

Rotational Thromboelastometry Profile among Critically ill COVID-19 Patients

Clinical and Applied
Thrombosis/Hemostasis
Volume 28: 1-4
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10760296221091213
journals.sagepub.com/home/cat



Indalecio Carboni Bisso¹ , Iván Huespe^{1,2,3}, Eduardo Prado¹,
Melina Garbarini¹, Marina Sol López^{4,5}, Luis Barrera^{4,5},
Marcos Las Heras¹, Jorge Sinner^{1,5} , and Marta Martinuzzo^{4,5}

Keywords

thromboelastometry, respiration, artificial, critical care, COVID-19, SARS-coV-2

Date received: 23 December 2021; revised: 21 February 2022; accepted: 14 March 2022.

Dear Editor,

Thromboinflammation has a contributing role in Coronavirus disease 2019 (COVID-19) pneumonia pathogenesis.¹ Rotational thromboelastometry (RT) evaluates viscoelastic changes during the coagulation process and could enable the identification of hypercoagulability, as an indirect marker of pulmonary microvascular thrombosis in real-time²⁻⁴. Therefore, we propose to study the modifications in maximum clot firmness (MCF) and other RT parameters in critically-ill COVID-19 patients compared with healthy controls (HC).

A prospective observational cohort study was performed at a high complexity hospital in Argentina. In the COVID-19 cohort, we included adult patients admitted to ICU due to COVID-19, between August and November 2020. In the HC cohort, we included healthy non-hospitalized volunteers. Exclusion criteria were: age <18 years or >80 years, anticoagulant use, tocilizumab use, transfusion of blood products (<7 days), hereditary thrombophilia or bleeding disorders, pregnancy, and active cancer.

In ICU patients, blood samples were collected at ICU admission (T1), and 5 (T5) and 10 days (T10) after ICU admission. In RT, only NaHEPTEM assay, which evaluates blood clot formation by recalcification without activators with adjunct heparinase, and is considered more sensitive to detect hypercoagulable states, was performed. RT were performed in a ROTEM® Delta instrument (Tem Innovations GmbH, Munich, Germany). Patient demographics and comorbidities were recorded. Also, standard basic coagulation tests were performed to all participants.

We calculate a sample size to test the hypothesis that the MCF was significantly higher in COVID-19 patients than in HC. We assumed a mean MCF of 69 mm for healthy people and 75 mm for COVID-19 patients, with a standard deviation of 6 for healthy people and 7 for COVID-19 patients, based

on the study of Pavoni *et al.*⁵ With a power of 80% and alpha of 0.5, a ratio of COVID-19/HC of 1.2, with a two-sided test, the sample size was 23 for COVID-19 patients and 19 HC. Statistical differences between groups were evaluated by the chi-squared test. Correlation by Spearman Rank test when appropriate. A two-tailed P-value < 0.05 was considered significant. All statistical tests were performed using IBM SPSS 23.

One hundred seventeen patients were admitted to our ICU with COVID-19 during the study period. Ninety-four patients were excluded, mainly due to convalescent plasma therapy. Thus, 23 COVID-19 patients and 19 HC were included in the final analysis (**Supplemental Material**)

We observed significantly higher values of MCF in COVID-19 patients at ICU admission (T1) against HC group (64 [IQR 59-68] vs 56 [IQR 52-60], $p < 0.001$). In the COVID-19 group the MCF also had a significant increase at T5 (69 [IQR 64-70]), compared to T1 ($p = 0.011$). Additionally, higher fibrinogen levels and MFC were found in COVID-19 group at any time point, (T1, T5 and T10) compared to HC (Figure 1).

¹ Intensive Care Unit, Hospital Italiano de Buenos Aires (Argentina)

² Instituto de Medicina Traslacional e Ingeniería Biomédica, HIBA, IUHI, CONICET

³ Área de Investigación en Medicina Interna, Hospital Italiano de Buenos Aires (Argentina)

⁴ Hematology and Hemostasis Section - Central Laboratory, Hospital Italiano de Buenos Aires (Argentina)

⁵ Instituto Universitario del Hospital Italiano (Argentina)

Corresponding Author:

Indalecio Carboni Bisso, Intensive Care Unit, Hospital Italiano de Buenos Aires, Tte. Gral. J. D. Perón 4190 (C1199ABB) - Buenos Aires - Argentina.
Email: indalecio.carbonibisso@hospitalitaliano.org.ar



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use,

reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

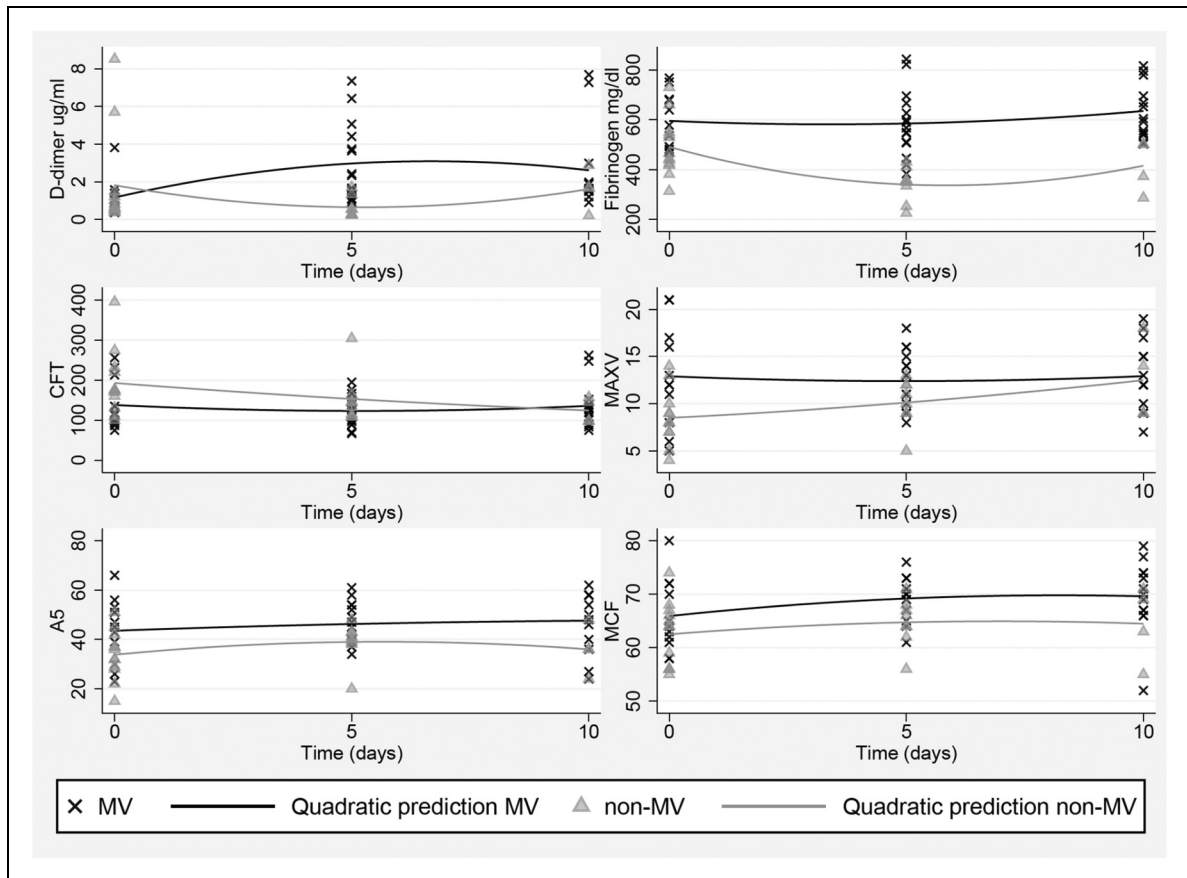


Figure 1. Evolution of medians of different parameters: D-Dimer and fibrinogen, as well as NaHEPTEM temograms parameters CFT, MaxV, A₅ and MCF, during the evaluation period (T1, T5 and T10) according to mechanical ventilation treatment or not. Green lines indicated the parameter median obtained in the healthy control group.

Abbreviations: DD, D-Dimer; CFT, Clot Formation Time, MaxV, Maximum velocity of clot formation; A₅, Amplitude at 5 min; MCF, maximal clot firmness; MV, mechanical ventilation; HC, healthy control.

Comparing COVID-19 MV patients with non-MV COVID-19 patients at T1, we observed significantly higher levels of fibrinogen and higher MaxV in MV patients. Also, higher A₅, as well as shorter clotting formation time (CFT) were registered, but without reaching statistical significance. However, the presence of a CFT <25th percentile or Amplitude at 5 min (A₅) >75th percentile of the HC range in temograms at T1 was associated with mechanical ventilation (MV) requirements at T1 (75% of MV vs 25% of non-MV [$p = 0.039$]). At T5, we observed significantly higher MCF and fibrinogen among MV patients. Finally at T10, we found a tendency of higher A₅ and MCF in MV patients without significant difference. This shorter CFT and higher Maximum velocity of clot formation (MaxV), observed in MV COVID-19 patients only on T1, could be explained due to the clot formation velocity increasing along with days from ICU admission in all patients.

In COVID-19 patients, a CFT below the lower quartile, and an A₅ above the higher quartile of the HC values at T1, was associated with MV requirement at T5 (same values in both parameters: 90.9% of MV vs 41.7% in non-MV [$p = 0.027$]). We hypothesize that the increment in clot formation velocity

(shorter CFT, higher MaxV, and A₅) could reveal high thrombin generation in the early ICU stage in COVID-19 MV patients, which may reflect more critical illness. Figure 2 shows the distribution RT parameters from samples taken on patients under MV or not, independently of ICU time after admission.

Our study suffers from several limitations. Firstly, we do not carry out a systematic search for deep vein thrombosis and pulmonary embolism among asymptomatic patients. Secondly, despite the sample-size calculation being adequate for testing the hypothesis, a relatively low number of patients were included for further analysis. As for strengths, we highlight the strict exclusion criteria implemented, the use of a test that is not affected by heparin presence, and the analysis of RT parameters at multiple time-points along with the study, which may reduce potential bias.

NaHEPTEM assays could detect hypercoagulation among critically ill patients with COVID-19, and also some RT parameters seem to be further altered in patients that required MV. Nevertheless, more studies are required to entirely comprehend hypercoagulation and hypoxemia relation, and test whether RT can be used in clinical settings for this purpose.

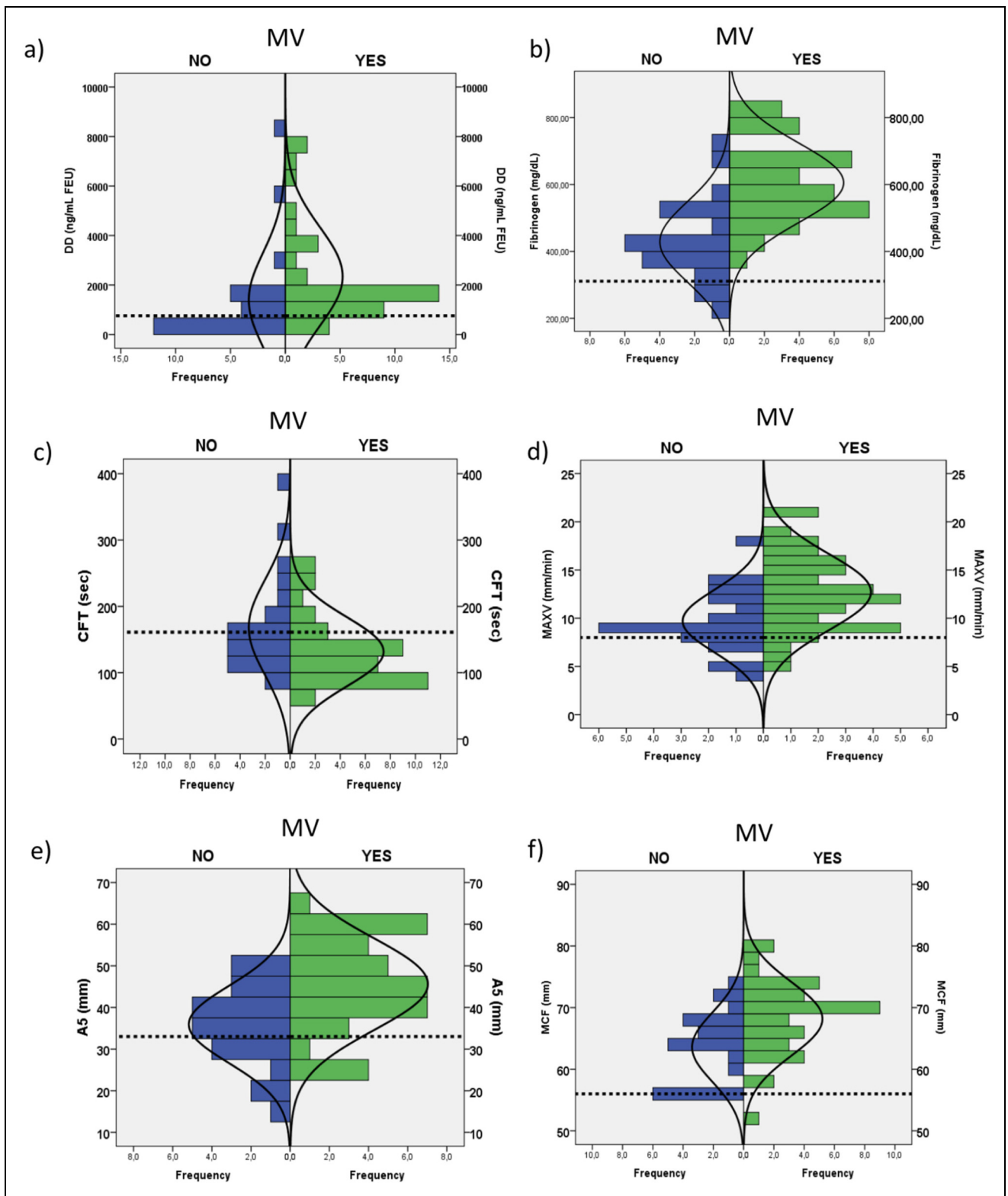


Figure 2. Distribution of hemostatic parameters: D-Dimer (a) and fibrinogen (b), as well as NaHEPTEM parameters CFT(c), MaxV(d), A₅(e) and MCF (f) in all blood samples performed from ICU patients with COVID-19, according to the need of mechanical ventilation treatment. Dashed lines indicated the parameter median obtained in the healthy control group. Abbreviations: DD, D-Dimer; CFT, Clot Formation Time; MaxV, Maximum velocity of clot formation; A₅, Amplitude at 5 min; MCF; maximal clot firmness; MV, mechanical ventilation.

Statements

The study was approved by the institutional ethics committee.

Informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Supplemental materials: All data can be accessed directly from the corresponding author upon a formal request.

Acknowledgements

Authors want to acknowledge FELSA SA (ROTEM ® distributor in Argentina) which provided NaHEPTTEM reagent and cups & pins for the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


Funding


The author(s) received no financial support for the research, authorship, and/or publication of this article.

Author Contribution

Indalecio Carboni Bisso, Eduardo Prado and Iván Huespe contributed to the concept and design of the study, prepared the figures and drafted the initial manuscript. Iván Huespe calculated statistics. Eduardo Prado and Melina Garbarini selected studies and extracted data. Marina Sol Lopez, Luis Barrera, Marcos Las Heras, and Jorge Sinner contributed to the concept of the study, processed samples and collected data. Marta Martinuzzo contributed to the concept and design of the study, calculated statistics, edited the manuscript, and administered the project. All authors revised the manuscript critically and approved the final version.

ORCID iDs

Indalecio Carboni Bisso  <https://orcid.org/0000-0002-4834-4676>

Jorge Sinner  <https://orcid.org/0000-0003-0815-4875>

Supplemental material

Supplemental material for this article is available online.

References

1. Gu SX, Tyagi T, Jain K, et al. Thrombocytopeny and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. *Nat Rev Cardiol*. Epub ahead of print 19 November 2020. doi: 10.1038/s41569-020-00469-1.
2. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemostasis*. 2020;18:1747–1751. doi:10.1111/jth.14854
3. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020;18:1738–1742. doi:10.1111/jth.14850
4. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemost* 2020;120:998–1000. doi:10.1055/s-0040-1714350
5. Pavoni V, Giansello L, Pazzi M, et al. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J Thromb Thrombolysis* 2020;50:281–286. doi:10.1007/s11239-020-02130-7