Journal of Associated Medical Sciences 2022; 55 (3): 68-75

JAMS
Journal of Associated Medical Sciences

Thai-Journal Citation Index Centre (TCI) & ASEAN Citation Index (ACI)

Journal of Associated Medical Sciences

Journal homepage: https://www.tci-thaijo.org/index.php/bulletinAMS/index

Prospective study of early onset coagulopathy as a predictor of outcome in septicaemic patients admitted to a tertiary care centre in eastern India

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ARTICLE INFO

Article history:
Received 14 March 2022
Accepted as revised 4 July 2022
Available online 18 July 2022

Keywords:
Early onset coagulopathy, sepsis, mortality, SIRS, APACHE II

ABSTRACT

Background: Severe sepsis and septic shock are among the leading causes of morbidity and mortality in intensive care units worldwide despite rapid advances in treatment protocols. Even with all advances, determining the prognosis of sepsis continues to remain tricky.

Objectives: This study was planned to assess early onset coagulopathy as a predictor of outcome and mortality in septicemic patients and to study the underlying risk factors associated with mortality in septicemic patients with underlying coagulopathy.

Materials and methods: 240 patients fulfilling the criteria of SIRS and sepsis were included in the study. Coagulation parameters including platelet count, prothrombin time – international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT) were evaluated within 48 hours of admission and 28-day mortality was evaluated. Independent predictors of 28-day mortality were evaluated using logistic regression model.

Results:Twenty-eight-day mortality rate was 77.77% (98/126) in patients with coagulopathy and a meagre 1.7% (2/114) in patients without coagulopathy which was statistically significant ($p<0.05$). Log Odd's ratio calculated using chi-square test was found to be 5.2781, 95% CI (1.633-17.321), which was highly significant. Univariate logistic regression for mortality showed PT-INR, aPTT and APACHE II scores to be independent variables. Multivariate logistic regression revealed severe increase in PT-INR [adjusted OR=1.622 (0.841, 3.092)], moderate increase in aPTT [adjusted OR=4.537 (0.989, 7.326)], and severe increases in aPTT [adjusted OR=3.851 (2.438, 4.996)], and APACHE II scores [adjusted OR=5.381 (1.925, 11.01)], were independently associated with 28-day mortality whereas age, sex, any severity of thrombocytopenia, mild to moderate increase in PT-INR, and mild increase in aPTT were not.

Conclusion: Early onset coagulopathy was found to be significantly associated with increased mortality risk in septicemic patients. Septicemic patients should be screened for coagulopathy within 24-48 hours of admission in appropriate clinical scenario to predict mortality outcome and take necessary action at the earliest.

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doi: 10.12982/JAMS.2022.026
E-ISSN: 2539-6056

Introduction

Sepsis is a well-known clinical syndrome that results from an overly aggressive systemic host response to infection.[1] Severe sepsis is characterized by hypotension, coagulopathy, and multisystem organ dysfunction, which are primarily caused by dysregulation of host-derived inflammatory mediators.[2] Coagulopathy is a condition in which the blood's ability to clot the blood is impaired.[3] Derangement of coagulation parameters is one of the common laboratory findings in septicemic patients.

The complex triad of infection, inflammation and ensuing coagulopathy have been variably implicated in the pathophysiology of severe sepsis. In sepsis, the inflammatory response of the host to an invading organism develops a procoagulant state. The relationship between tissue factor (TF) and inflammatory cytokine release is crucial to this process of initiating the coagulation cascade.[4] Tissue factor is responsible for binding and activating Factor VII on cell surfaces, resulting in the formation of the enzyme-cofactor complex that stimulates the formation of Factor Xa. TF are also expressed by endothelial cells, mononuclear phagocytes such as monocytes and macrophages in various organs like lung, kidney, and brain astrocytes. After TF expression, proinflammatory cytokines including TNF, IL-8, and IL-6 are upregulated and they play a significant role in natural anticoagulant suppression and endothelial damage.[5] Next, platelet-activating factor (PAF) is released directly as a result of inflammation which accelerates the process of thrombosis by expression of platelet p-selectin which in turn increases monocyte TF expression and platelet adhesion to leukocytes and endothelium. When platelets are attached to leukocytes and endothelium, they serve as a surface for thrombin production and cellular signalling of other coagulation factors.[6] In severe sepsis, the disruption of three intrinsic anticoagulants (tissue factor pathway inhibitor, activated protein C, and thrombomodulin) lead to the onset of hyper-coagulopathy.

Severe sepsis and septic shock remain among the leading causes of morbidity and mortality in intensive care units worldwide despite rapid advances in treatment protocols.[7,8] Several trials and protocols have focused on developing better methods for detecting sepsis early, managing it effectively, and preventing complications. Even with all advances, determining the prognosis of sepsis continues to remain tricky. This study was planned to assess early onset coagulopathy as a predictor of outcome and mortality in septicemic patients and to study the underlying risk factors associated with mortality in septicemic patients with underlying coagulopathy.

Materials and methods

This was a hospital based prospective observational study carried out from November 2018 to October 2020 in IMS and SUM Hospital, Bhubaneswar after approval from institutional ethics committee. Based on previous literature, prevalence of coagulopathy in sepsis being around 48%, the sample size was calculated to be around 240 with 8% allowable error at 5% level of significance and 80% power of test. Patients with suspected or documented infection (via culture reports), fulfilling the criteria of Systemic inflammatory response syndrome (SIRS) were included in the study. Patients less than 16 years of age, patients admitted with trauma, surgical patients, pregnant women, and unwilling patients were excluded from the study. Detailed history regarding onset of symptoms and comorbidities was obtained. Risk factors included diabetes mellitus, hypertension, chronic kidney disease (CKD), chronic liver disease (CLD), malignancy (on treatment with either chemotherapy/ radiotherapy except palliative care), HIV infection, and ischemic heart disease (IHD). Coagulation parameters were obtained within 48 hours of admission which included platelet count, prothrombin time – international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT), and other tests e.g. procalcitonin (PCT) (done as per Clinician discretion). Acute physiology and chronic health evaluation score (APACHE II) was calculated based on clinical and laboratory parameters and interpreted accordingly.[9] Patients were followed up over a period of 28 days, and 28-day mortality was noted, if any. Data obtained was categorized as mentioned in Table 1. Patient was considered to have coagulopathy even if any one of these parameters were deranged which include platelet count <1,50,000, PT-INR>1.5 times the upper limit of normal (ULN) and aPTT>1.5 times ULN.3,10 Patients admitted with septicemia having coagulation parameters deranged within 48 hours of admission were considered to have early-onset coagulopathy in our study.[11]

Table 1 Categorization of data.

Platelet count (cells/mm^3)	
>1,50,000	No thrombocytopenia
1, 50,000-75,000	Mild thrombocytopenia
75,000-50,000	Moderate thrombocytopenia
50,000-25,000	Severe thrombocytopenia
<25,000	Life-threatening thrombocytopenia
International Normalized Ratio (INR)	
Normal	
more than 1-1.5 times ULN	Grade 1 (mild derangement)
more than 1.5-2 times ULN	Grade 2 (moderate derangement)
more than 2 times ULN	Grade 3 (severe derangement)
Serum procalcitonin	
PCT<0.5 ng/mL	Local bacterial infection possible, systemic infection (sepsis) unlikely.
PCT>0.5 & <2 ng/mL	Suggests systemic infection (sepsis).
PCT>2 & <10 ng/mL	Suggests severe sepsis.
PCT>10 ng/mL	Suggests exclusively septic shock

Statistical analysis was carried out with the help of SPSS (version 20) for Windows package (SPSS Science, Chicago, IL, USA) and appropriate statistical methods were used to analyse the data. The description of the data was done in form of mean±SD for quantitative data while in the form of frequency and proportion for qualitative (categorical) data. The p values of p<0.05 were considered significant. For quantitative data, Student's t-test was used to test statistical significance of difference between two independent group means. Chi square test (or Fisher's exact test in case of small frequencies in cell) was used to examine the association between patients with diabetes, chronic liver disease or chronic kidney disease and patients with and without thrombocytopenia. To determine the independent variables among various parameters like age, sex, thrombocytopenia, elevated PT-INR, aPTT and APACHE II scores on 28-day mortality, a univariate logistic regression analysis was performed, and then multivariate logistic regression was calculated to calculate the independent predictors of mortality using the 28-day mortality as the dependent factor. When appropriate, the odds ratio (OR) was calculated.

Observation and discussion

The study was conducted on 240 subjects fulfilling the inclusion and exclusion criteria. Mean age of the patients was 56.27 years (19-101, SD=15.05) in our study. Maximum number of patients (32.9%) were in 61-70 years age group followed by 23.3% patients in 71-80 years age group. There was a male preponderance (53% vs 43%). Diabetes mellitus was observed to be the most common underlying illness present in 32.5% cases followed by hypertension (HTN) in 19.6%, chronic liver disease (CLD) in 15.0%, ischemic heart disease (IHD) in 12.5% and malignancy in 11.7%. Chronic kidney disease (CKD) was present in 6.7% cases and human immunodeficiency virus (HIV) infection in 4.6% cases.

In our study we observed that 55.8% (134/240) of septicemic patients did not have thrombocytopenia whereas 20% (48/240) patients had mild thrombocytopenia, 5.8% had moderate (14/240), 12.1% (29/240) had severe and 6.3% (15/240) had life threatening thrombocytopenia within 48 hours of admission which was in concurrence with a retrospective analysis by Venkata C *et al*. in 2013, where thrombocytopenia occurred in 47.6% of the sepsis-related 304 cases admitted in ICU.[12] Most critically ill patients with a systemic inflammatory response have coagulation disorders and thrombocytopenia is often the most frequent finding.[10]

Sepsis leads to deranged coagulation, ranging from mild alterations up to severe disseminated intravascular coagulation (DIC). PT-INR levels were normal in 33% (80/240) study subjects whereas 29.6% (71/240) had mild derangement, 15% (36/240) moderate and 22.1% (53/240) had severe derangement in PT-INR value. The aPTT values were normal in 37.1% (89/240) study subjects whereas 35.4% (85/240), 19% (46/240), 8.3% (20/240) of study subjects had mild, moderate, and severe aPTT derangements respectively. Similar findings were seen in a study of 235 patients by Chakraverty *et al*. wherein INR was deranged in 66% cases.[13]

Coagulopathy was seen in 52.5% (126/240) study subjects and was absent in the rest of the study subjects. Thrombocytopenia related coagulopathy was seen in 44.1% (106/240) patients; PT-INR derangement related coagulopathy was seen in 37.08% (89/240) patients and aPTT derangement related coagulopathy was observed in 27.5% (66/240) patients.

Lower 28-day mortality, 14.1% (19/134) was observed in with patients having normal platelet counts whereas 54.16% (26/48) mortality was seen in mild thrombocytopenia, 92.85% (13/14) in moderate thrombocytopenia, 93.1% (27/29) in severe thrombocytopenia and 100% (15/15) mortality in life threatening thrombocytopenia (Figure 1). This was found to be statistically significant by using Fisher's exact test ($p<0.05$). Sharma *et al*. in their study of 69 patients with septic shock in 2007, observed that incidence of thrombocytopenia in their study was 55% and platelet count was found to be predictor of increased mortality.[14]

Patients with normal PT-INR had 3.7% (3/80) mortality whereas mortality was 22.53% (16/71) in mild PT-INR derangement, 88.8% (32/36) in moderate and 92.4% (49/53) in severe PT-INR derangement respectively, which was found to be statistically significant with Fisher's exact test ($p<0.05$) (Figure 2). Chakraverty *et al*. observed that PT-INR derangement was associated with poorer outcome in critically ill patients.[13]

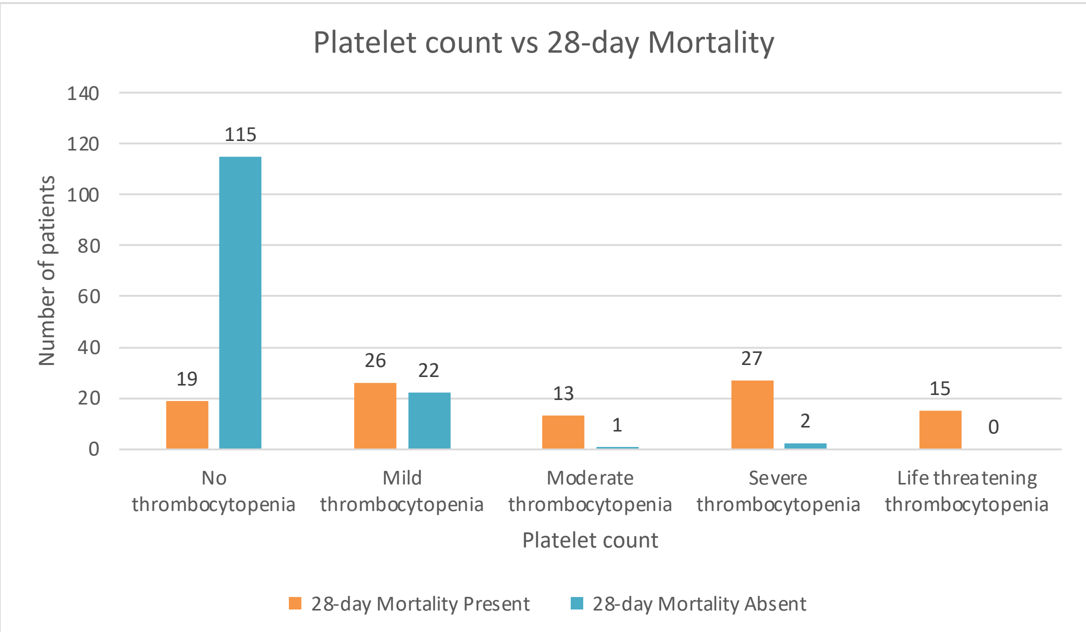

Figure 1*. Analysis of 28-day mortality with thrombocytopenia in study subjects (p<0.001).*

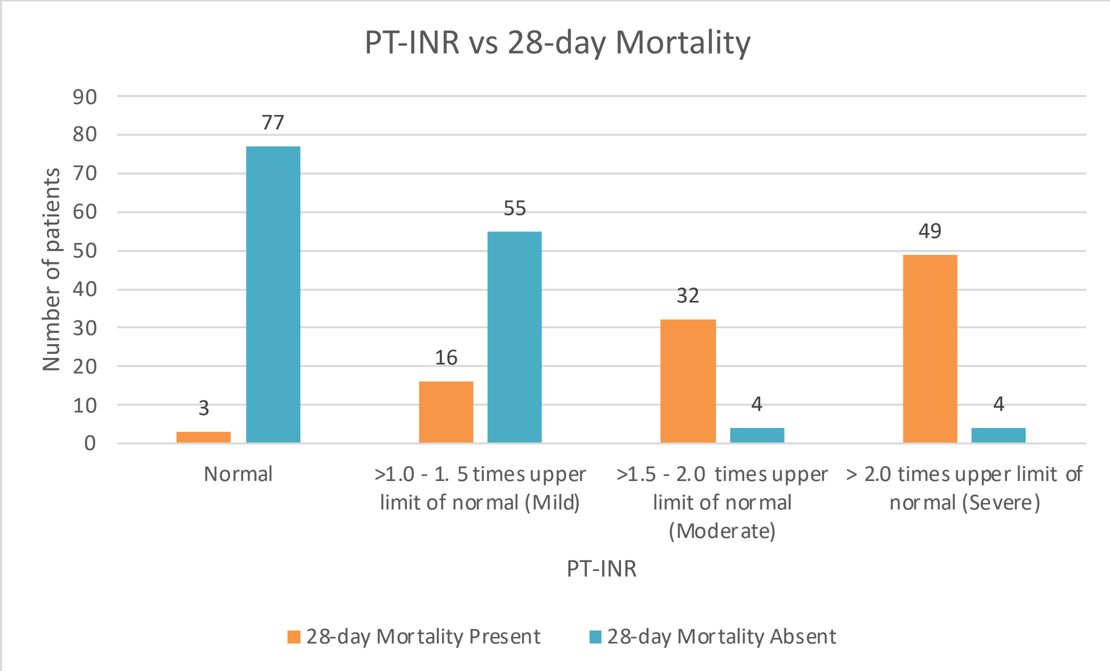

Figure 2. *Analysis of 28-day mortality with PT-INR in study subjects (p<0.001).*

Mortality was 10.1% (9/89) in patients with normal aPTT values; 34.1% (29/85) in mild aPTT derangement, 95.6% (44/46) in moderate and 90% (18/20) in severe aPTT derangement which was again statistically significant ($p<0.05$) (Figure 3).

28-day mortality rate was 77.77% (98/126) in patients with coagulopathy and a meagre 1.7% (2/114) in patients without coagulopathy which was statistically significant ($p<0.05$). Log Odd's ratio calculated using chi-square test was found to be 5.2781, 95% CI (1.633-17.321), which was highly significant.

Mortality in patients having thrombocytopenia related coagulopathy was 76.41% (81/106), and amongst non-thrombocytopenic patients was 14.1% (19/134) (Figure 4). This finding contrasted with the observation made by Venkata *et al*. in a retrospective analysis in 2013, which included 304 patients where no significant mortality difference was seen in thrombocytopenic (32.4%) and non-thrombocytopenic patients (24.5%).[11] This apparent difference could partly be explained by the presence of other coexistent abnormal coagulation parameters in our patients, however adjusted Odd's ratio was not found to be significant.

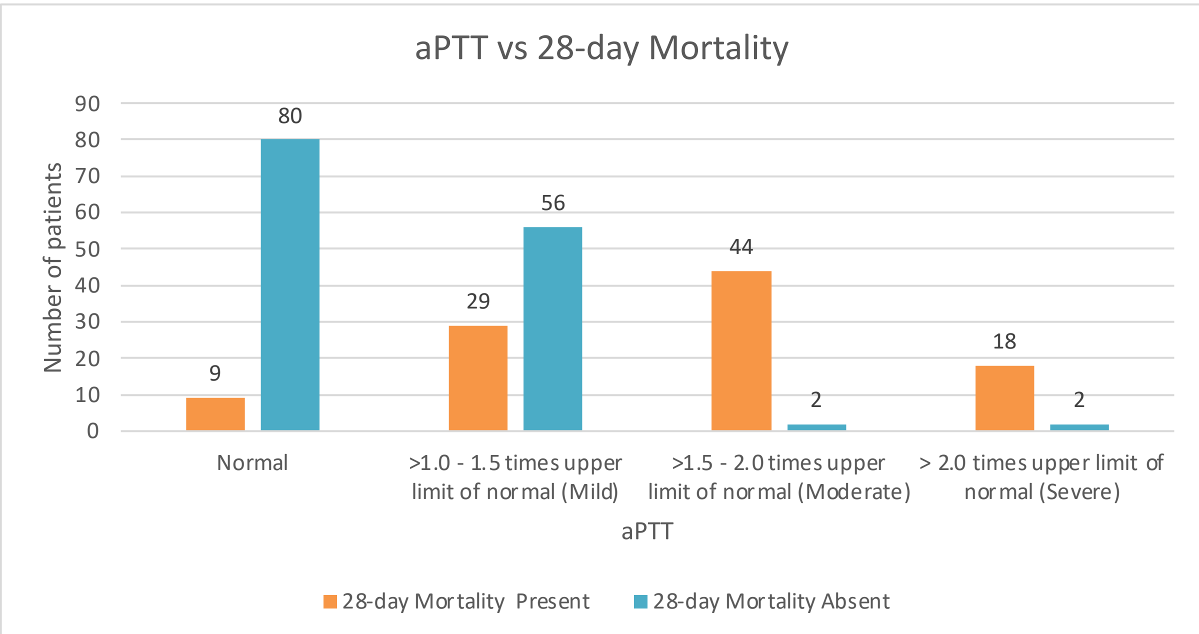

Figure 3. *Analysis of 28-day mortality with aPTT in study subjects (p<0.001).*

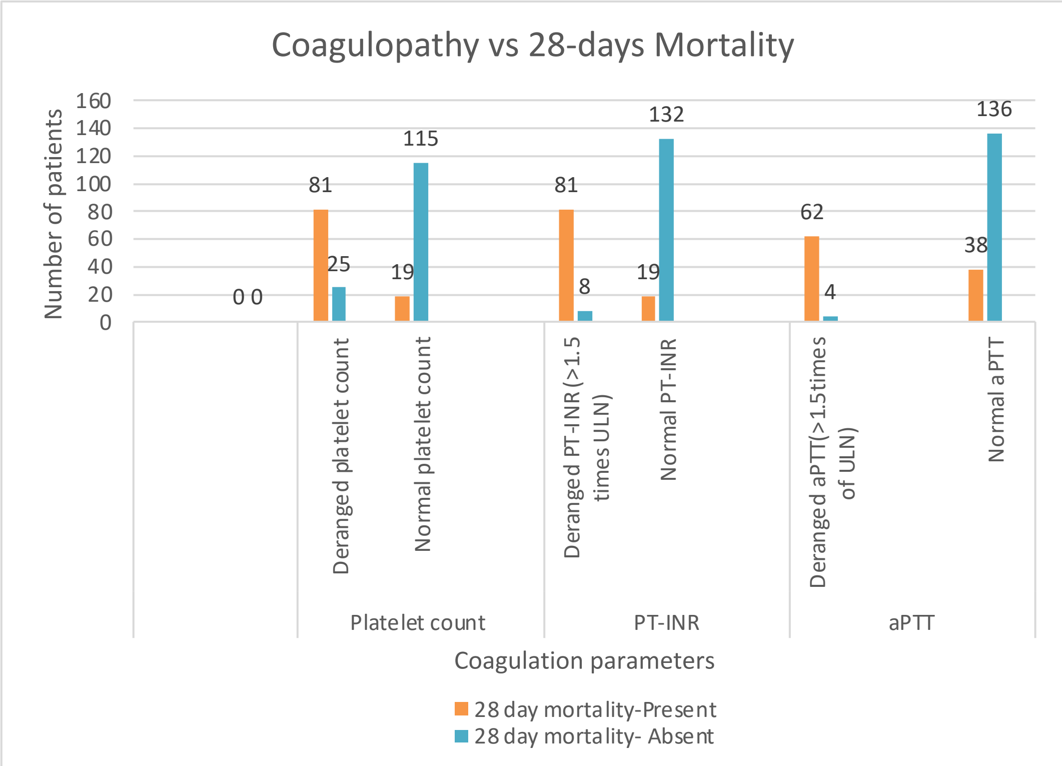

Figure 4*. Analysis of 28-day mortality with coagulopathy in relation to individual coagulation parameters in study subjects (p<0.001).*

Twenty-eigth-day mortality in patients with coagulopathy associated with PT-INR derangement was 91% (81/89) and in patients with coagulopathy associated with aPTT derangement was 93.9% (62/66) (Figure 4). Significant statistical association was observed by using Fisher's exact test (p<0.05) between 28-day mortality and coagulopathy.

In our study, 28-day mortality was seen in overall 41.7% (100/240) study subjects and remainder 58.3% (140/240) subjects survived during the 28-day follow up. Todi *et al*. in a multicentric prospective observational study conducted in India in 2010, which included 5,478 admissions, observed that the mortality rate among admissions related to sepsis was 59.26%[15]. Mortality rates seen in our study was considerably higher as compared to western literature. This difference was possibly due to sample size bias.

Measurement of procalcitonin (PCT) can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis[16]. In our study, PCT was done in 42 subjects, at clinician's discretion, wherein 26.2% (11/42) had normal PCT levels, 9.5% had levels between 0.51-2.0 ng/ml (suggestive of sepsis), 21.4% had levels between 2.01-9.99 ng/mL (suggestive of severe sepsis) and 42.9% had levels >10 ng/mL (suggesting septic shock).[16,17] Observed mortality rate increased with higher PCT values such that no mortality 0% (0/29) was seen in subjects with normal PCT values and 100% (18/18) mortality was seen in subjects with values >10 ng/mL. Thus, high PCT level was associated with increased mortality risk. Relationship between 28-day mortality and PCT level was found to be statistically significant by Fisher's exact test (p<0.05). Similar findings were observed in 2015 by Li *et al*. in a retrospective analysis of 115 patients admitted in ICU with ventilator associated pneumonia where serum procalcitonin was found to be an independent prognostic biomarker of mortality in critically ill patients.[17] Also, relationship between PCT and coagulopathy was assessed in our study. Coagulopathy was absent i.e., 0% (0/11) in subjects with normal PCT levels; however, prevalence of coagulopathy increased to 100 % (18/18) in subjects having PCT>10.0 ng/mL. This association was also shown to be statistically significant with Fisher's exact test (p<0.05).

Mortality was also seen to increase with an increase in APACHE II score. In our study, 0 % (0/110) mortality was seen with APACHE II score 5-14 whereas 100% (91/91) mortality was seen with APACHE II score >25 (Figure 5). This association was shown to statistically significant with Fisher's exact test (p<0.05). This was in concurrence with a study conducted by Naved *et al*. which included all patients admitted to ICU wherein 84.6% deaths had APACHE II score between 31-40.[18] Desai *et al*. in a prospective study in rural ICU setting observed mortality rate of 87.5% (i.e., 21 out of 24 non-survivors) having APACHE II score >21.[19]

Presence of coagulopathy was seen to increase with an increase in APACHE II score. Coagulopathy was present in 18.18% (20/110) patients with APACHE II score 5-14, 30% (9/30) patients with APACHE II score 15-19, 66.66% (6/9) in patients with APACHE II score 20-24 and 100 % (91/91) in patients with APACHE II score >25 (Figure 5). This was found to be statistically significant using Fisher's exact test (p<0.05). This was in concurrence with a prospective multi-national clinical trial study in 2005, conducted by Dhainaut *et al*., where alteration in coagulation parameters was associated with increased 28-day mortality rate and integrating composite coagulopathy with the APACHE II score improved the ability to predict which patients would develop multiple organ failure and die.[20]

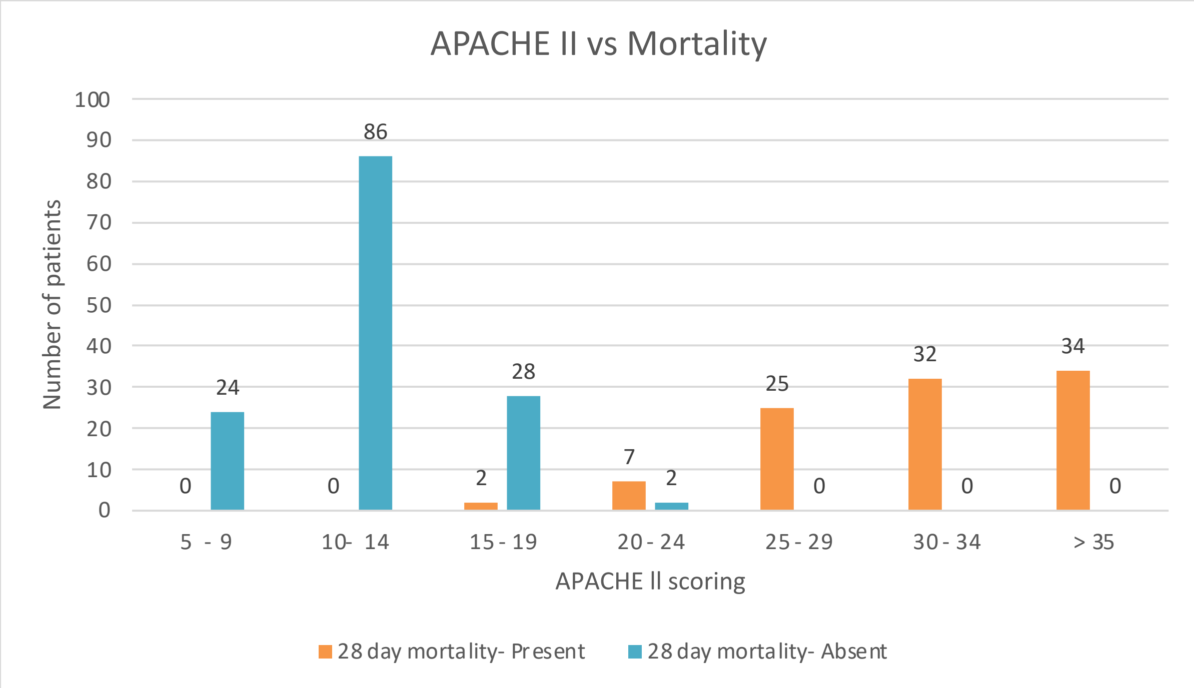

Figure 5. *Analysis of 28-day mortality with APACHE II scoring in study subjects.*

In our study, out of 126 subjects who were found to have coagulopathy, maximum mortality was seen in <40 years age group and with >60 years age group. 100% mortality was seen in age group <40 years (9/9) and 81-90 years age group (13/13), whereas 82.7% (72/87) mortality was seen in age group above 60 years. Relationship between age group and 28-day mortality was seen to be statistically significant using Fisher's exact test (p<0.05). Higher mortality rates (50-60%) was seen in elderly age group admitted with sepsis in studies conducted by Nasa *et al*. in 2012 and Martin *et al*. in 2006.[21,22] Because of its association with comorbidities, impaired immunological responses, malnutrition, greater exposure to presumably resistant strains in healthcare facilities, and increased use of medical devices such as indwelling catheters and central venous lines, the elderly age group is most likely a risk factor for mortality.[23] However, when age group less than 40 years were considered, out of 18 patient in-toto enrolled in our study, 50% (9/18) had coagulopathy, out of which 100% (9/9) died. Contrasting results were obtained by Martin *et al*. in their longitudinal observational study in 2006, involving 10,422,301 adult septicemic patients over 24 years wherein younger septicemic patients had decreased mortality rate. This difference could be due to the different sample size. Also, in our study, septicemic patients were having additional coagulopathy element were taken into consideration unlike Martin *et al* study which included only septicemic patients[21]. Younger age group patients admitted with septicemia and having additional element of coagulopathy had significantly increased mortality rate. However, we could not find any major study in previous literature to compare our findings.

In our study, 58.2% (57/98) mortality was observed in male population and 41.8% (41/98) was observed in female population. This relationship of gender with 28-day mortality was observed to be statistically significant using Fisher's exact test (p<0.05). Gender related differences in mortality rate was also seen by Adrie *et al*. and women were found to have much lower mortality rates as compared to male population.[24] The higher immune system activation, sex hormone profile and sex-related gene polymorphisms in females could probably explain this variation.[24]

The mortality rate amongst patients with coagulopathy and comorbidities were also assessed. Malignancy (28/28) and HIV (11/11) were associated with 100% mortality whereas diabetes, hypertension, CKD, IHD, CLD were found to be 89.74% (35/39), 93.75% (30/32), 91.6% (11/12), 90.9% (10/11) and 52.7% (19/36) respectively. In our study, significant proportion of patients with underlying medical illnesses developed coagulopathy followed by mortality. However, coagulopathy observed in patients with CLD was possibly related to the underlying CLD itself and hence observed mortality amongst CLD was on lower side as compared to other illnesses. Wang *et al*. in 2012 in their longitudinal study observed association between baseline chronic medical conditions and sepsis and hence they inferred that patient's comorbidities and functional health status were also important determinants of outcomes in sepsis.[25]

Univariate logistic regression for mortality showed PT-INR, aPTT and APACHE II scores to be independent variables. Multivariate logistic regression revealed severe increase in PT-INR [adjusted OR=1.622 (0.841, 3.092)], moderate increase in aPTT [adjusted OR=4.537 (0.989, 7.326)], and severe increases in aPTT [adjusted OR=3.851 (2.438, 4.996)], and APACHE II scores [adjusted OR=5.381 (1.925, 11.01)], were independently associated with 28-day mortality whereas age, sex, any severity of thrombocytopenia, mild to moderate increase in PT-INR, and mild increase in aPTT were not.

Conclusion

Early onset coagulopathy is significantly associated with increased mortality risk in septicemic patients. Septicemic patients should be screened for coagulopathy within 24-48 hours of admission in appropriate clinical scenario to predict mortality outcome and take necessary action at the earliest. Significant correlation exists between APACHE II scoring and coagulopathy. Role of PCT in septicemic patients with coagulopathy might have considerable prognostic significance. Underlying medical illnesses, age and gender are of important consideration while treating septicemic patients and hence should be carefully assessed. Younger age group patients admitted with septicemia having additional coagulopathy element may have increased mortality risk. However larger studies are required to confirm this observation on wider scale.

Limitations

Sample size was small. This being a tertiary care hospital-based study, it may induce bias by selecting more seriously ill patients which are referred from peripheral hospitals and therefore may be associated with increased mortality rate. Pregnant females and trauma related sepsis were excluded from our study. Also, differences in treatment protocols between clinicians could affect outcome and we would require large multicentric trials for reducing the bias.

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