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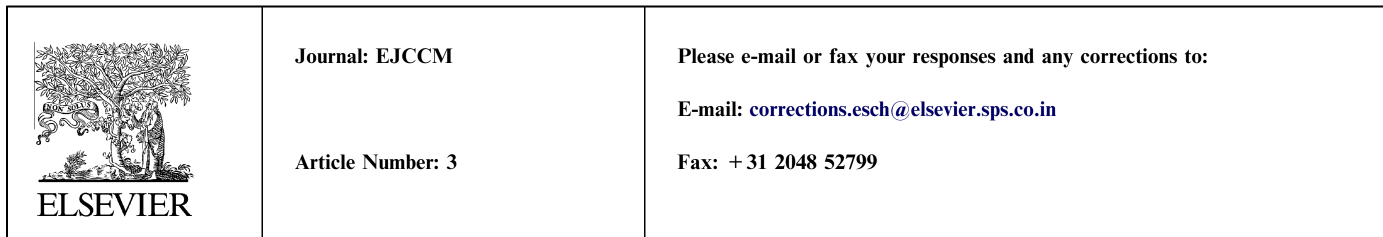

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ORIGINAL ARTICLE

Applications of the international scoring system for Disseminated Intravascular Coagulopathy (DIC) and its interaction with Sequential Organ Failure Assessment Score (SOFA) in prediction of prognosis and final outcome in ICU

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KEYWORDS
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Quantitative D-dimer level;
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APACHE II score ⩾25;
SOFA score;
DIC score;
Clinical outcome and mortality

Abstract *Introduction:* Disseminated Intravascular Coagulopathy (DIC) is a consumptive syndrome that is characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites. It is described as the combination of thrombocytopenia, decreased coagulation factors V and X causing prolonged prothrombin time, together with decreased fibrinogen and increased D-dimer levels.

Objectives: (1) To investigate the relation between DIC and increased mortality, (2) to explain the impact of the changes that occur in ISTH score for DIC in critically ill patients, (3) to determine the prognostic role of interacting DIC and SOFA scores in critically ill patients and their predictive capability when combined together than either score alone.

Design: A prospective, comparative, cohort, non-controlled, single center study from July 2011 to January 2012.

Setting: Intensive care unit at Critical Care Department in Kasr-Alainy Hospital of Cairo University.

Patients: Fifty critically ill patients with APACHE II score ⩾25, not including those with disseminated malignancies, chronic liver failure, renal failure or chronic haematological disorders.

Measurements: For all included patients with *APACHE II score* ⩾25 on admission, *DIC and SOFA scores* were calculated at baseline (on admission) and subsequently thereafter every 48 h until

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ICU discharge or death or up to a total of 28 days. Clinical outcome (duration of stay in the ICU, need for mechanical ventilation, need for inotropic/vasopressor support, need for haemodialysis, and final outcome of survival/mortality rates) were recorded.

Results: Through follow up of DIC score trend in both groups (*survivors and non-survivors*); increasing value was associated with poor prognosis (96.8% of non-survivors had DIC score value on admission lower than that before death), while decreasing or constant value was associated with better prognosis (94.4% of non-survivors had DIC score value on admission higher than or equal to that before discharge). There was a significant correlation between combined DIC and SOFA scores together with mortality and final outcome in ICU (*P* value was 0.002 at day 4 and 0.012 on discharge or at death).

Conclusion: A significant correlation exists between SOFA and DIC scores together in critically ill patients with APACHE II score ⩾25 as regards MODS and mortality. The combination of DIC and SOFA scores highly improves the prognostic performance of either score alone. It's recommended to combine these scores together for better mortality prediction.

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Introduction

Disseminated Intravascular Coagulopathy (DIC) is a complex systemic thrombohemorrhagic disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets. The resultant clinical condition is characterized by intravascular coagulation and hemorrhage. The use of the letters "DIC" as an acronym for *"death is coming"* serves to remind us that much progress remains to be made in the management of this not uncommon condition [1].

It is an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction [2].

DIC is not an illness on its own but rather a complication or an effect of progression of other illnesses and is estimated to be present in up to 1% of hospitalized patients. DIC is always secondary to an underlying disorder. Morbidity and mortality depend on both the underlying disease and the severity of coagulopathy [3].

DIC is caused by widespread and ongoing activation of coagulation, leading to vascular or microvascular fibrin deposition, thereby compromising an adequate blood supply to various organs [4]. There are a number of different triggers that can cause a hemostatic imbalance, giving rise to a hypercoagulable state. Inflammatory cytokines are the most important mediators responsible for this imbalance. It is clear that there is cross-communication between coagulation and inflammatory systems, whereby inflammation gives rise to activation of the clotting cascade, and the resultant coagulation stimulates more vigorous inflammatory activity [5].

The four different mechanisms that are primarily responsible for the hematologic derangements seen in DIC include increased thrombin generation, suppression of anticoagulant pathways, impaired fibrinolysis and inflammatory activation [6].

The pathogenesis of DIC starts at the level of the endothelium of the capillary bed where the main interaction between inflammation and coagulation takes place. Endothelial cell damage results in the release of tissue factor into the circulation, and that initiates the activation of the clotting cascade [7]. The inflammatory Cytokines (including; tumor necrosis factor α [TNF-α] & interleukin 1 [IL-1]) produced in sepsis and other generalized inflammatory states produce a state of intense inflammatory activity. Exposure to tissue factor in the circulation occurs via endothelial disruption, tissue damage, or inflammatory or tumor cell expression of procoagulant molecules. Tissue factor activates coagulation by the extrinsic pathway involving factor VIIa [8]. Evidence suggests that the intrinsic pathway is also activated in DIC, while contributing more to hemodynamic instability and hypotension than to activation of clotting [9].

Extensive bleeding is evident in the form of epistaxis, gingival bleeding, mucosal bleeding, haemoptysis, bruising, ecchymosis purpura & petechiae [10]. Manifestations of macrovascular thrombosis occur, such as deep venous thrombosis (DVT). Manifestations of microvascular thrombosis present as renal failure [11,12]. Pulmonary involvement is common

Table 1 ISTH scoring system for DIC [2].

Risk assessment	Does the patient have an underlying disorder compatible with DIC (e.g., sepsis, trauma, major operation, shock or ARDS)?
Laboratory tests	Prothrombin time
	Platelet count
	D-dimer level
	Fibrinogen level
Scoring	Platelet count: >100 = 0 points, <100 = 1 point, <50 = 2 points
	D-dimer: <1 μg/ml = 0 points, 1–5 μg/ml = 2 points, >5 μg/ml = 3 points
	Prolonged PT: <3 s = 0 points, 3–6 = 1 point, >6 = 2 points
	Fibrinogen level: >1 gm/l = 0 points, ⩽1 gm/l = 1 point
Interpretation	A score ⩾5 is compatible with overt DIC
	A score <5 is suggestive of non-overt DIC

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due to ARDS [13]. Neurological changes are also possible [14]. Jaundice can be seen because of comorbid liver disease as well as rapid hemolytic bilirubin production [15]. Skin manifestations are not uncommon as purpura fulminans, localised infarction and gangrene [16]. Manifestations of complications may be present as shock and MODS [17].

Diagnosis of DIC requires a clinical suspicion, predicated by the presence of an appropriate underlying disease and abnormal laboratory studies [18]. The diagnosis is made based on the clinical picture in combination with laboratory studies Patients with DIC can present with a wide range of abnormalities in their laboratory values. Typically, prolonged coagulation times, thrombocytopenia, high levels of fibrin breakdown products as elevated D-dimer and fibrin degradation products (FDPs), reduced fibrinogen and microangiopathic pathology (schistocytes) on peripheral blood smears are suggestive findings [19]. The International Society on Thrombosis and Haemostasis (ISTH) developed a simple scoring system for the diagnosis of overt DIC as shown in Table 1. The diagnostic imaging is based on the areas suggestive of thrombosis and hemorrhage. Other tests are directed towards the underlying cause of DIC.

Patients and methods

It is a *prospective study* including *fifty* critically ill patients who were admitted to the Critical Care department at Cairo University from July 2011 to January 2012.

Inclusion criteria:

- Age group (⩾15 and ⩽80 years).
- Informed consent given by the patient or first degree relative.
- Critically ill patients with high APACHE II score ⩾25 on admission or within 24 h of ICU admission (predicted mortality ⩽50%).

Exclusion criteria:

- Extremes of age (<15 and >80 years).
- Disseminated malignancies (Liver metastasis).
- Chronic liver cell failure classified as Child-Pugh class C.
- Chronic renal failure on regular dialysis.
- Chronic haematological disorders (e.g. leukemia, lymphoma, and purpura).
- Patients known to have coagulation defects or receiving anticoagulation therapy.
- Concomitant treatment with carcinostatics or irradiation.
- Post-cardiopulmonary resuscitation status.
- APACH II score on admission or within 24 h of admission <25.
- Delay more than 24 h after meeting inclusion criteria.
- Patients went out from ICU against medical advice.
- Those whose investigations could not be done or lost.
- Unknown outcome or loss of patient follow up due to transfer to other hospitals.
- Missing values of any included patient.
- Refusal of the patient or relatives to sign consent form.

APACHE II score was evaluated in the first 24 h of admission and patients with score ⩾25 who didn't meet any of the exclusion criteria were include in our study as shown in Tables 2 and 3.

All studied patients were subjected to signed *consent*, medical *ethics committee approval*, detailed *history* taking, careful physical *examination*: including; *conscious level*: using Glasgow

Table 2 Acute physiology points of APACHE II score.

Physiologic variables	High abnormal range					Low abnormal range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal)	⩾41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	⩽29.9
Mean arterial pressure	⩾160	130–159	110–129		70–109		50–69		⩽49
Heart rate	⩾180	140–179	110–139		70–109		6–9	40–54	⩽39
Respiratory rate	⩾50	35–49		25–34	12–24	10–11			⩽5
Oxygenation: (mmHg) A-aDO2 or PaO2 a. FiO_2 ⩾0.5 record A-aDO_2 b. FiO_2 ⩽0.5 record only PaO2	⩾500	350–499	200–349		<200 PaO2 >70	PaO2 61–70		PaO2 55–60	PaO2 <55
Arterial pH	⩾7.7	7.6–7.69		7.5–7.59	7.3–7.49		7.25–7.32	7.15–7.24	<7.15
Serum sodium	⩾180	160–179	155–159	150–154	130–149		120–129	111–119	⩽110
Serum potassium	⩾7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine	⩾3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrite	⩾60		50–59.9	46–49.9	30–45.9		20–29.9		<20
White cell count (in 1000 s/cm)	⩾40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Serum HCO3 (if PH is not available)	⩾52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15
Glasgow Coma Scale [20] = 15 – actual GCS									
A total APS = sum of 12 variable points									

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Table 3 Age points of APACHE II score.

Age (in years)	Points
⩽44	0
45–54	2
55–64	3
65–74	5
⩾75	6

Coma score (GCS), *hemodynamics* and *systemic examination*. Routine laboratory investigations were done together with special laboratory investigations (Quantitative Fibrinogen and D-dimer assays) on day of admission and repeated every 48 h till discharge.

Length of ICU stay, the need of mechanical ventilation, need of vasopressor or inotropic support, need of renal replacement therapy (haemodialysis) and final outcome were evaluated.

DIC and SOFA scores were evaluated on day of admission and serially every 48 h until discharge as shown in Tables 1 and 4. All patients were followed up clinically and laboratory for a total of 28 days. Patients were classified as survivors and non-survivors and 28-days mortality were studied.

Statistical methods

All obtained data was analyzed statistically by SPSS (Statistical Package for Social Science) program. Statistical significance was analyzed using analysis of variance (ANOVA). All values was expressed as ranges and means ± SD (Standard Deviation) for numerical data or numbers and percentages for categorical data.

Prevalence rate was determined from the number of identified cases at the time of the study divided by all patients examined. P value ⩽0.05 was considered statistically significant. Chi square was used as a test of significance for the qualitative data. The relationship between the studied parameters was assayed by Pearson's correlation coefficient. The cut-off points will be used as <0.3 for weak correlation, 0.3–0.7 for moderate correlation, and >0.7 for strong correlation.

Chronic health points

If there was severe organ insufficiency or immunocompromization:

a. For nonoperative or emergency postoperative patients: five points.
b. For elective postoperative patients: two points.

APACHE II score equals the summation of APS points, Age points and chronic health points.

Results

Descriptive data

(1) Demographic analysis
A total number of 50 patients were involved in our study. They included 22 males (44%) and 28 females (56%) with a mean age of 63.8 ± 12.7 years. Average length of ICU stay was 12 ± 8.9 days.

(2) Age groups
Age groups contributed variably to the whole patient groups in our study as shown in Table 5.

(3) Gender distribution
In the current study, there was a discrepancy between males and females for cause of admission. Post-operative ICU care was the commonest cause for admission in females (32.1%), while major trauma represent the commonest cause for admission in males (36.3%) as shown in Table 6.

(4) Outcome of study population
The clinical outcome of studied patients was evaluated at day 28 as shown in Table 7.

Through comparison between *patients who improved or survived* and *those who died within 28 days of ICU admission*, we found that there was a significant variance between both

Table 5 Percentage of age groups for studied patients.

Age groups (years)	Percentage of patients
11–20	2
21–30	0
31–40	2
41–50	10
51–60	22
61–70	28
71–80	36

Table 4 SOFA score.

SOFA score components	1	2	3	4
Respiration: $Pa02/FiO_2$ (mmHg)	300–399	200–299	100–199	<100
Coagulation: platelets ($\times 10^3/mm^3$)	150–100	50–100	20–50	<20
Liver: bilirubin (mg/dl)	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular: hypotension	MAP <70 mmHg	Dopamine ⩽5 ug/kg/min or dobutamine (any dose)	Dopamine >5 ug/k/min or Epinephrine <0.1 ug/kg/min or Norepinephrine ⩽0.1 ug/kg/min	Dopamine >15 ug/kg/min or Epinephrine <0.1 ug/kg/min or Norepinephrine >0.1 ug/kg/min
Cental nervous system: Glasgow Coma Scale [20]	13–14	10–12	6–9	<6
Renal: creatinine (mg/dl) or urine output	1.2–1.9	2.0–3.4	3.5–4.9 or <500 ml/day	>5.0 or <200 ml/day

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194 groups in DIC score at day 2, day 4 and upon discharge (P value 0.01, < 0.001 and < 0.001, respectively). While patients who died showed a significant increase in DIC score, those who improved showed a significant decrease in DIC score as shown in Table 8.

Table 6 Cause of admission for males versus females.

Cause of admission	Percentage from total admitted males	Percentage from total admitted females
Trauma	36.3	7.1
Post-operative care	4.5	32.1
Respiratory failure	18.1	21.4
Sepsis	27.2	14.2
Septic shock	13.6	25

Table 7 Final outcome of studied patients.

Outcome	Frequency	Percent
Survivors	18	36
Non-survivors	32	64

Table 8 DIC score of studied patients at day 2, day 4 and on discharge.

Outcome	DIC score at day 2	DIC score at day 4	DIC score on discharge
Survivors			
Mean	2.83	2.67	2.33
Std. Deviation	0.99	0.91	1.09
Non-survivors			
Mean	3.59	3.91	4.34
Std. Deviation	0.95	1.17	1.00
P value	0.01	< 0.001	< 0.001

199 *Correlations with patients' outcome*

200 Fig. 1 shows a statistically significant correlation between DIC scores at day 4 and patients' outcome (P value < 0.001).

Similarly, there was a statistically significant correlation between DIC scores on discharge or at death and patients' outcome (P value < 0.001) as shown in Fig. 2. 204

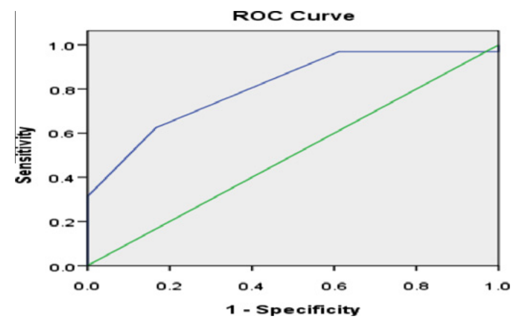


Figure 3 ROC curve for DIC score at day 4 as a determinant of outcome.

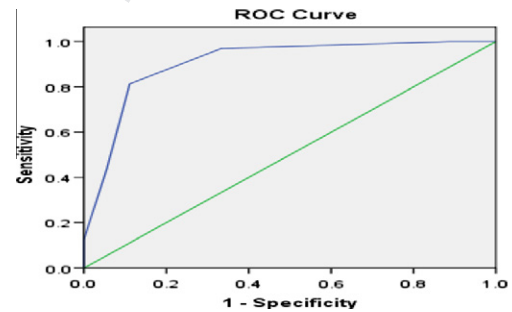
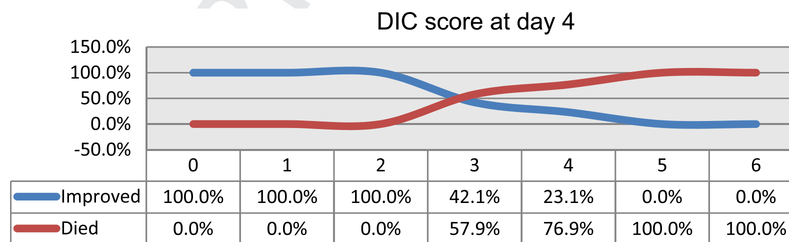
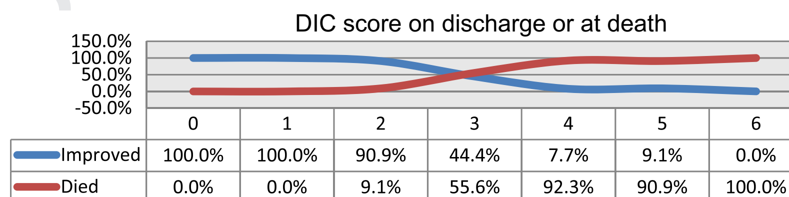


Figure 4 ROC curve for DIC score on discharge as a determinant of outcome.



	0	1	2	3	4	5	6
Improved	100.0%	100.0%	100.0%	42.1%	23.1%	0.0%	0.0%
Died	0.0%	0.0%	0.0%	57.9%	76.9%	100.0%	100.0%

Figure 1 DIC score at day 4 in relation to outcome.



	0	1	2	3	4	5	6
Improved	100.0%	100.0%	90.9%	44.4%	7.7%	9.1%	0.0%
Died	0.0%	0.0%	9.1%	55.6%	92.3%	90.9%	100.0%

Figure 2 DIC score on discharge in relation to outcome.

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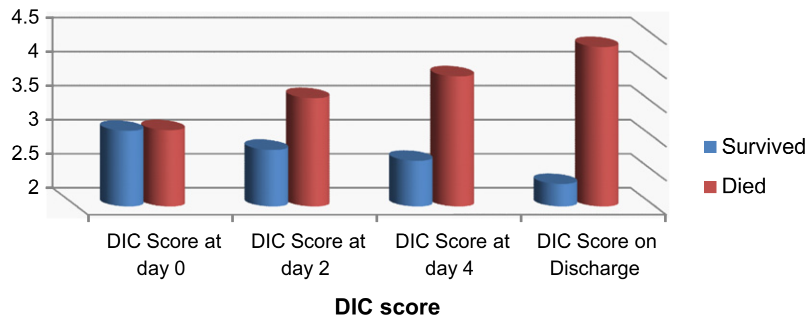

Figure 5 DIC score trend in survivors and non-survivors.

Receiver operating characteristic (ROC) curves analyses

When ROC curve was used to determine DIC score at day 4 as a determinant of outcome, the area under the curve was 80.9% and the best cut-off value was 2.5 with a sensitivity of 96.9% and a specificity of 38.9% (Fig. 3).

When ROC curve was used to determine DIC score upon discharge as a determinant of outcome, the area under the curve was 90.6% and the best cut-off value was 2.5 with a sensitivity of 96.9% and a specificity of 66.7% (Fig. 4).

Table 9 Cause of admission in relation to patients' mortality.

Percentage of patients with DIC score ⩾5	Percentage of non-survivors	Cause of admission
70	100	Shock
42.8	70	Trauma
42.8	70	Post-operative care
16.6	60	Respiratory failure
50	20	Sepsis

Mortality data

In the current study, 32 out of 50 critically ill patients died while 18 survived with an average mortality rate of 64%. About 71.4% of our studied patient with DIC score ⩾5 on day 0 (i.e. diagnosed as overt DIC since admission) died. About 46.87% of our included critically ill patients who died in our study have DIC score ⩾5 either on admission or during follow up.

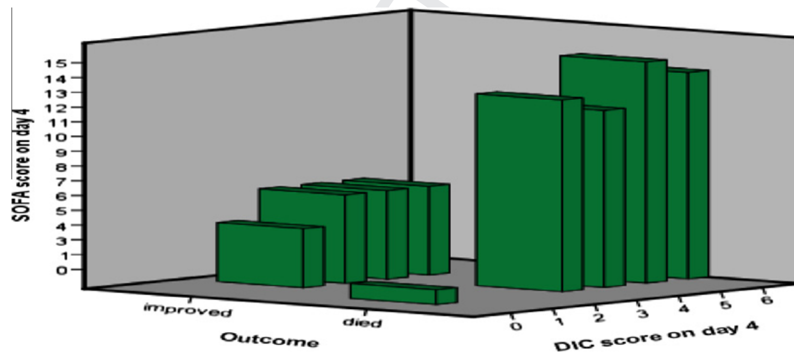

Figure 6 Correlation between interacting DIC and SOFA scores at day 4 with mortality.

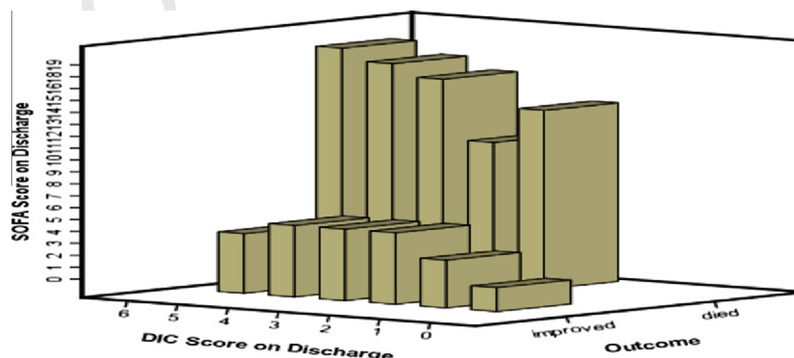

Figure 7 Correlation between interacting DIC and SOFA scores on discharge with mortality.

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Following the DIC score trend of both groups of studied patients (those who improved and those who died), our study showed that: about 96.8% of our study patients who died have DIC score value on admission lower than that before death. In contrast, about 94.4% of our study patients who survived have DIC score value on admission higher than or equal to that before discharge as in Fig. 5.

The relation between the cause of admission and patients' mortality in non-survivors was shown in Table 9.

Interacting SOFA and DIC scores on mortality

In the present work, we explored interactions of combined SOFA score and DIC score at day 4 and on discharge or death upon patients' outcome (improved or died).

- *Combined SOFA and DIC scores at day 4*: Odds of outcome occurrence (i.e. death) increases 1.17 times with each unit increase in SOFA & DIC scores, interacting together (*P* value 0.002). As shown in Fig. 6, survivors had lower SOFA & DIC scores, while non-survivors had higher SOFA & DIC scores.
- *Combined SOFA and DIC scores on discharge*: Odds of outcome occurrence (i.e. death) increases 1.5 times with each unit increase in SOFA & DIC scores, interacting together (*P* value 0.012). As shown in Fig. 7, survivors had lower SOFA & DIC scores, while non-survivors had higher SOFA & DIC scores.

Discussion

Early assessment of critically ill patients and accurate prediction of prognosis in the intensive care unit are important to allow appropriate treatment decisions by patients, relatives, and medical attendants [21]. In general, the earlier an accurate diagnosis is made and appropriate treatment started, the greater the chance of survival, fewer complications, better quality of life, and lower health care costs [22,23]. Therefore, the need to identify scores that aid clinicians in diagnosis, prognosis, and disease monitoring is driving the clinical scientific research [24,25]. The most commonly available tools for prediction of prognosis in ICU are APACHE II score (Acute Physiology and Chronic Health Evaluation) and SOFA score (Sequential Organ Failure Assessment) which predict morbidity and mortality of critically ill patients [26,27].

These scoring systems are based on several physiological indices and chemical variables. Over the years, several problems, pitfalls, and limitations of these scoring systems have been identified. Furthermore, they are very cumbersome and time consuming to apply, as they are based on several biochemical measurements and several physiological indices [21]. Although numerous scoring systems have been evaluated to predict morbidity and mortality of critically ill patients in the intensive care setting, yet none of them has proven entirely useful.

Interest has been developed in the use of DIC (Disseminated Intravascular Coagulopathy) score as a prognostic marker for critically ill patients in ICU [28]. Our study used a simple scoring system that was developed by the International Society of Thrombosis and Haemostasis (ISTH) as a diagnostic approach with good sensitivity and high specificity depending on a set of criteria for the diagnosis of DIC including the presence of an underlying disorder, platelet count, prothrombin time, quantitative D-dimer and fibrinogen levels. A score of five points or greater indicates overt DIC, while a score of less than five points does not rule out DIC but may indicate non-overt DIC [2].

In the current study, *DIC score* was higher on admission in patients with APACHE II score $\geqslant 25$ who died when compared to those who survived or improved with no statistical significance (*P* value 0.967) this might be due to limited number of studied patients. However, there was a statistically significant higher DIC score in patients with APACHE II score $\geqslant 25$ who died when compared to those who survived or improved at day 2, day 4 and upon discharge or at death (*P* value 0.01, < 0.001 and < 0.001, respectively). Our study also reported that there was a significant correlation between DIC score at day 4 and on discharge or at death with the outcome of patients with APACHE II score $\geqslant 25$ (*P* value < 0.001).

In agreement with our results, Battah et al. conducted a study in 2010 showing that DIC score in the first 48 h was an accurate predictor of clinical course and outcome [29]. However, the latter study included only patients with sepsis and used SOFA and DIC scores only during the first 48 h of admission. Furthermore, Battah et al. used only two of the coagulation variables needed to calculate DIC score (platelets count and prothrombin time). In contrast, our study included various etiologies for ICU admission, and used SOFA and DIC scores at day 0, day 2 and day 4 during ICU stay and upon discharge or at death, in addition to the use of all of the four essential parameters needed to calculate ISTH score for DIC (including; platelets' count, prothrombin time, quantitative serum fibrinogen and D-dimer levels).

In our study, the changes that occured in DIC score from admission to 48 h later represented an accurate predictor of clinical course and may have reflected improvement or worsening of the underlying disease. We chose to award points even when the absolute values of PT and/or platelet count were within normal range. This may highlight the value of change over time rather than single admission score.

These results agree with the results of the study of Dhainaut et al. who noted in 2005 that worsening coagulopathy correlated with worsening outcome in patients with severe sepsis [30]. However, Dhainaut et al. didn't use the ISTH scoring system in his study to diagnose patients with DIC.

Also the present study showed that there was a statistically significant correlation between combined DIC and SOFA score in both groups of patients and clinical outcome at day 4 and on discharge or at death. Since the studied scores used to prognosticate patients' outcome have shown variable data in various studies and regarding the previously discussed conflicting data for these scores, we recommend combining APACHE II, SOFA and DIC scores together in order to improve the prognostic capability of these scores.

In our work, we have combined SOFA score together with DIC score to improve the predictive power of the scoring systems used in critically ill patients with APACHE II score $\geqslant 25$. Our results were supported by a retrospective study conducted in 2006 by Kazuhiro et al. showing that combination of APACHE II score and DIC score predicted mortality better than the APACHE II score alone [31].

In contrast, we disagree with the study of Hiromoto et al. that was performed in 2012 on patients with severe trauma showing that DIC and SOFA scores at day 0 were not predic-

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tive of the progression of DIC in traumatic patients [32]. This might be explained by the use of DIC and SOFA scores only on day 0 in their study, while our study compared DIC and SOFA score on day 0, 2, 4 and upon discharge or at death.

Our research demonstrated that DIC score could be used as a potentially useful marker that is easy to perform and interpret for the evaluation of critically ill patients when admitted to the ICU and for early prognosis and prediction of their adverse outcomes and rapid risk stratification that might allow clinicians to make more rational therapeutic decisions and to ensure that the hospital resources are used efficiently and appropriately which is of particular significance in the intensive care environment.

Conclusion

There is a strong correlation between Disseminated Intravascular Coagulopathy (DIC) in critically ill patients with poor final outcome and increased mortality in ICU.

Increasing value of DIC score during follow up of critically ill patients is associated with poor prognosis even if it is incompatible with the diagnosis of overt DIC (i.e. DIC < 5), while decreasing or constant value of DIC score is associated with better prognosis.

The combination of the different scoring models strongly supports and highly improves the prognostic performance of either model alone.

Recommendation

We recommend using the promising ISTH scoring system for DIC to predict mortality and prognosis in critically ill patients with APACHE II score $\geqslant 25$. Serum quantitative D-dimer and fibrinogen levels are required to calculate DIC score.

Not only using single measurement of DIC score, but also following up the trend of DIC score of critically ill patients with APACHE II score $\geqslant 25$ every 48 h during ICU stay, whether it is declining or constant or increasing is essential in order to help in determination of the clinical course of the underlying disease and to detect the response to applied treatment.

We also do recommend the combined use of SOFA score together with DIC score for better prediction of mortality of critically ill patients in intensive care unit.

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