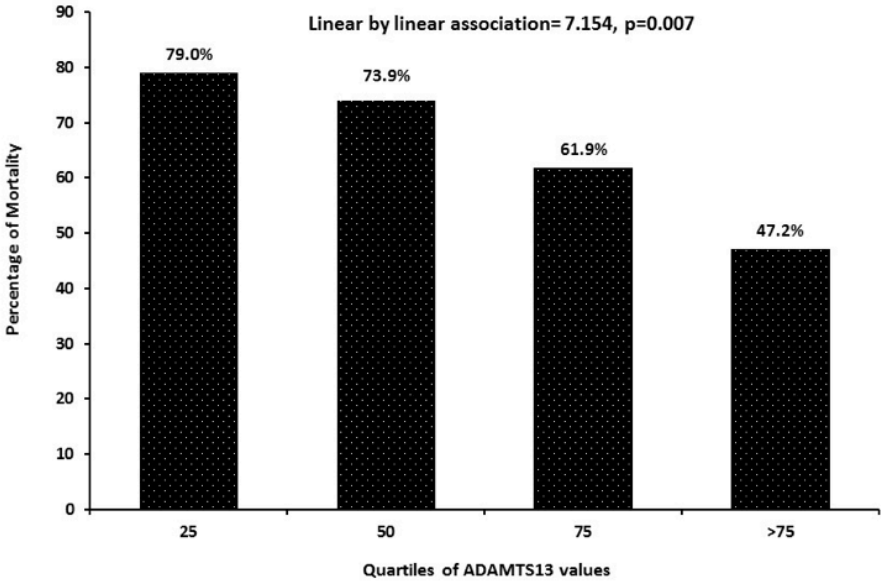

FIGURE 4. Percentage of mortality rate at different quartiles of ADAMTS13 levels. There was a significant trend of increased mortality rate at decreasing levels of ADAMTS13.

Our study showed a significant association between low level of ADAMTS13 level and poor survival in patients with severe sepsis and septic shock. The ICU mortality was high in patients who had low ADAMTS13 levels and this was particularly significant from the blood samples taken between 24 and 48 hours (i.e., the 2nd blood sample). The explanation for the 2nd sample being significant is unclear, but possible reasons include disease severity on the second day, population differences and strict inclusion and exclusion criteria.

Martin *et al*. [19] observed lower ADAMTS13 activity in patients with severe sepsis in comparison with patients who had developed organ failure without sepsis. Their study showed no clear association between the level of ADAMT13 and mortality. Kremer-Hovinga *et al*. [20] also correlated sepsis with decrease ADAMTS13 activity. Peigne *et al*. [21] emphasized the role of ADAMTS13 as a prognosis factor in septic shock and Ono *et al*. [22] described decreased ADAMTS13 levels in 109 patients with sepsis-induced disseminated intravascular coagulation (DIC). Recently, a meta-analysis [23] revealed three studies that showed ADAMTS13 was significantly lower in sepsis than other critically ill non-septic patients [14,19,24].

Our study also illustrated the significant association between low ADAMTS13 and high APACHE II score (score >20; p=0.017). The other variables used in the study, such as use of mechanical ventilation, length of stay (LOS), vasopressor agents and number of organ failure on admission, also showed correlations with low ADAMTS13 levels but these correlations were not statistically significant. The positive correlation between ADAMTS13 and APACHE II has been shown previously, but this was done in patients with severe acute pancreatitis [25].

A recently published paper by Aibar *et al*. [17] showed a negative correlation between ADAMTS13 levels and APACHE II scores. Whereas Aibar *et al*. included patients varying from SIRS without infection to sepsis, our study included patients with severe sepsis and septic shock.

Our study showed increased mortality in patents with high DIC score (i.e., scores 4 - 8). Clemens *et al*. [26] also demonstrated that low ADAMTS13 levels were associated with a significantly higher DIC-score, but Peigne [21] observed no correlation between ADAMTS13 deficiency and DIC.

Further studies are needed to confirm whether low ADAMTS13 levels and high DIC scores are independent predictors of mortality in patients with severe sepsis and septic shock. Low ADATMS13 levels were positively correlation with low diastolic and mean arterial blood pressure (MAP) and it has been observed [27,28] that low MAP is a significant predictor of organ dysfunction. The significance of isolated low diastolic blood pressure with mortality has been studied, but these studies were done in normal and cardiogenic shock patients [29,30]. Further studies are needed to determine its significance in patients with severe sepsis and septic shock.

Low fibrinogen levels are common in patients with severe sepsis because of fibrinolytic and DIC activity, but it was not associated with ADAMTS13 levels in our study [31]. Other aspects of the coagulation profile were also low but the decreases were not statistically significant (Table 2). Huang *et al*. [32] have shown fatal outcomes of septic shock in the presence of low fibrinogen level in children. Platelets counts <150 count /μL were found in 26 of our patients (48.15%) with low ADAMTS13 levels, but the differences were not statistically significant. Previous studies have shown a significant association between thrombocytopenia and low ADAMTS13 with mortality [19,33].

The strict exclusion criteria and serial ADAMTS13 level estimations are the strength of our study. We excluded patients with end stage liver disease because, in patients with fulminant hepatic failure and liver cirrhosis, the plasma levels of VWF were remarkably high [34,35] and the activity of ADAMTS13 was low in the patients with acute hepatitis [36] and liver cirrhosis [37]. The low level of ADAMTS13 has also been found in patients with chronic renal disease including diabetic nephropathy [38]. Other conditions such as pregnancy [39] and thrombotic and bleeding disorders [40] were excluded as there is evidence that these conditions may influence estimation of ADAMTS13 levels.

We included in our methodology the measurement of serial ADAMTS13 levels (i.e., three samples taken serially at 24 hour intervals). The purpose of these serial samples was to investigate the trend of disease severity. No previous evidence was available until recently, when serial estimations of vWF and ADAMTS13 ratio were reported [41]. Further studies are needed to see the significance of serial ADAMTS13 levels in defining the trends, therapeutic monitoring and outcomes in patients with severe sepsis and septic shock.

The limitations of our study include the small sample size and the absence of a control group. Although there are no universally-accepted levels for ADAMTS13 to date, a working group has recently been formed by World Health Organization to set a standard level of ADAMTS13 [42].

This is the first clinical study in a Middle Eastern population showing the prognostic value of ADAMTS13 in patients with severe sepsis and septic shock. Our study indicates that decreased ADAMTS13 levels were not only associated with increased ICU mortality in patients with septic shock, but were comparable to APACHE II scores, which is a well-established standard tool to predict mortality in critically ill patients. The trend of the ADAMTS13 levels in the serial samples further illustrates the difference between survivors and non-survivors of severe sepsis and septic shock.

Conclusions

Low ADAMTS13 levels are associated with increased mortality in patients with severe sepsis and septic shock and are comparable to APACHE II scores in predicting mortality; thus, ADAMTS13 levels may be a useful biomarker for predicting the prognosis in patients with severe sepsis and septic shock. Further studies, with a control group and with larger sample sizes, are needed to confirm the prognostic significance of ADAMTS13 in patients with severe sepsis and septic shock.

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