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Original Article

Can disseminated intravascular coagulation scores predict mortality in COVID-19 patients?

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خلاصة

أهداف البحث: تؤدي المضاعفات المرتبطة بـ كوفيد-١٩ إلى تخثر منتشر داخل الأوعية، الأمر الذي تم الإبلاغ عنه على أنه أحد أسباب الوفيات لدى هذه الفئة من المرضى. هدفت هذه الدراسة إلى تحليل حدوث التخثر المنتشر داخل الأوعية لدى غير الناجين ولتقييم العلاقة بين التخثر المنتشر داخل الأوعية والأمراض المصاحبة.

طرق البحث: تم تحليل السجلات الطبية لـ ١٥٤ من غير الناجين من كوفيد-١٩، الذين تم إدخالهم إلى المستشفى بين أبريل ٢٠٢٠ ويوليو ٢٠٢٠ بأثر رجعي. تم تطبيق معايير الجمعية الدولية للتخثر والإرقاء لتحديد حدوث اعتلال التخثر. وتم استخدام تحليل خواص التشغيل المتلقي لتقييم الارتباط بين التخثر المنتشر داخل الأوعية والأمراض المصاحبة.

النتائج: من بين ١٥٤ من غير الناجين، لوحظ وجود تخثر منتشر داخل الأوعية غير العلني في ٩٤.٨٪ من المرضى بينما استوفى ٥.٢٪ فقط المعايير العلنية للتخثر المنتشر داخل الأوعية بمتوسط عمر ٦٤.٦سنة. وكان معدل الوفيات ٥.٤مرات أعلى بين الذكور مقارنة بالإناث. وكان مستوى د-دايمر> ٢٥٠نانوغرام / مل في ٦٨.٨٪ من المرضى بما في ذلك ٨٨.٩٪ من المرضى غير الصريحين و١٠٠٪ من مرضى التخثر المنتشر داخل الأوعية العلني. وكان زمن البروثرومبين في حالات التخثر المنتشر داخل الأوعية غير العلنية والعلنية ١٧.٣ثانية و ٢٤.٤ ثانية على التوالي. كما تم العثور على الحدث

التخثري وأمراض الكلى المزمنة لتكون من العوامل الرئيسية للتنبؤ ويليها داء السكري وارتفاع ضغط الدم، دون دلالة إحصائية.

الاستنتاجات: نستنتج أن درجة معايير الجمعية الدولية للتخثر والإرقاء لتحديد حدوث اعتلال التخثر لا يمكن أن تتنبأ بالوفيات لأن التخثر المنتشر داخل الأوعية المرتبط بـ كوفيد-١٩ تختلف عن التخثر المنتشر داخل الأوعية الذي يسببه الإنتان. من بين المرضى الذين يعانون من أمراض خطيرة، فإن المرضى الأكبر سنا الذين يعانون من أمراض مصاحبة، وزيادة مستويات د-دايمر وزمن البروثرومبين المطول هي معايير أكثر موثوقية بين غير الناجين من كوفيد-١٩.

الكلمات المفتاحية: زمن البروثرومبين؛ كوفيد-١٩؛ التخثر المنتشر داخل الأوعية؛ إنتان؛ وفيات

Abstract

Objectives: Complications related to coronavirus disease 2019 (COVID-19) may lead to disseminated intravascular coagulation (DIC), which has been reported to be among the known causes of mortality in such patients. This study aims to analyse the incidence of DIC in COVID-19 non-survivors and to assess the association between DIC and its comorbidities.

Methods: The medical records of 154 non-survivors of COVID-19, hospitalised between April 2020 and July 2020, were retrospectively analysed. The International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC were applied to identify the occurrence of coagulopathy. The receiver-operating characteristic (ROC) analysis was used to assess the association between DIC and its comorbidities.

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Results: Out of 154 non-survivors, non-overt DIC was observed in 94.8% of the patients, whereas only 5.2% fulfilled the overt criteria of DIC with a mean age 64.6 years. The mortality rate was 4.5 times higher among men than women. The D-dimer level was >250 ng/ml in 68.8% of the patients including 88.9% of the non-overt and 100% of the overt DIC patients. Prothrombin time (PT) in non-overt and overt DIC cases was 17.3 s and 24.4 s, respectively. Thrombotic event and chronic kidney disease were found to be the main predictors of DIC ($p < 0.0001$ and 0.03, respectively) followed by diabetes mellitus (DM) and hypertension (statistically insignificant).

Conclusions: Our study concludes that the ISTH DIC score cannot predict mortality as the COVID-19 related DIC differs from the sepsis-induced DIC. Among the seriously ill, older patients with comorbidities, increased levels of D-dimer and prolonged PT are more reliable parameters among COVID-19 non-survivors.

Keywords: COVID-19; Disseminated intravascular coagulation; Mortality; Prothrombin time; Sepsis

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which belongs to *genus Betacoronavirus*.[1] It was first noticed when cases of pneumonia of unknown aetiology emerged in November 2019 in Wuhan, the capital of the Hubei province in China which were reported to the world as 2019-nCoV on 31 December 2019. By 7 January 2020, its genome was successfully sequenced[2] and molecular surveillance of the virus is continuing as it has strong potential to undergo further mutations.[3] The World Health Organization (WHO) confirmed the epidemic to be a Public Health Emergency of International Concern on 30 January 2020, officially naming it as coronavirus disease 2019 (COVID-19) in February 2020.[2] In March 2020, it was recognised as a global pandemic[4] and so far, its mortality rate has been reported to be 2.35%. As time passes on, data regarding different aspects of SARS-CoV-2 infection is being reported in Pakistan where cases have crossed the figure of 327,929 with a mortality rate of 2.3% (dated 23 November 2020). There is a wide consensus that the disease spreads through aerosols of infected individuals.[5] Elderly males with comorbidities are at a higher risk of the disease.[1,6] Moreover, the spectrum of COVID-19 severity is quite variable and has been revised many times as most of the patients present with mild symptoms and only 14% of them end up in a critically ill state.[1,7] Pneumonia, coagulopathy, multi-organ dysfunction and sepsis are among the major complications observed as the severity of the disease increases.[2,8]

Disseminated intravascular coagulation (DIC) has a potentially fatal outcome in many conditions and occurs when multiple small thrombi accumulate in small blood vessels of the body, leading to ischaemia of the vital organs.[9] These thrombi are a result of fibrin deposition due to an exaggerated host inflammatory response and imbalance between coagulation and fibrinolysis, thus resulting in the activation of coagulation cascade[9] and the simultaneous consumption of coagulation factors and platelets. Clinically, this may present as thrombocytopenia, bleeding and ultimately multi-organ failure.[10,11] Infections, malignancy, gynaecological trauma and obstetric disorders along with certain other conditions have been implicated for the occurrence of DIC.[9] Notably, worse clinical outcomes have been reported where the disease has been complicated by DIC, which has led to an increase in morbidity and mortality. Several studies in the past explored the causation and pathophysiology of this condition with the paradigm gradually shifting to an early recognition and timely management before the end organ damage sets in. DIC scores help to identify coagulopathy at the earlier stage and higher scores correlate with more severe outcomes and mortality.[12] The International Society on Thrombosis and Haemostasis (ISTH) DIC score, based on four simple laboratory parameters, has been found to be useful for diagnosing DIC both in infective and non-infective cases, with a sensitivity of 91% and specificity of 97%. Overt DIC is diagnosed when the score is ≥ 5, while a score of <5 is considered as non-overt DIC and an increasing score is associated with increased mortality.[9] Subsequently, coagulation abnormalities resembling DIC have been observed in COVID-19 patients. Whether DIC is due to viral infection itself or due to superimposed infection/hypoxia in critically ill patients is still debatable.[13]

This study aimed to analyse the incidence of DIC based on the ISTH DIC scoring criteria in patients who died of SARS-CoV-2 infection. Another aim of this study was to assess the association between different comorbidities and DIC in these patients.

Materials and Methods

Patient sample

This was a retrospective analysis of patients with COVID-19 between April 2020 and July 2020, carried out at the Department of Pathology at the Pakistan Emirates Military Hospital which is affiliated with Army Medical College, Rawalpindi. The study was approved by the Ethical Review Committee at our institute. Patients were diagnosed with SARS-CoV-2 based on a real-time polymerase chain reaction (RT-PCR) and/or radiological findings. All of the deceased with complete medical records irrespective of age and gender fulfilled the inclusion criteria. Survivors and those with missing laboratory data were excluded. A total of 170 deaths were reported from different medical units in our hospital and were screened for inclusion. Sixteen patients

dropped out because of absence of consent (N = 10) and incomplete laboratory data (N = 6). A total of 154 patients fulfilled the inclusion criteria and were coded in order to avoid disclosure of identity. Demographic and clinical data included age, sex, the presence of comorbidities (e.g. diabetes mellitus [DM], hypertension, ischaemic heart disease [IHD], chronic kidney disease [CKD], malignancy, etc.) along with any complications and length of stay at the hospital.

In accordance with the hospital ethics committee protocol, an informed consent regarding treatment as well as the use of patient data for research purposes was taken at the time of admission from every COVID-19 infected patient and information sheets were provided to patients/guardians. This study was conducted in accordance with the Declaration of Helsinki declaration and all the ethical aspects were met.

Laboratory parameters

All suspected COVID-19 patients visiting the hospital were diagnosed using the nasopharyngeal swabs followed by an RT-PCR. Baseline investigations were performed that also included haematological, chemical and inflammatory markers. Radiological investigations included chest x-rays and High-Resolution Computed Tomography (HRCT) in order to categorise the disease severity. The patients were observed by treating clinicians and laboratory tests were repeated at regular intervals; notably, this activity occurred at admission, every second day in the ward and every day in ICU and was based on the progression and severity of disease. Laboratory data of included patients was retrospectively retrieved from electronic records. In our study group, the patients were in either the severe to critically ill stages of the disease at the time of presentation or progressed from milder forms. For the estimation of the coagulopathy, an ISTH criterion of DIC was applied on all patients. A risk assessment was done using the underlying disorders reported in the patients' documents. Laboratory tests were carried out using Stago coagulation analyser/Sysmex CS-1600 (prothrombin time [PT]), and Sysmex XP-100 (Complete blood count including platelets), respectively. Latex agglutination test (Domain-dimer [D-dimer]) and Clauss fibrinogen assay (Fibrinogen) were carried out using kits by 'Helena'. The variables were graded as per the ISTH DIC score criterion. Peripheral blood smears were performed for all patients with thrombocytopenia on complete blood count to rule out pseudo-thrombocytopenia and also for those with two or more altered parameters on coagulation analysis. Micro aggregates were also noted on smears.

Statistical analysis

A statistical analysis was performed using the IBM SPSS 26 software. Continuous variables for normally distributed data were expressed using means, standard deviation and median where required. Frequencies were calculated for categorical values and were given as counts (N) and percentages. A receiver-operating characteristic (ROC) analysis was used to assess the prognostic value of the scores with comorbidities and thrombotic complications. A test with p-value < 0.05 was considered statistically significant.

Results

Out of the 154 deceased patients who met the inclusion criteria, viral RNA was detected using an RT-PCR for 135 patients (87.7%), whereas the rest (N = 19, 12.3%) had a negative RT-PCR result but showed a ground glass appearance of lung parenchyma on HRCT, which is typical of SARS-CoV-2 infection. The majority of the deceased patients were males (N = 126, 81.8%) whereas only 28 (18.2%) were females. The mean age of the patients was 62.4 years (SD ± 14.8, range 1−94 years old). The further stratification of age categories revealed that the maximum number of COVID-19 patients (N = 110; 71.4%) were between the age groups of 50 to 75 years followed by 24 patients (15.6%) who were greater than 75 years of age. Only 20 patients (13.0%) belonged to the younger age group (<50 years old), indicating a lower incidence of worse outcome and mortality in this age group. The number of patients in each age category are graphically represented in Figure 1.

The mean values of laboratory parameters for our sample in comparison to the normal reference range are given in Table 1. The analysis showed that the normal mean platelet count of our sample was 189.6 × 10^3/μl, with only less than a quarter of the patients (23.4%) having a platelet count below 100 × 10^3/μl. The mean levels of fibrinogen (270.6 mg/dl) remained within normal reference range and none of the
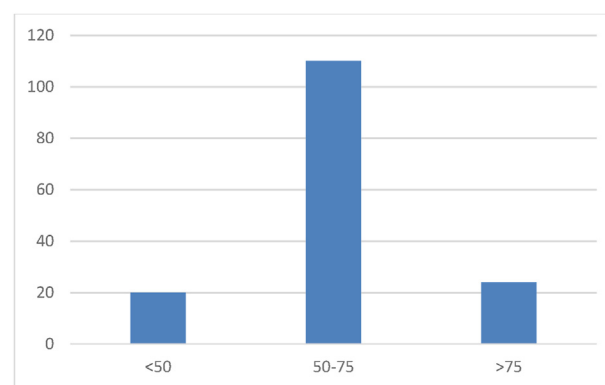
Figure 1: Frequency (N) of COVID-19 non-survivors in different age groups.

Table 1: Laboratory coagulation parameters of 154 COVID-19 non-survivors.

Parameter	Mean ± SD	Median	Sample Range
Platelet count (× 10^3/μl)	189.6 ± 114	180	11−579
Fibrinogen (mg/dl)	270.6 ± 23.8	270	200−400
Prothrombin Time (sec)	16.9 ± 11	14	14−144
D-dimer (ng/ml)	Level	Count (N)	Percentage
	<250	48	31.2%
	250−500	104	67.5%
	>500	2	1.3%

Normal reference range: Platelets: 150−450 × 10^3/μl; Fibrinogen: 200−450 mg/dl; PT: 11−14 s; D-dimer: < 250 ng/ml.

Table 2: Coagulation parameters and sample scores based on the ISTH criteria of DIC (N = 154).

Parameters	Total Count N (%)
ISTH[a] criterion of DIC Score	
0	37 (24%)
1	9 (5.8%)
2	54 (35.1%)
3	30 (19.5%)
4	16 (10.4%)
5	5 (3.3%)
6	3 (1.9%)
Platelet Count (× 10^3/μl)	
>100 (0 point)	118 (76.6%)
50−100 (1 point)	27 (17.5%)
<50 (2 points)	9 (5.9%)
D-dimer[b] (ng/ml)	
<250 (0 points)	48 (31.2%)
>250 (2 points)	104 (67.5%)
>500 (3 points)	2 (1.3%)
Prolongation of PT [c] (sec)	
0-3 (0 point)	111 (72.1%)
3−6 (1 point)	30 (19.5%)
>6 (2 points)	13 (8.4%)
Fibrinogen (mg/dl)	
>100 (0 point)	154 (100%)
<100 (1 point)	0 (0%)

[a] International Society on Thrombosis and Haemostasis.
[b] Domain-dimer.
[c] Prothrombin time.

We recalculated the score for 16 (10.4%) patients with a borderline score of 4, but none showed any change. Around 54 patients (35.1%) with a score of 2 had raised D-dimer as the only abnormal finding in their analysis (Table 2).

Table 3 describes the patient characteristics and laboratory coagulation parameters of our sample, which are stratified as overt and non-overt DIC according to ISTH criteria. Among our patients, the incidence of non-overt (early asymptomatic) DIC (ISTH score < 5) was 94.8% as these 146 patients did not meet the ISTH criteria of overt DIC at any time of their hospital admission. Among these 146 patients, 37 had the ISTH score of zero (mean age 64.1 years) with their mean length of stay at the hospital at 5.9 days (range: 1−18 days). Mean platelet count, fibrinogen and PT were all in normal range for these patients, while only one patient had D-dimer levels above 250 ng/ml. For the remaining 109 patients (mean age 61.6 years) with non-overt DIC (ISTH scores 1−4), their mean length of stay at the hospital was 8.1 days (range: 1−26 days). These patients had normal mean platelet counts and fibrinogen levels, while PT was prolonged (mean 17.3 s); moreover, 97 patients had D-dimer > 250 ng/ml.

On the other hand, based on the ISTH criteria of DIC scoring, only eight patients (5.2%) were found to have overt DIC (ISTH score ≥ 5). The mean length of stay at the hospital for these patients was 17.3 days (range: 8−26 days) and the overt DIC developed between 8 and 15 days in 62.5% of the group and between 19 and 22 days in the remaining 37.5%. The mean age of these patients was 64.6 years and half of them were ≥70 years of age. These patients with overt DIC showed a drop in platelet count, a moderate to marked elevation of D-dimer, and prolonged PT but they maintained normal fibrinogen levels (Mean platelet count: 49.6 × 10^3/μl, mean PT: 24.4 s; D-dimer raised > 250 ng/ml, mean fibrinogen level: 265 mg/dl).

Diabetes mellitus (DM), hypertension (HTN), ischaemic heart disease (IHD), chronic liver disease (CLD), respiratory diseases, chronic kidney disease (CKD) and malignancy [kidney (N = 1), gall bladder (N = 1), liver (N = 1), bone (N = 1), oral cavity (N = 2)] were the comorbid conditions noted in our patients (Figure 2). The bar

patients had deranged levels. Mean PT was minimally raised (16.9 s) in our patients with 72.1% of them scoring zero (0−3 s prolonged) on the ISTH scoring system for PT. The D-dimer, on the contrary, was found to be elevated (>250 ng/ml) in a significantly larger number of patients (N = 106; 68.8%), whereas in 48 patients (31.2%) no agglutination was seen and the levels were less than 250 ng/ml. The values of coagulation parameters and ISTH scores in our sample of 154 patients are given in Table 2.

**Table 3: Patient characteristics and coagulation parameters stratified as overt and non-overt DIC.**

Parameter (Mean ± SD)	Non-overt DIC (N = 146)		Overt DIC (N = 8)
	Score 0	Score 1-4	Score ≥ 5
Total count (N)	37	109	8
Gender (Male/Female)	30/7	90/19	6/2
Length of stay (days)	5.9 ± 4.7	8.1 ± 5.5	17.3 ± 5.8
Platelet count (× 10^3/μl)	203.5 ± 103.2	186.1 ± 113	49.6 ± 30.9
Fibrinogen (mg/dl)	275.1 ± 15.7	269.5 ± 19.5	265 ± 70.9
Prothrombin time (sec)	14.2 ± 1.2	17.3 ± 12.8	24.4 ± 5.2
D-dimer (Count-N)			
<250 (ng/ml)	36	12	0
250−500 (ng/ml)	1	95	8
>500 (ng/ml)	0	2	0
Age in years (Mean ± SD)	64.1 ± 12.6	61.6 ± 15.6	64.3 ± 14.2
<50 (Count N)	2	17	1
50−75	30	74	6
>75	5	18	1

Normal reference range: Platelets: 150−450 × 10^3/μl; Fibrinogen: 200−450 mg/dl; PT: 11−14 s; D-dimer: < 250 ng/ml.
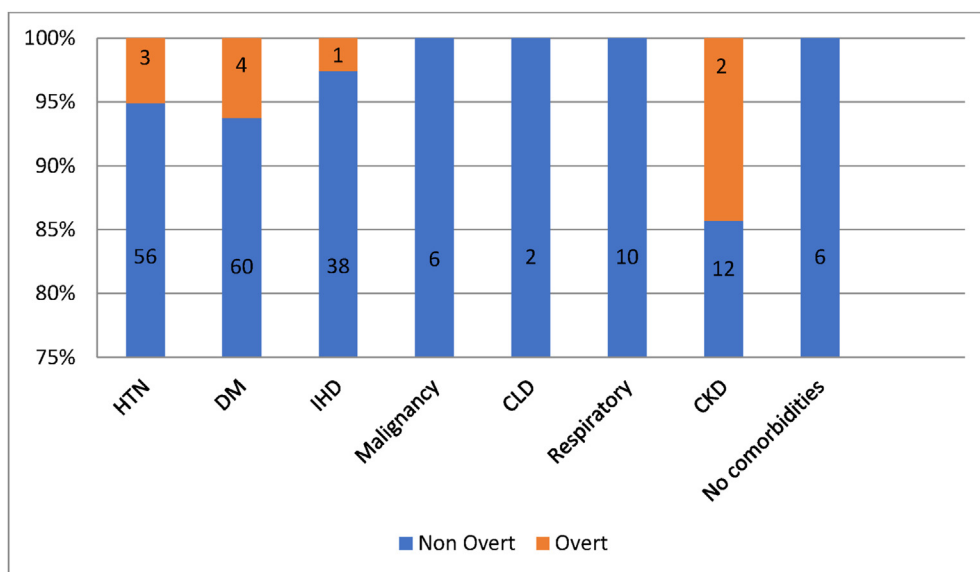
Figure 2: Frequency (Count N and %) of comorbidities in cases with overt and non-overt DIC.
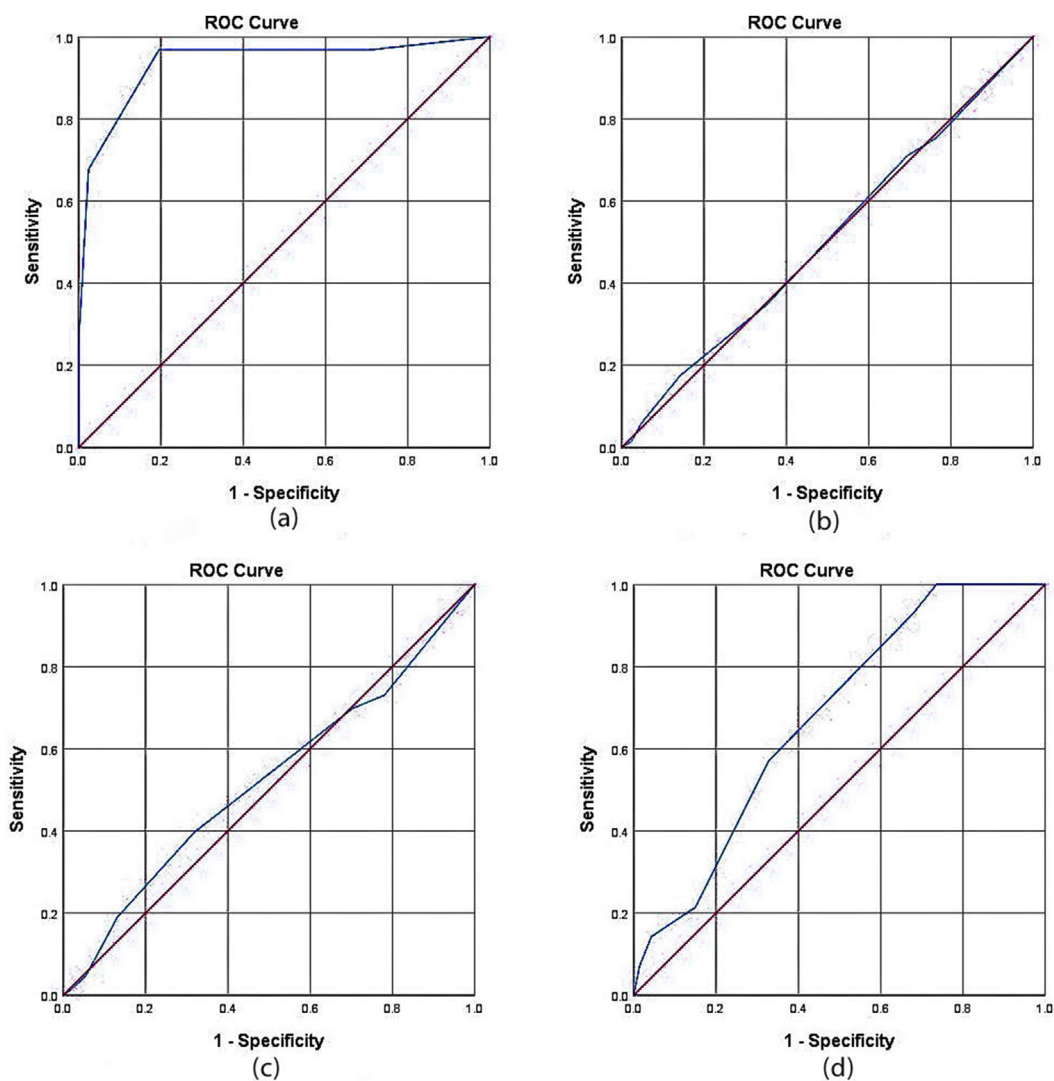
Figure 3: Receiver-operating characteristic (ROC) curves of comorbidities with DIC score. (a) Thrombotic event, (b) diabetes mellitus, (c) hypertension and (d) chronic kidney disease.

diagram shows the distribution of the frequencies of different comorbidities in patients with overt/non-overt DIC: HTN (3/56); DM (4/60); IHD (1/38); CLD (0/2); CKD (2/12); Respiratory diseases including asthma; chronic obstructive disease and pneumonia caused by other infectious causes (0/10); and Malignancy (0/6). Six patients with no comorbid conditions had non-overt DIC. During the course of admission, five patients developed an embolism among which four had pulmonary embolisms and one had a stroke (two with overt and three with non-overt DIC); seven developed sepsis (two with overt and five with non-overt DIC). In our sample, six patients were on anticoagulation therapy before admission for deep vein thrombosis (DVT), valvular heart disease, and had a coronary artery bypass graft (CABG).

The receiver operating characteristic curves were obtained for the DIC score and the different comorbidities and complications in these patients. According to the criteria of assessing the area under the curve (AUC), a thrombotic event was observed to be an excellent predictor of DIC followed by CKD as shown in Figure 3. The AUC from the ROC curves statistically showed a significant association of thrombotic event and CKD with the DIC score (AUC = 0.935; p-value < 0.001 and AUC = 0.675; p-value = 0.03 respectively). No significant association with DIC was observed for HTN (AUC = 0.521; p-value = 0.65); DM (AUC = 0.506; p-value = 0.91); IHD (AUC = 0.493; p-value = 0.91) and CLD (AUC = 0.470; p-value = 0.82).

Discussion

The novel corona virus disease (COVID-19) associated mortality rate is increasing worldwide as the total cases are exponentially increasing. In severely ill patients, respiratory failure is an initial phenomenon followed by a more complicated multiple-organ failure mainly attributed to the occurrence of coagulopathy and thromboembolic disease.[14,15] The coagulation abnormalities in COVID-19 are not fully understood yet and its pathophysiology differs from the usual sepsis-induced DIC. Hence, identification and a better understanding of these coagulation derangements can have a high prognostic value and therapeutic importance. Thus, inventing diagnostic and prognostic coagulation markers and the application of coagulation scores that can predict the progression of the disease from mild or moderate to severe or critically ill at an early stage of the disease is the key in preventing mortality. This is especially the case in low-income countries where it is difficult to provide more sophisticated and novel approaches of managing advanced coagulopathy. Therefore, this study aimed at analysing the incidence of DIC and the utility of the DIC score in predicting mortality among COVID-19 patients. Our findings reveal a high incidence of non-overt DIC using the ISTH DIC scoring criteria; moreover, they highlight the importance of elevated D-dimer and PT among COVID-19 non-survivors.

A higher incidence and mortality rate (4.5 times) among males compared to females in our cohort is in line with what has been reported by Deng et al. (2020) who found significantly more male patients among non-survivors (67%)

compared to survivors (44.0%); correspondingly, Huang et al. (2020) reported that 73% of their COVID-19 patients were males.[16,17] In our sample, this could mainly be due to cultural trends of more males working outside leading to a higher exposure to the virus. Notably, our cohort was comprised of relatively older patients (mean age of 62.4 years) with 15.6% of the patients above 75 years of age. This finding of a higher incidence of mortality among elder patients is similar to what has been reported by Wu et al. (2020), who found age ≥65 years to be a significant risk factor for development of acute respiratory distress syndrome (ARDS) and death among COVID-19 patients.[6] A higher death rate among older patients is thought to be from a weak immune system and the presence of comorbidities — specifically DM, HTN, and IHD — which are all extremely prevalent among South Asians and have been reported to be risk factors for COVID-19 associated mortality.[16,17] In this study, we also found DM to be a predictor for DIC along with a thrombotic event and CKD.

Studies have increasingly reported the existence of a syndrome similar to DIC in deaths related to COVID-19.[18] This makes the role of the DIC scoring systems even more important to diagnose early coagulation abnormalities; moreover, there should be timely therapeutic intervention to prevent the progression to full-blown DIC. The ISTH criteria for detection of DIC is an internationally used scoring system that classifies DIC into early asymptomatic (non-overt) or late symptomatic and advanced stage (overt) DIC. As COVID-19 associated coagulopathy (CAC) differs from the usual sepsis-induced DIC, the role of such a score in predicting DIC associated mortality in COVID-19 patients is an extremely important research question that still remains unanswered. Detection of non-overt DIC in COVID-19 patients could be a key factor in preventing mortality. In this study, we report a far higher incidence of non-overt DIC (94.8%) compared to the overt DIC (5.2%) among the non-survivors. This result supports the previously reported findings by Deng et al. (2020) who reported 6.4% of non-survivors with overt DIC[16] and Daniela et al. (2020) who found 6.2% of cases fulfilling ISTH overt DIC criteria.[19] Notably, our finding is in contradiction with Tang et al. (2020) who found overt DIC in 71.4% of non-survivors.[18]

The main principle of DIC in bacterial and SARS-CoV-2 infections still remains as a systemic activation of a strong inflammatory response leading to the extensive release of cytokines (IL-1β, TNFα and IL-6) and complement proteins often labelled as a 'cytokine storm' causing endothelial damage, activation of platelets and the von Willebrand factor (VWF).[20] Yet, contrary to this, one of the most important differences among the two is the level of D-dimer, which is not increased in sepsis-induced DIC owing to the inhibition of fibrinolysis[21] — but is remarkably raised in CAC.[19] The elevated D-dimer levels observed in non-survivors and critically ill COVID-19 patients has been reported to be likely due to a virus associated with direct endothelial injury as well as alveolar macrophage release of a urokinase type of plasminogen activator which causes fibrinolysis.[1,6,18] We also found elevated levels of D-dimers in 68.8% of our patients. Interestingly, in our study, among the other parameters involved in scoring, mean platelet count and fibrinogen levels remained normal and mean PT was minimally prolonged. These findings are in line with the data published by Wang et al. (2020) who also revealed elevated

D-dimer levels and normal PT among non-survivors.[22] Tang et al. (2020) also revealed a higher level of D-dimers among non-survivors compared to survivors and proposed it as a predictor of mortality.[18] Another difference in septic DIC and CAC is the presence of thrombocytopenia, which is prominent in sepsis-induced DIC,[23] but it is not a common feature of CAC. A meta-analysis carried out on a large population cohort found thrombocytopenia to be a risk factor for developing severe disease and also death.[24] Subsequent studies which reported the presence of thrombocytosis and hyperfibrinogenaemia in COVID-19 patients contradicted this theory,[25] thus consumptive coagulopathy is not that prominent in patients with SARS-CoV-2 infection. Although our mean platelet count for the whole sample and for non-overt cases was normal, we did find mild thrombocytopenia among cases with overt DIC. This may be due to superimposed bacterial infections in seven patients who developed sepsis during their hospital admission with two of them having overt DIC. Another unique feature of CAC is that makes it difficult to establish overt DIC on the ISTH score, which reported hyper-fibrinogenaemia in all stages of infection when compared with healthy controls[26]; this is in contrast to the septic DIC which is associated with significantly lower fibrinogen levels. We reported normal fibrinogen levels in both non-overt and overt DIC patients. In contrast, Tang et al. (2020) reported a drop in fibrinogen levels among non-survivors in a later stage of the disease just before their death.[18]

The increasing evidence of normal platelet count − normal to high fibrinogen levels and minimally prolonged PT in COVID-19 − makes it difficult to predict overt DIC on the ISTH scoring system, therefore leading to a low incidence of overt DIC. This is unlike sepsis-induced DIC where its value is already established and overt DIC is predicted in 30% of the cases.[18] This fact diminishes the role of the ISTH score in predicting mortality in COVID-19 patients. Furthermore, sometimes the clinical conditions and comorbidities of patients with non-overt DIC puts them at a higher risk of mortality compared to overt DIC patients. We found a moderately prolonged PT (17.3 s) for non-overt DIC patients (scores 1−4) and a substantial prolongation (24.4 s) among overt DIC cases (score ≥ 5). Additional D-dimers were raised (>250 ng/ml) in all of the overt DIC patients and in 88.9% of the non-overt DIC group with scores of 1−4. Studies have revealed that an increased level of D-dimer, which indicates higher thrombin levels, is an important biomarker to predict severity and mortality among COVID-19 patients.[14] The discovery of micro thrombi in small vessels of organs like lung and skin during autopsy sections[27] and increased lactate dehydrogenase were suggestive of thrombotic microangiopathy as part of CAC.[25,28] Complement-induced injury to capillary vessels similar to hemolytic uremic syndrome (HUS) is noted and has raised the utility of anti-complement therapies to be adopted at the earliest possible time to avoid progression to the severe stages of the disease.[29] Based on the low incidence of overt DIC among non-survivors in our sample, the increasing evidence related to the predictive role of D-dimers, our observation of a

prolonged PT and incidence of microangiopathy in individual organs, we recommend the use of D-dimer and PT levels rather than the DIC score. The complete understanding of coagulation abnormalities in COVID-19 relies not on simple DIC-based coagulopathy, but rather on a combination of many procoagulant and pro-inflammatory conditions.

Studies have reported a significantly lower mortality rate among COVID-19 patients treated with low molecular weight heparin compared to those not treated with it.[30,31] Also, in our patients, anticoagulation was started once overt DIC was established or they were already in the intensive care unit (ICU) on assisted ventilation. Contrary to this, the findings of a greater contribution of pre-existing comorbidities to a higher death rate[32,33] indicate towards the role of multifactorial aetiology for COVID-19 related mortality and not just the coagulopathy. Meta-analysis involving data from global epidemic centres showed that 84.1% of COVID-19 patients had a presence of one or more comorbidities. This accounts for a higher fraction of patients ending up in ICUs[34] and among non-survivors[18] and requires an early recognition and intervention.[35] In our study we also found an association of CKD, DM and HTN with DIC.

The incidence of overt DIC in our sample was significantly lower than non-overt DIC, therefore we believe that deaths reported for COVID-19 patients could be caused by multiple factors − for example, thrombotic microangiopathy, presence of comorbidities and older age group. The limitations of our study are a smaller sample size, the study being single centred and the absence of a survivor group. The reported findings need to be further explored in larger cohorts, including survivors using survival analysis. Our findings do support previously reported data but they still need to be replicated in a better powered cohort.

Conclusions

We conclude that the ISTH DIC score cannot predict mortality as COVID-19 related DIC differs from sepsis-induced DIC. Among seriously ill, older patients with comorbidities, increased levels of D-dimer and prolonged PT are more reliable parameters among COVID-19 non-survivors.

Recommendations

We recommend that our findings of DIC in COVID-19 non-survivors need to be further explored in larger cohorts, including survivors and by using the survival analysis.

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Conflicts of interest

The authors have no conflict of interest to declare.

Ethical approval

Ethical approval (ERC/ID/74) dated 13-11-2020, was obtained from the Ethical Review committee at Army Medical College, Rawalpindi Pakistan.

Authors' contributions

NA, FA and SAK contributed to the conception and design of the study. NA, ST and AO conducted the literature review. FA, AN, NA and ST collected and organised the data. NA, ST and AO performed the data analysis and all authors contributed to interpretation. NA and AO conceived the initial draft and all authors revised it. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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