Original Article

Use of rotational thromboelastometry to predict the outcome of COVID-19 patients: A retrospective observational study

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Abstract

Background and Aims: The hypercoagulability occurring in COVID-19 patients is detected only by Rotational thromboelastometry (ROTEM). However, the benefit of performing ROTEM in the management of disease and predicting the outcome of COVID-19 patients is yet to be established.

Material and Methods: The data of 23 critically ill and 11 stable COVID-19 adult patients were extracted from the hospital information system admitted between July and August 2020 and patient charts and analyzed retrospectively. The critically ill patients were divided as a survivor and non-survivor groups. The Intrinsic pathway part of ROTEM (INTEM) and Fibrinogen part of ROTEM (FIBTEM) were performed on day 0 for both critically ill and stable patients, and on day 10 for critically ill patients. The statistical package for social science (SPSS) version 26 was used for statistical analysis.

Results: The median FIBTEM amplitude at 5 min (A5) and maximum clot firmness (MCF) were elevated in both stable and critically ill patients (24 vs 27 mm, $P = 0.46$ and 27.5 vs 40 mm, $P = 0.011$) with a significant difference in FIBTEM MCF. But there was no significant difference between number of survivors and non-survivors with FIBTEM MCF >25 at day 0 and day 10.

Conclusion: The Hypercoagulability state as detected by ROTEM parameters at day 0 and day 10 had no association with the outcome (mortality) of critically ill COVID-19 patients. Hence it cannot be used as a prognostic test. The increasing age, comorbidities and D-dimer values were associated with a poor prognosis in COVID-19 patients.

Keywords: Coagulation parameters, D-dimer, intensive care, mortality, novel coronavirus pneumonia, rotational thromboelastometry, thrombotic complications

Introduction

The clinical spectrum of coronavirus disease-19 (COVID-19) ranges from asymptomatic to severe viral pneumonia with respiratory failure and even death.[1,2] The exact pathophysiology is not yet known. The proposed mechanism of acute respiratory distress syndrome occurring in severe COVID-19 disease is widespread micro-thrombosis in the pulmonary circulation.[3] The other mechanisms include cytokine storm and activation of coagulation cascade leading to hypercoagulability.[4] It is recommended to perform D-dimer, prothrombin time (PT), and platelet count in patients with COVID-19 infection to stratify the need for admission and hospital admission by the International Society of Thrombosis and Haemostasis.[5] The incidence of hypercoagulable in the form of venous thromboembolism and arterial thrombosis is 25% to 48% in critically ill patients.[6] The conventional coagulation including PT,

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international normalized ratio (INR), and activated partial thromboplastin time (aPTT) give an idea of the initiation of clotting process. But these conventional coagulation tests do not detect hypercoagulability, which is generally seen in COVID-19 patients. Assessment of coagulation status by conventional coagulation tests in these patients is insufficient. While D-dimer reflects the increased coagulation process but it is non-specific and the amount or strength of clot formation cannot be detected. However, a few studies have identified D-dimer as a prognostic marker for clinical severity and mortality in COVID-19 patients.[7-9] The Rotational thromboelastography (ROTEM) is a point of care test that evaluates clot initiation, whole clot formation, stabilization and dissolution.[10] The hypercoagulability occurring in COVID-19 disease and the severity of it as identified by clot strength and maximum clot firmness (MCF) can be detected in ROTEM. This quantitative measure of clot strength was associated with the disease severity in previously conducted studies.[11]

We could not find any study that evaluated the association of ROTEM parameters showing hypercoagulability and outcome in COVID-19 patients. Since hypercoagulability is well documented in COVID-19 patients, we had decided to do ROTEM initially in all the admitted patients. Hence, this retrospective analysis was intended to know whether ROTEM values can predict the clinical course and outcome of COVID-19 patients.

The primary objective was to evaluate the association between FIBTEM maximum clot firmness (MCF) and the outcome (mortality or survival) in critically ill COVID-19 patients. Secondary objectives were to evaluate an association between INTEM and FIBTEM with the severity of the illness and to compare the Sequential Organ Failure Assessment score (SOFA), age, co-morbid illnesses, Acute Physiology and Chronic Health Evaluation score (APACHE), biochemical investigations, conventional coagulation tests, and acute inflammatory markers between stable and critically ill patients and within critically ill patients.

Material and Methods

The Institutional ethical committee approval and waiver of consent were obtained for the retrospective data analysis. The data of consecutive COVID-19 adult patients confirmed by RT-PCR admitted from 1st July 2020 to 30th August 2020 in a tertiary care center of western Rajasthan were retrieved and analyzed. The exclusion criteria were patients with pre-existing thrombotic or bleeding disorders, pre-existing acquired coagulopathies, on chemotherapy, active malignancy, and pregnancy. The patients were categorized as stable (who did not require oxygen supplementation and were admitted in regular ward), and critical (patients who were categorized as severe to critical disease according to WHO classification of COVID-19 disease and admitted to critical care unit).[12] The critically ill patients were categorized as survivor and non-survivor groups based on 30-day mortality.

Demographic details including age, sex, co-morbidities, the device used for oxygen supplementation, and clinical data such as APACHE-II, and SOFA at admission were recorded. Acute phase reactants including procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6), baseline investigation including hemoglobin, complete blood count (CBC), kidney function test (KFT), and liver function test (LFT), standard coagulation profile like PT/INR, aPTT, and D-dimer at day 0, 5 and 10 of hospital and at ICU admission were retrieved from the patient's records and the hospital information system and analyzed.

ROTEM analysis was performed by using the ROTEM delta apparatus. INTEM by using phospholipid and ellagic acid and extrinsically activated test along with platelet inhibitor cytochalasin D and tissue factor (FIBTEM) were measured. FIBTEM reflects the contribution of fibrinogen by blocking platelet contribution to clot formation in the coagulation process. ROTEM tests were done on the days 0 and 10 of admission in both critically ill and stable COVID-19 patients. The variables in INTEM and FIBTEM measured were: clotting time (CT, sec) the time between initiation of clot formation and clot 2 mm in amplitude, clot formation time (CFT, sec) the time from CT to clot of 20 mm in amplitude, clot firmness at 5 min (A5, mm) and at 10 min (A10, mm), maximum clot firmness (MCF, mm), and area under the curve (AUC), lysis index at 60 min (LI60%).

Sample size and statistical analysis

Time-bound retrospective study with a convenient sample size of 34 RT-PCR confirmed COVID -19 patients. Statistical analysis was done by using SPSS v26. The Shapiro-Wilk test was applied to find normality of the data. The data with normal distribution were expressed as mean with standard deviation (SD) and others as median with interquartile range (IQR). Unpaired *t*-test was used for non-categorical and Chi-Square test was used for categorical data (ASA Classes, comorbid illness) respectively. The statistical test of significance used for non-normality data was Mann-Whitney test and for comparison of the same group on different time was paired t-test for. The statistical significance was with $P < 0.05$.

Results

The demographic parameters, conventional laboratory tests, and ROTEM data of 35 confirmed COVID-19 patients (23 critically ill and 12 stable) admitted in the hospital were analyzed [Table 1]. Among all patients, 66.7% were male and 34.3% were female. The mean age was higher in critically ill, compared to stable COVID-19 patients (61.6 ± 15.8 vs 41.4 ± 16.7 years; $P = 0.001$). Comorbid illness such as diabetes, hypertension, stroke, and coronary artery disease were found in 43.4%, 65.2%, 8% and 21.7% respectively in critically ill COVID-19 patients [Table 1]. Mean APACHE-II and SOFA score at admission were statistically significant in critically ill compared to stable patients (11.4 ± 7.2 vs 4.4 ± 3 and 2.3 ± 1.4 vs 0.5 ± 0.7 respectively, $P < 0.001$). The baseline urea [47 (31) vs 22.9 (12.8)], creatinine [(1.45 (0.9) vs 0.8 (0.15)] and C-reactive protein [150.0 (36.6) vs 22.5 (22.0)] were significantly significant in critically ill compared to stable patients. The baseline hematological parameter such as PT/INR, and aPTT were statistically significant between groups but values were within the normal range. The inflammatory marker such as D-dimer and IL-6 were elevated beyond the normal limit in critically ill patients, which was statistically significant ($P < 0.001$).

Table 2 depicts ROTEM (INTEM, FIBTEM) test results in critically ill and stable COVID-19 patients at admission. The values of INTEM-CFT was in supranormal range in critically ill patients ($P = 0.009$). The difference in INTEM-A5 values was also statistically significant between the stable and critically ill patients ($P = 0.02$) but was within the normal range in all patients. Only FIBTEM-MCF was 31.2% higher in critically ill compared to stable patients that were clinically and statistically significant ($P = 0.011$) [Figure 1].

While all critically ill COVID-19 patients were received prophylactic dose of LMWH, Prothrombin time and aPTT were higher in the non-survivor group on days 0, 5, and 10, with a statistically significant only at day 5 ($P < 0.05$). INR was 1.4 in the non-survivor group and 1.0 in the survivor group

Table 1: Demographic parameters, comorbidity, blood and coagulation parameters at admission

	Total *n*=35	Critically ill *n*=23	Stable *n*=12	*P*
Age (Mean±SD)	54.7±18	61.6±15.8	41.4±16.7	0.001
Gender				
Male, *n* (%)	23 (65.7%)	16 (69.6%)	7 (30.4%)	0.70
Female, *n* (%)	12 (34.3%)	7 (58.3%)	5 (41.7%)	
COMORBIDITY				
Diabetes Mellitus, *n* (%)	12 (34.2%)	10 (43.4%)	2 (16.7%)	0.149
Hypertension, *n* (%)	17 (48.5%)	15 (65.2%)	2 (16.7%)	0.006
Stroke, *n* (%)	2 (5.7%)	2 (8%)	0	0.536
Coronary Artery Disease, *n* (%)	5 (14.3%)	5 (21.7%)	0	0.141
APACHE on day 0 (Mean±SD)	8.3±7.3	11.4±7.2	2.3±1.4	<0.001
SOFA on day 0 (Mean±SD)	3.0±3.1	4.4±3	0.5±0.7	<0.001
Ventilation support				
RA and NP, *n* (%)	12 (34%)	0	12 (100%)	<0.001
NRBM, *n* (%)	8 (22.9%)	8 (100%)	0	
HFNO, *n* (%)	10 (28.6%)	10 (100%)	0	
Invasive Ventilation, *n* (%)	5 (14.3%)	5 (100%)	0	
Hb, Median (IQR)	12.1 (3.7)	12.2 (2.8)	12.1 (4.4)	0.619
Platelet, Median (IQR)	238 (152)	264 (121)	228 (158)	0.719
Urea, Mean	38.7 (28.5)	47 (31)	22.9 (12.8)	0.015
Creatinine, Mean	1.3 (0.8)	1.45 (0.9)	0.8 (0.15)	0.05
PT, Median (IQR)	13.4 (1.8)	12.4 (1.6)	13.6 (2.1)	0.002
INR, Median (IQR)	1.0 (0.14)	0.97 (0.06)	1.04 (0.15)	0.019
aPTT, Median (IQR)	31 (9.3)	22.9 (8.15)	35.3 (10.4)	<0.001
D-Dimer, Median (IQR)	0.6 (2.48)	0.435 (0.27)	2.39 (4.9)	0.002
C-Reactive Protein, Mean	102.2 (70.0)	150.0 (36.6)	22.5 (22.0)	<0.001
PCT, Mean	16.2 (0.87)	0.03 (0.03)	0.76 (1.44)	<0.001
IL-6, Median (IQR)	173.25 (332.7)	238.2 (526.7)	173.25 (291.8)	0.976
Mortality, *n* (%)	12/35 (34.2%)	12/23 (52.2%)	0	0.002

APACHE: Acute physiological and chronic health evaluation, SOFA: Sequential organ failure assessment, RA: room air, NP: Nasal pronge, NRBM: Non rebreathing mask, HFNO: High frequency nasal oxygenation, Hb: Haemoglobin, PT: Prothrmobintime, INR: International normalized ration, aPPT: Activated partial thrombin time, PCT: Procalcitonin, IL-6: Interleukin-6.

on day 5 ($P = 0.005$). The D-dimer level was higher in the non-survivor group on all 3 days with a statistically significant difference on day 0 and 5 ($P < 0.05$). IL-6 was higher in the non-survivor group with a statistically significant difference on day 10 ($P = 0.04$). Hemoglobin was consistently low in the non-survivor group with a statistically significant difference on day 5 ($P = 0.006$). There was no significant difference in PCT and HsCRP between both groups [Table 3].

Table 4 depicts the ROTEM values at day 0 and 10 in critically ill patients. The FIBTEM A5, A10 and MCF values were higher at day 0 and day 10 in both survivor and non-survivor groups without a statistically significant difference between the groups. The FIBTEM MCF was more than 25 mm in 22 (95.7%) patients at day 0, while 8 (72.7%) patients at day 10 in critically ill patients. There was no significant difference between the survivor and non-survivor groups in raised FIBTEM MCF values [Figure 2, Table 5].

Table 2: ROTEM parameters at admission in stable and critically ill COVID-19 patients

ROTEM	Reference value	Stable patient	Critically ill patients	*P*
INTEM CT	137-246 sec	200 (37.5)	202 (86)	0.82
INTEM CFT	30-110	66.5 (18.2)	94 (129)	0.009
INTEM A5	38-57	50.5 (11)	41 (26)	0.02
INTEM A10	44-66	61.5 (12.5)	56 (18)	0.09
INTEM AUC		6813 (1162)	6954 (900)	0.54
INTEM MCF	52-72	68 (12.3)	70 (7.5)	0.69
FIBTEM CFT		75.5 (290)	109 (182)	0.62
FIBTEM A5	4-17	24 (21.5)	27 (16)	0.46
FIBTEM A10	7-23	22 (24.3)	32 (17.5)	0.11
FIBTEM AUC		2693.5 (2522)	3684 (1765)	0.11
FIBTEM MCF	9-25 mm	27.5 (25.5)	40 (18)	0.011

CT: Clotting time, CFT: Clot formation time, A5, A10, AUC: Area under curve, MCF: Maximum clot formation.

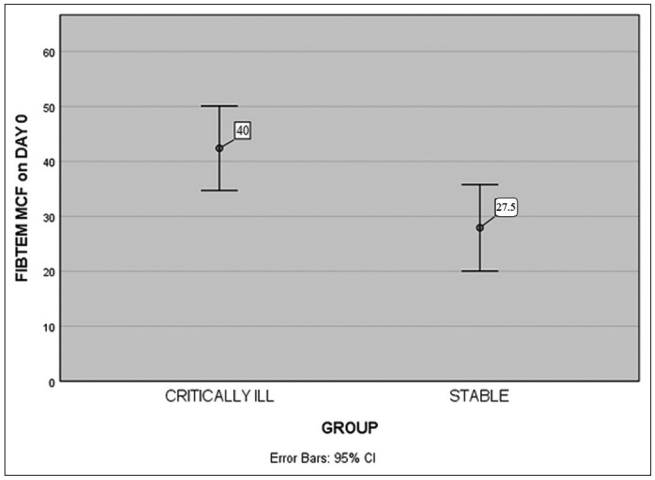

Figure 1: FIBTEM MCF on day 0 in Critically ill and stable patients. Normal of FIBTEM MCF is 9-25 mm. It is raised in both the groups and significantly high in critically ill patients. ($P = 0.011$)

Discussion

This retrospective study showed that the FIBTEM MCF was abnormally elevated in 95.7% of critically ill and 72.7% stable patients at day 0. This was in line with previously conducted studies on the western population.[11,13,14] While the hypercoagulability detected by ROTEM was present in both groups, the severity of hypercoagulability was more in critically ill patients. The age, comorbidities, and prognostic markers including SOFA, and APACHE II at admission is strongly associated with the severity of illness and morbidity in COVID-19 patients. Baseline Urea, creatinine and D-Dimer were higher in critically ill COVID-19 patients.

Almskog *et al.*[11] evaluated ROTEM parameters in critically and stable patients, found that hypercoagulability was early feature in mild to moderate disease, and more marked in severe diseases. Gönenli *et al.*[15] correlated ROTEM parameters with the severity of the disease and found that as the disease severity increases, the MCF value increases proportionately.

One of the early mechanisms of hypoxia in COVID-19 patients is microvascular thrombosis of the pulmonary vasculature. The tendency of microvascular thrombosis increases with the severity of disease. In our study, IL-6 level, D-dimer, C-reactive protein were higher in critically ill patients indicating cytokine storm. This cytokine storm and occurrence of hypercoagulability was already established in critically COVID-19 patients.[16-19] The Detection of these thromboembolic complications can be helpful to prioritize the care of these patients.[11] Though D-dimer is routinely estimated, it is non-specific, has a low positive predictive value and has no correlation with the severity of the disease in COVID-19 patients. Routine

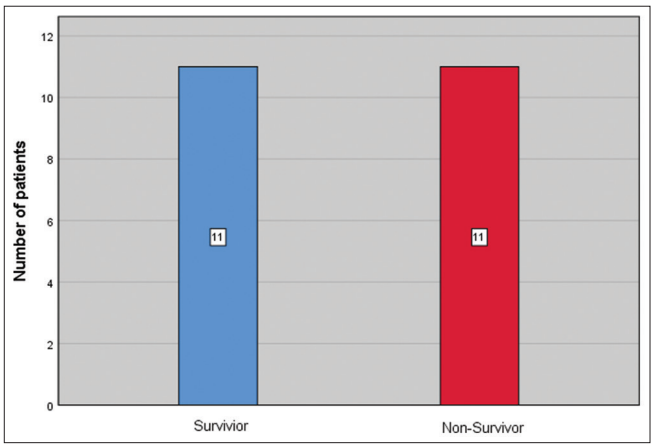

Figure 2: Number of patients with FIBTEM MCF more than 25 mm in survivor and non-survivor group. It was similar in both the groups without any statistical significant association

Table 3: Laboratory parameters of alive and dead in critically ill COVID-19 patientsat day 0, 5 and 10

Variables	Day 0 (*n*, 23)			Day 5 (*n*, 14)			Day 10 (*n*, 10)		
	Mean±SD		Sig.	Mean±SD		Sig.	Mean±SD		Sig.
	Alive (*n*, 11)	Dead (*n*, 12)		Alive (*n*, 8)	Dead (*n*, 6)		Alive (*n*, 7)	Dead (*n*, 3)	
Haemoglobin	12.1±2.5	11.3±2.7	0.44	12.8±1.8	9.1±2.4	0.006	12.1±2.1	9.5±2.9	0.14
Total leucocyte count	10.4±3.6	12.4±4.3	0.23	25.3±32.4	25.8±14.6	0.96	14.8±8	11.9±1.2	0.56
Platelet	266.9±130.3	249.7±99.2	0.72	339.8±234.1	135.2±80.8	0.06	295.9±122.1	184.7±66.4	0.18
Urea	36.5±16.6	56.7±38.3	0.12	44.9±17.5	62.1±40.6	0.29	36.9±20.9	61.3±24.7	0.14
Creatinine	1.1±0.1	1.8±1.3	0.12	1±0.1	1.9±1.6	0.15	1±0.4	1±0.1	0.85
PT	13.7±1.3	15.4±3.9	0.17	13±0.3	18±3.4	0.005	13.4±1.1	14.5±2.2	0.31
INR	1±0.1	1.1±0.2	0.15	1±0.1	1.4±0.3	0.005	1.1±0.2	3±3.1	0.13
Aptt	34.9±5.6	36.1±5.4	0.60	30.9±5.6	46.4±16.1	0.05	27.6±2.4	49.4±46.4	0.21
D-Dimer	2.5±2.6	8.3±8	0.05	3.4±3.9	11.6±6	0.02	5.6±7.5	14.3±9.9	0.16
CRP	149.4±35.2	150.6±40	0.94	93.5±45.8	65.3±38.4	0.29	33.7±37.9	42.9±53.4	0.77
PCT	28.5±92.5	22.2±47.5	0.84	0.2±0.3	0.9±0.8	0.15	0.6±1.2	0.5±0.4	0.89
IL-6	781.3±1772.8	227.9±181.1	0.42	79.8±105.6	1711±1462.2	0.23	94.3±167.9	644.9	0.04

PT: Prothrombin time, INR: International normalized ration, aPPT: Activated partial thrombin time, CRP: C-reactive protein, PCT: Procalcitonin, IL-6: Interleukin-6.

Table 4: ROTEM parameters in critically ill patients at day 0 and 10 and its association to the outcome

Variables	Zero Day (*n*, 23)		Sig.	10th Day (*n*, 11)		Sig.
	Mean (SD)			Mean (SD)		
	Alive (*n*, 11)	Dead (*n*, 12)		Alive (*n*, 7)	Dead (*n*, 4)	
INTEM CT	183.6 (55.6)	238.3 (74.9)	0.06	236.4 (35)	156 (56.2)	0.016
INTEM CFT	122 (95.7)	139 (76.2)	0.64	97.9 (35.4)	128 (81.1)	0.40
INTEM MCF	68.9 (12.5)	66.3 (6.3)	0.52	62.4 (8)	56.8 (18.6)	0.49
INTEM A5	41.3 (20.1)	36.3 (13.5)	0.49	39.4 (9.1)	39.3 (17.7)	0.98
INTEM A10	57.2 (14.4)	48.3 (17.5)	0.20	50.1 (9.8)	48.3 (18.5)	0.82
INTEM LI30	97.2 (9.3)	100 (0)	0.30	100 (0)	99.8 (0.5)	0.20
INTEM LI60	99.8 (0.4)	99.2 (2.3)	0.37	99.3 (1.1)	99 (1.4)	0.71
INTEM AUC	6608.5 (2228.5)	6632.9 (646.4)	0.97	4334 (3146.5)	5647.5 (1867.6)	0.48
FIBTEM CT	121.3 (88.7)	148.3 (82.5)	0.45	74.5 (9.8)	84 (30.2)	0.45
FIBTEM CFT	161.2 (195.2)	200.2 (196.8)	0.64	628.8 (726)	357.5 (486.2)	0.53
FIBTEM MCF	41.2 (11.4)	43.5 (22.6)	0.76	26.4 (11.9)	32.3 (13)	0.46
FIBTEM A5	28.2 (9.1)	29.7 (23.4)	0.84	17.9 (6.7)	26.8 (11)	0.12
FIBTEM A10	32.7 (9.3)	38.9 (25.1)	0.45	20.6 (7.6)	29.5 (12.6)	0.17
FIBTEM LI60	99.1 (1.9)	99.5 (1.7)	0.59	99.7 (0.8)	100 (0)	0.47
FIBTEM AUC	4249.9 (2010.3)	4021 (2467.7)	0.81	2235 (861.2)	3209.3 (1278.3)	0.16

Table 5: Association of Abnormal ROTEM parameters in critical ill patients with outcome at day 0 and day 10

Abnormal ROTEM values	Total, *n* (%)	Alive, *n* (%)	Dead, *n* (%)	*P*
INTEM CT <137 on day 0	2/23 (8.7%)	1 (50.00%)	1 (50.00%)	1.00
INTEM CT <137 on day 10	1/11 (9.1%)	0	1 (100.00%)	0.36
INTEM CFT <30 on day 0	0/23	0	0	1.00
INTEM CFT <30 on day 10	0/11	0	0	1.00
INTEM MCF >72 on day 0	6/23 (26%)	5 (83.30%)	1 (16.70%)	0.07
INTEM MCF >72 on day 10	3/11 (27.3%)	2 (66.70%)	1 (33.30%)	1.00
FIBTEM MCF >25 on day 0	22/23 (95.7%)	11 (50.00%)	11 (50.00%)	1.00
FIBTEM MCF >25 on day 10	8/11 (72.7%)	5 (62.50%)	3 (37.50%)	1.00

standard coagulation parameters including PT, INR, and aPTT also have no role in diagnosing hypercoagulability.[19,20] ROTEM is a point of care device that measures global clot formation and dissolution in real-time technique that can detect hypercoagulability.[21]

All the critically ill patients received LMWH in a prophylactic dose that could have prolonged the conventional coagulation parameters. Despite the prophylactic anticoagulation therapy, all critically ill patients had increased strength of clot (FIBTEM A5, A10, and MCF). Though ROTEM

parameters were associated with the severity of the disease, no studies were done to evaluate the association between ROTEM and the outcome of the disease. Hence, our study was first to evaluate the association between the ROTEM values and the outcome of COVID-19 patients. There was no significant association between hypercoagulability and the outcome of critically ill patients. Both survivor and non-survivor groups showed increased FIBTEM MCF values without any significant difference between them. The values of INTEM and FIBTEM were persistently elevated in non-survivor at 10, while it was in decreasing trend in the survivor group.

The mortality in our study was 52% in critically ill patients, while 0% in stable patients. In literature, the reported mortality varies from 12%-45% in critically ill COVID-19 patients.[22] The ROTEM values were almost similar in both survivor and non-survivor groups [Figure 2]. Performing ROTEM at early stage of disease can detect patient at high risk of developing hypercoagulopathy and thrombotic complications. However, the final outcome of the disease cannot be predicted by performing ROTEM. The mortality in COVID-19 patients is multifactorial and based on the results of this study, the hypercoagulable state occurring in COVID-19 disease doesn't seem to contribute to the increased mortality in critically ill COVID-19 patients.

Limitations

The limitations of this study included that, as a relatively small sample size, retrospective in nature, fibrinogen levels were not measured and ROTEM values were not compared with the healthy control group. The results of routine screening of deep vein thrombosis and post-mortem findings were not available for confirmation of hypercoagulability or thrombosis as a cause of mortality in COVID-19 patients. Our findings should be confirmed in an adequately powered clinical study.

Conclusions

The hypercoagulability was found in both stable and critically ill patients and it can be detected with FIBTEM MCF. However, INTEM or FIBTEM cannot be used for the prediction of mortality in critically ill COVID-19 patients. Age, comorbid medical illness, and prognostic scores like SOFA, and APACHE II at admission have a strong association with the severity of illness, morbidity and mortality of COVID-19 patients. The PT/INR, aPPT, and D-dimer were statistically significantly prolonged at day 0 in stable patients compared to critically ill COVID-19 patients.

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Conflicts of interest

There are no conflicts of interest.

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