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Original research article

Cardiac injury and COVID-19 associated coagulopathy in patients with acute SARS-CoV-2 pneumonia: A rotational thromboelastometry study

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ABSTRACT

Purpose: Coronavirus disease 2019 (COVID-19) is a systemic inflammatory condition associated with coagulopathy which may result in severe thromboembolic complications. Cardiac injury is not uncommon in hospitalized COVID-19 patients and therefore we aimed to investigate whether it stems from an abnormal coagulative state.
Materials and methods: We conducted a retrospective cross-sectional study on consecutive patients hospitalized due to COVID-19. Traditional coagulation and whole blood rotational thromboelastometry tests were compared between patients with and without cardiac injury. Cardiac injury was defined by increased levels of high-sensitivity cardiac troponin I (hs-cTnI).
Results: The study population consisted of 104 patients (67% males, median age 65 years), of whom 40 (38%) developed cardiac injury. No clinical differences in the traditional coagulation parameters were observed between patients with and without cardiac injury. Thromboelastometry analysis revealed abnormal maximum clot firmness (MCF) levels in FIBTEM assay in 80 (77%) patients. No significant differences in MCF values ($p = 0.450$) and percentage of abnormal MCF ($p = 0.290$) were detected between patients with and without cardiac injury. Cardiac injury - not hypercoagulability - was associated with mortality ($p = 0.016$).
Conclusions: No differences in traditional coagulation and rotational thromboelastometry parameters were found among hospitalized COVID-19 patients with and without cardiac injury. Other mechanisms besides hypercoagulability may be a main culprit for cardiac injury in COVID-19 patients.

1. Introduction

The understanding of coronavirus disease 2019 (COVID-19) has evolved from a mere respiratory infection into a systemic inflammatory disease which can also affect the cardiovascular system [1]. Acute cardiac injury, defined by the elevation of cardiac troponin (cTn) [2] in blood analysis, is observed in about 34% of COVID-19 patients during the hospital stay [3] and has been associated with worse outcomes [4–6]. Although several mechanisms have been proposed to explain COVID-19-associated rise in cTn [7], many aspects of the pathogenesis remain elusive, and namely, the role of hypercoagulability (due to the systemic inflammatory response) and coronary microvascular thrombosis. COVID-19-associated coagulopathy (CAC), characterized by massive thrombin formation with micro- and macroangiopathic thromboembolic complications, is common in symptomatic COVID-19 patients [8,9]. The hallmarks of CAC are elevated D-dimer and fibrinogen levels, as well as increased clot strength measured by rotational thromboelastometry [10]. CAC may lead to a coronary microvascular thrombosis, hence the increased cTn levels found in COVID-19 patients [11]. Autopsies have revealed epicardial and, more often, microvascular coronary thrombi in the heart of several COVID-19 patients [12,13] pointing to microthrombi as the most likely pathologic cause of myocyte necrosis in

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COVID-19 [14]. Nevertheless, univocal data from invasive or non-invasive assessments of the coronary circulation are lacking. Therefore, we aimed to retrospectively evaluate both traditional coagulation and whole blood (WB) rotational thromboelastometry parameters in a group of patients with acute COVID-19 pneumonia.

2. Materials and methods

We conducted a retrospective study on a group of 112 consecutive patients with laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as defined by the World Health Organization (WHO) [15], and with clinical and radiological signs of acute COVID-19 pneumonia admitted to the Intensive Care Unit (ICU) or the Internal Medicine Unit (IMU) of Padova University Hospital between March and May 2020. Exclusion criteria were: known congenital and/or acquired bleeding/thrombotic conditions, incomplete panel of coagulation laboratory data or cTn, refusal to provide informed consent.

We collected data on demographic characteristics, cardiovascular risk factors and main comorbidities.

Upon admission, all patients underwent traditional coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and antithrombin, as well as platelet count and WB rotational thromboelastometry profiles. Platelet count was performed by automatic methods (Counter Sysmex XE-2100 Dasit Spa, Milan, Italy) and traditional coagulation tests were performed on a BCT-Analyser (Dade Behring, Marburg, Germany) according to the manufacturer's instructions. WB rotational thromboelastometry profiles were obtained within 3 h of blood collection via a ROTEM® delta apparatus (Instrumentation Laboratory – Werfen, Barcelona, Spain) according to the manufacturer's recommendations, as previously described [16]. In particular, we performed INTEM and EXTEM assays (evaluation of intrinsic and extrinsic coagulation pathways) and FIBTEM assay (evaluation of fibrinogen contribution to blood clot).

The following parameters were considered for analysis:

i) Clotting Time (CT, sec), the time from the beginning of the coagulation analysis until an increase in amplitude of the thromboelastographic trace of 2 mm. CT evaluates the activation phase of clot formation;
ii) Clot Formation Time (CFT, sec), the time elapsed for an increase in amplitude of the thromboelastogram from 2 to 20 mm. CFT explores the propagation phase of clot formation;
iii) Maximum Clot Firmness (MCF, mm), the maximum amplitude in millimetres reached in the thromboelastogram;
iv) Maximum Lysis (ML, %) as the maximum percentage of clot lysis.

A hypercoagulable thromboelastometry profile was defined as either shorter CT/CFT values or higher MCF values vs. controls [17]. Hemoglobin, lymphocytes, C-reactive protein (CRP), serum ferritin, interleukin-6 (IL-6) and lactate dehydrogenase (LDH), fraction of inspired oxygen (FIO_2), arterial partial pressure of oxygen (PaO_2) and PaO_2/FIO_2 ratio were evaluated upon admission and every 48/72 h throughout the hospital stay. D-dimer (STA® -Liatest® D-Di, Stago, France) and high-sensitivity cardiac troponin I ((hs-cTnI; Abbott Architect Stat High Sensitive Troponin I assay, Abbott Diagnostics, Chicago, IL, USA) tests were performed in all patients upon admission. Serial assays were collected during the hospital stay, according to clinical evaluation.

Cardiac injury was defined as a rise of (hs-cTnI) levels above the 99th percentile upper reference limit (32 ng/L for males, 16 ng/L for females) without signs or symptoms of acute myocardial ischemia [18].

Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at therapeutic doses were administered in patients who developed a thrombotic complication (deep vein thrombosis – DVT, or pulmonary embolism – PE) or presented with other indications for anticoagulation such as atrial fibrillation. LMWH at subtherapeutic dose (enoxaparin at dosage between 4000 IU and 50 IU/Kg twice daily) was administered as thromboprophylaxis in patients who required invasive or non-invasive ventilation. The remaining population received LMWH at prophylactic dose, except for those with major bleeding or other specific complications (e.g. end-stage kidney failure).

2.1. Ethical issues

Study data and clinical information were collected and managed by medical staff using REDCap electronic data capture tools hosted at Padova University, Italy [19,20]. All clinical investigations were conducted in compliance with the principles of the 1964 Declaration of Helsinki with its later amendments. The study protocol was approved by the in-house cardiovascular Ethics subcommittee on Human Research of Padova University Hospital, Italy.

2.2. Statistical analysis

Descriptive statistics were carried out for all clinical variables. Data are presented as median (interquartile range, IQR) for continuous variables and as percentages (absolute numbers) for categorical variables. To compare differences between patients with and without cardiac injury, we used the Mann-Whitney *U* test or Chi-Square test, as appropriate. A two-sided $p < 0.05$ was considered statistically significant. SPSS software package (version 26.0) was used for statistical analysis.

3. Results

3.1. Baseline characteristics

During the study period, 112 patients were admitted to our hospital. Eight patients were excluded due to missing hs-cTnI values; hence, 104 patients (male 67%, median age 65 years) constituted the study population. During hospitalization, n = 40 (38%) patients developed cardiac injury, and n = 15 (14%) died. Thirty-five patients (33%) were admitted to ICU while the remaining 69 (77%) were managed in our IMU. The median hospital length of stay was 14 days (IQR 8–23).

Patients with cardiac injury were older (77 vs. 61 years; $p < 0.001$), and more frequently had arterial hypertension (70 vs. 51%; $p = 0.005$), chronic kidney disease (15 vs. 2%; $p = 0.004$), chronic heart failure (25 vs. 2%; $p<0.001$) and peripheral artery disease (35 vs. 8%; $p<0.001$) (Table 1).

3.2. Relationship between cardiac injury and coagulative parameters

No statistically significant differences in D-dimer (292 vs. 249 μg/L), aPTT (27 vs. 26 sec; $p = 0.260$) and fibrinogen levels (557 vs. 571 mg/dL; $p = 0.860$) were observed between patients with and without cardiac injury. We found statistically significant differences in PT (13.7 vs. 13.1 s; $p = 0.023$) and antithrombin values (90 vs. 101%; $p = 0.022$) between the two study groups (Table 2).

In ROTEM® analysis, 80 (77%) patients showed abnormal MCF values in FIBTEM assay. However, there were no statistically significant differences in MCF values (28 vs. 28 mm; $p = 0.450$) and percentage of abnormal MCF (70 vs. 83%; $p = 0.290$) between patients with and without cardiac injury (Fig. 1).

3.3. Cardiac injury, hypercoagulability and outcomes

Patients with cardiac injury had longer hospitalization (23 vs. 12 days; $p < 0.001$), were more frequently referred to ICU (50 vs. 23%; $p = 0.006$), and subsequently died (25 vs. 8%; $p = 0.016$). Patients referred to ICU showed statistically significantly higher values of MCF in FIBTEM (34 vs. 28 mm; $p = 0.002$), peak D-dimer (1860 vs. 377 ng/L; $p < 0.001$) and peak hs-cTnI (47 vs. 13 ng/L; $p = 0.001$) than those treated in IMU. Furthermore, ICU patients more frequently developed DVT than the IMU patients (29 vs. 3%; $p < 0.001$) (Table 3).

Table 1
Baseline characteristics in patients with and without myocardial injury.

	All patients n = 104	Cardiac injury n = 40	No cardiac injury n = 64	*p* value
Age, years	67 (58–77)	77 (68–84)	61 (53–70)	**<0.001**
Female sex	34 (32.7)	16 (40.0)	18 (28.0)	0.211
Hypertension	61 (58.7)	28 (70.0)	33 (51.6)	**0.006**
Diabetes Mellitus	23 (22.1)	12 (30.0)	11 (17.2)	0.055
Smoke	24 (23.1)	8 (20.0)	16 (25.0)	0.813
Chronic CAD	12 (11.5)	6 (15.0)	6 (9.4)	0.260
CKD	7 (6.7)	6 (15.0)	1 (1.6)	**0.004**
COPD	6 (5.8)	3 (7.5)	3 (4.7)	0.441
Malignancy	9 (8.7)	5 (12.5)	4 (6.3)	0.186
CHF	11 (10.6)	10 (25.0)	1 (1.6)	**<0.001**
PAD	19 (18.3)	14 (35.0)	5 (7.8)	**0.001**
Laboratory findings – Admission (reference values)				
Hs-cTnI, ng/L (0.0–16.0)	14 (5–37)	43 (17–96)	6 (3–14)	**<0.001**
Hemoglobin, g/dL (12.3–15.3)	128 (114–140)	119 (111–132)	132 (119–142)	**0.003**
Htc, % (36–45)	40 (36–44)	37 (35–42)	41 (38–44)	**0.006**
Lymphocytes, x 10^9/L (4.4–11.0)	880 (582–1227)	720 (400–1132)	940 (672–1400)	**0.019**
CRP, mg/L (0.0–6.0)	63 (30–123)	84 (44–133)	50 (25–111)	**0.015**
LDH, U/L (135–214)	301 (249–367)	285 (254–407)	308 (239–367)	0.774
PaO2/FIO2 ratio	280 (167–333)	252 (169–292)	288 (167–347)	0.230
Laboratory findings – Peak values (reference values)				
Hs-cTnI, ng/L (0.0–16.0)	17 (6–67)	124 (43–475)	8 (3–14)	**<0.001**
Hemoglobin, g/dL (12.3–15.3)	108 (93–122)	90 (83–102)	118 (107–128)	**<0.001**
Lymphocytes, x 10^9/L (4.4–11.0)	605 (367–940)	390 (282–687)	740 (520–1025)	**<0.001**
D-Dimer, ug/L (0–300)	784 (283–2435)	1738 (788–4143)	419 (237–1160)	**<0.001**
LDH, U/L (135–214)	349 (269–477)	405 (277–578)	342 (263–401)	0.080
CRP, mg/L (0.0–6.0)	120 (69–210)	189 (90–260)	100 (46–170)	**0.001**
Serum ferritin, ug/L (11–328)	1121 (497–2066)	1215 (471–2117)	1059 (513–2066)	0.997
IL-6, ng/L (0–5.9)	51 (14–147)	58 (18–242)	35 (11–121)	0.277
PaO2/FIO2 ratio	200 (90–287)	162 (67–270)	232 (123–311)	0.109

Categorical variables are presented as number of patients (%).
Continuous values are expressed as median (25th-75th percentile).
Bolded values indicate statistical significance.
Abbreviations: MI, myocardial injury; CAD, coronary artery disease; CKD, chronic kidney disease; CHF, chronic heart failure; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; Hs-cTnI, high-sensitivity cardiac troponin I; Htc, hematocrit; CRP, C-reactive protein; LDH, lactate dehydrogenase; IL- 6, interleukin-6; FIO2, fraction of inspired oxygen, PaO2, arterial partial pressure of oxygen.

Among the 35 ICU patients, 8 (23%) received UFH, 11 (31%) LMWH at (sub)therapeutic dose, and 24 (69%) LMWH at prophylactic dose. Among the 69 IMU patients, 20 (29%) received no anticoagulants, 12 (17%) LMWH at (sub)therapeutic dose, and 37 (54%) LMWH at prophylactic dose (Supplementary Table 1). We observed no mortality benefit in patients who received full-dose anticoagulant or LMWH at prophylactic dose (Supplementary Table 2).

Peak values of hs-cTnI were statistically significantly higher in non-survivors than survivors (137 vs. 14 ng/L; p = 0.001) and in the ICU patients than in the IMU patients (26 vs. 14 ng/L; p = 0.023). MCF values in FIBTEM assay did not differ between survivors and non-survivors (28 vs. 33 mm; p = 0.247) (Table 4; Fig. 2).

Table 2
Traditional coagulation tests and rotational thromboelastometry parameters.

	All patients n = 104	Cardiac injury n = 40	No cardiac injury n = 64	*p* value
Traditional coagulation tests (reference values)				
D-dimer, ug/L (0–300)	254 (152–713)	292 (195–801)	249 (150–487)	0.152
PT, sec (9.5–13.8)	13.4 (12.7–14.4)	13.7 (13.0–14.9)	13.1 (12.5–14.4)	0.023
aPTT, sec (22–32)	26 (23–30)	27 (24–31)	26 (23–29)	0.260
Fibrinogen, mg/dL (150–450)	565 (434–673)	557 (441–669)	571 (434–673)	0.860
Antithrombin, % (83–118)	99 (87–107)	90 (76–99)	101 (91–109)	0.022
Rotational Thromboelastometry parameters				
INTEM				
CT, sec	177 (162–192)	184 (164–198)	174 (162–186)	0.022
CFT, sec	47 (40–60)	51 (41–59)	47 (39–61)	0.530
MCF, mm	69 (65–74)	69 (65–73)	70 (66–74)	0.530
ML, % (range)	0 (0–1)	0 (0–1)	0 (0–2)	0.310
EXTEM				
CT, sec	67 (61–81)	72 (59–87)	66 (61–76)	0.210
CFT, sec	48 (38–60)	51 (42–63)	45 (37–56)	0.070
MCF, mm	73 (67–75)	71 (66–75)	73 (67–76)	0.440
ML, % (range)	0 (0–1)	0 (0–1)	0 (0–1)	0.910
FIBTEM				
MCF, mm	28 (25–35)	28 (24–38)	28 (25–33)	0.450
Abnormal MCF, n (%)	80 (77)	28 (70)	52 (83)	0.290
Outcome				
DVT/PE	12 (12)	6 (15)	6 (9)	0.300
Length of stay, days	14 (8–23)	23 (14–41)	12 (7–17)	<0.001
Referred to ICU	35 (34)	20 (50)	15 (23)	0.006
Death	15 (14)	10 (25)	5 (8)	0.016

Categorical variables are presented as number of patients (%).
Continuous values are expressed as median (25th-75th percentile).
Abnormal MCF is defined with MCF>24 mm.
Abbreviations: PT, Prothrombin Time; aPTT, activated Partial Thromboplastin Time; CT, Clotting Time; CFT, Clot Formation Time; MCF, Maximum Clot Firmness; ML, Maximum Lysis; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism; ICU, Intensive Care Unit.

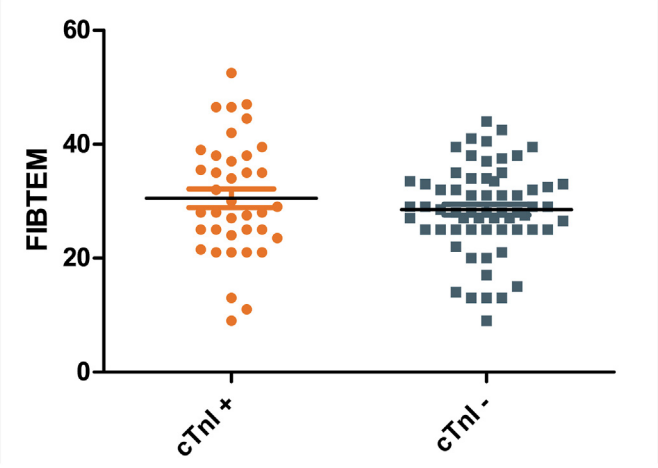

Fig. 1. Box plot showing no difference in MCF levels in FIBTEM assay in patients with and without cardiac injury.

4. Discussion

The aim of our present study was to investigate any possible relationship between hypercoagulable profiles and cardiac injury in a group of consecutive patients hospitalized with acute COVID-19 pneumonia.

Table 3
Laboratory findings and outcome in different settings.

	All patients n = 104	ICU n = 35	IMU n = 69	*p value*
MCF in FIBTEM, mm	28 (25–35)	34 (27–40)	28 (25–32)	0.002
Peak Hs-cTnI, ng/L	17 (6–67)	47 (11–246)	13 (5–25)	0.001
Peak D-Dimer, ug/L	784 (283–2435)	1860 (758–5161)	377 (235–1151)	<0.001
Outcome				
DVT/PE	12 (11.5)	10 (28.6)	2 (2.9)	<0.001
Length of stay, days	14 (8–23)	25 (17–45)	12 (7–17)	<0.001
Death	15 (14.4)	10 (28.6)	5 (14.3)	0.005

Categorical variables are presented as number of patients (%).
Continuous values are expressed as median (25th-75th percentile).
Abbreviations: ICU, intensive care unit; IMU, internal medicine unit; MCF, Maximum Clot Firmness; Hs-cTnI, high-sensitivity cardiac troponin I; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism.

Table 4
Relationship between hypercoagulability and cardiac injury and mortality.

	Survivors n = 89	Non survivors n = 15	*p value*
MCF in FIBTEM, mm	28 (25–34)	33 (24–41)	0.247
Hs-cTnI, ng/L	14 (5–39)	137 (10–1009)	0.001

Categorical variables are presented as number of patients (%).
Continuous values are expressed as median (25th-75th percentile).
Abbreviations: MCF, Maximum Clot Firmness; Hs-cTnI, high-sensitivity cardiac troponin I.

Our main finding was that although both hypercoagulability and cardiac injury are common occurrences in patients with acute COVID-19 pneumonia, there appears to be no association between the two. Moreover, cardiac injury rather than hypercoagulability (via ROTEM®) predicts mortality during the hospitalization. Patients who received LMWH (full or prophylactic dose) or direct oral anticoagulants (DOACs) had similar mortality to those who did not. We performed traditional coagulation tests and WB rotational thromboelastometry to assess the presence of CAC, focusing on the MCF in FIBTEM assay - a proven marker of excessive fibrin polymerization and hypercoagulability in COVID-19 patients [10,17,21]. Excessive fibrin polymerization was observed in over 75% of our study population, in line with previous reports in the literature [10,17]. We found higher MCF values in the ICU patients vs. the IMU patients, which may account for the higher prevalence of DVT/pulmonary embolism in the former (29% vs. 3%; $p < 0.001$).

Cardiac injury, as defined by elevated hs-cTnI, was detected in 40/104 (38%) patients. Elevated hs-cTnI levels were more common in older patients who often presented additional risk factors such as arterial hypertension, chronic kidney disease, chronic heart failure and peripheral artery disease. The presence of cardiac injury had no bearing on the prevalence of DVT or the coagulation profiles — via traditional coagulation and rotational thromboelastometry analyses. Although peak D-dimer levels were higher in patients with cardiac injury, we hypothesize that the correlation may lie in the severity of the disease since both troponin I and D-dimer have been found to be significantly elevated in severe COVID-19 patients [6,22]. This may explain why the coronary microcirculation was rarely involved in the widespread thrombotic phenomena described in the lungs and other organs in recent autoptic series [12–14]. In fact, a recent pathological study on COVID-19 autoptic specimens by Basso et al. [12] reported coronary microvascular thrombi only in 4/21 (19%) patients and increased myocardial interstitial macrophage infiltration in 18/21 (86%). Similarly, Halushka et al. [13]

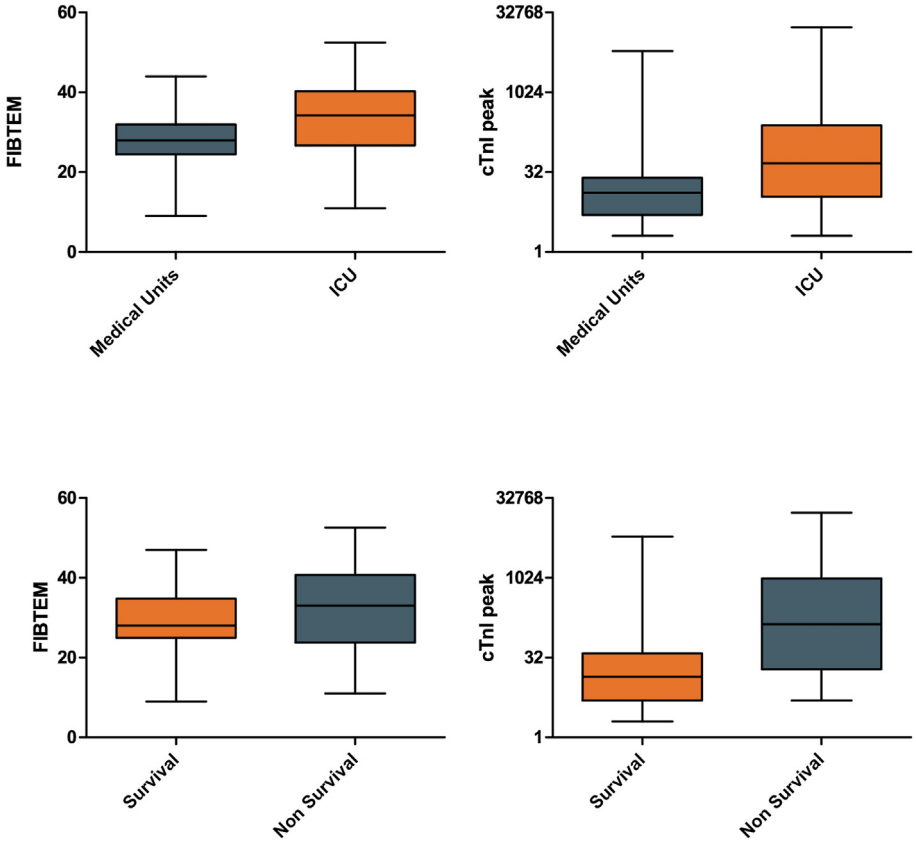

Fig. 2. Box plot showing comparison of MCF levels in FIBTEM assay and hs-cTnI in patients admitted to ICU (top) or Medical Units (top), and among Survival or Non Survival patients (bottom).

found a 10.8% prevalence of coronary microvascular thrombi in a 277 heart specimen series. However, Bois et al. [23] described non-occlusive fibrin microthrombi in 12/15 (80%) autoptic heart specimens from COVID-19 patients, although they were not able to establish a clear relationship between cardiac microthrombi and ischemic injury.

Our findings suggest that cardiac injury — and not hypercoagulability detected by ROTEM® - is associated with mortality in COVID-19 patients. We hypothesize, that it may be attributable to the fact that cardiac injury occurs mainly in the most severe forms of COVID-19 pneumonia; furthermore, anticoagulation therapy may be effective in contrasting complications stemming from CAC. Multiple mechanisms may be involved in the pathogenesis of cardiac injury in COVID-19: imbalance between oxygen demand and supply, direct myocardial damage and coronary microvascular thrombosis. However, the contribution of thrombotic phenomena to myocyte necrosis might be more limited than previously thought.

4.1. Limitations of the study

We would be remiss not to mention some of the limitations of our study. The monocentric nature of the study and the small sample size — which did not allow for a multiple regression analysis — may weaken the generalizability and statistical power of our findings. Viscoelastic tests are not able to evaluate primary hemostasis — the complex interactions between endothelium and platelets that culminate with the formation of the platelet plug. In addition, viscoelastic tests only provide partial information on platelet function and specifically, the mechanisms of platelet activation mediated by thrombin. Although WB rotational thromboelastometry is a reliable tool for the study of coagulation disorders, some unknown pro-coagulable mechanisms involved in the COVID-19 pathophysiology may go undetected. Other useful tests to assess susceptibility to thrombotic phenomena, such as thrombin generation [24] or platelet reactivity tests, were not performed. Finally, the strict safety protocols, unbearable workload and the logistical limitations at the onset of the COVID-19 outbreak meant that detailed electrocardiography and echocardiography data were not available for the whole cohort.

5. Conclusions

No differences in traditional coagulative and thromboelastometry parameters were found between hospitalized COVID-19 patients with and without cardiac injury. Our findings suggest that other mechanisms besides CAC may be a main culprit for COVID-19-associated cardiac injury. Larger studies are needed to further clarify our results.

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The author contribution

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Data Interpretation: Federico Capone, Alberto Cipriani, Leonardo Molinari, Anna Poretto, Nicolò Sella, Annalisa Boscolo, Elena Campello, Alois Saller, Roberto Vettor, Paolo Navalesi, Anna Maria Cattelan, Paolo Simioni, Luca Spiezia

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Literature Search: Federico Capone, Alberto Cipriani, Leonardo Molinari, Luca Spiezia

Funds Collection: n/a

Availability of data and material

The data, analytic methods, and study materials will be available to other researchers for purposes of reproducing the results or replicating the procedure on reasonable request. Federico Capone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of competing interest

None of the authors have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advms.2021.12.001.

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