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Clot Stiffness Measured By Seer Sonorheometry As a Marker Of Poor Prognosis In Hospitalized COVID-19 Patients

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Abstract

A high risk of thrombotic complications has been observed among severely ill COVID-19 patients. Viscoelastic tests (VET) have shown a hypercoagulable profile in these patients, although so far there is no clear evidence on the use of these tools as predictors of risk in the clinical course of patients. In this study we aimed to evaluate the association between Quantra® sonorheometry VET parameters, standard coagulation tests and inflammatory markers in 69 patients with COVID-19 on hospital admission with disease severity and outcome. Inflammatory markers were elevated in a high percentage of patients, as were coagulation-related parameters such as fibrinogen and D-dimer levels. Quantra® sonorheometry analysis revealed increased clot stiffness (CS), especially due to increased fibrinogen contribution (FCS) in 63.7%. Analysis of clot stability to lysis (CSL) on the Quantra showed a value of 100%, suggesting hypofibrinolysis, in 32.4%. Age > 65 years, elevated values of fibrinogen, D-dimer, LDH, increased CS and CSL were significantly associated with worsening disease. The combination of elevated FCS and D-dimer values showed a particularly high prognostic value in distinguishing patients with severe symptomatology. In conclusion, FCS measured by Quantra® system and its combination with D-dimer could be established as a powerful tool to identify poor prognosis in COVID-19 patients on hospital admission.

Keywords

thrombosis, hematology, communicable diseases, COVID-19, diagnosis

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Introduction

At the moment of writing this article, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already killed more than 6 million people worldwide.[1] The development of an extreme inflammatory response and prothrombotic state is associated with poor prognosis and remains the major cause of the high morbidity and mortality rate associated with this condition.[2,3]

Previous studies on the hemostatic status of COVID-19 patients identified several parameters such as fibrinogen and D-dimer that could be established as markers of thrombotic risk and helped in the clinical management of patients.[3–5] Elevated D-dimer levels (>1000 ng/mL) have also been proposed as an indicator of risk for pulmonary embolism.[6] However, these parameters have drawbacks that affect their reliability and clinical use to predict outcomes in COVID-19. In particular, D-dimer has important limitations that raises

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questions on its true prognostic value for thrombosis in COVID-19. Although highly elevated levels of D-dimer in COVID-19 have been attributed to acute lung injury with intra-alveolar fibrin deposition and subsequent breakdown of this extravascular fibrin, D-dimer values may be elevated for a variety of reasons and therefore increased values are not only indicative of increased thrombotic risk.[7–10] For this reason, there is a need to identify new biomarkers that provide a rapid and effective assessment of thrombotic risk in COVID-19.

Viscoelastic tests (VET) are recognized powerful tools for the rapid identification and characterization of hypercoagulable state in infectious diseases and several groups have already evaluated the use of VET in COVID-19 patients.[11,12] In general, the available data indicate a high frequency of increased clot stiffness (CS) and fibrinolysis shutdown but with weak evidence on the association of this hypercoagulable profile with disease severity.[12,13] Wider studies with larger numbers of patients are therefore needed to confirm these important findings.

Sonic Estimation of Elasticity by Resonance (SEER) sonorheometry (Quantra® system) is a novel ultrasound-based VET technology.[14] With this system, a hypercoagulable profile has been reported in hospitalized COVID-19 patients.[15,16] The objective of this study is to investigate whether the Quantra parameters, as well as a panel of inflammation markers and routine coagulation tests, are associated with disease severity and outcomes of hospitalized COVID-19 patients.

Materials and Methods

Patients and Diagnosis Criteria

A total of 69 patients, positive for SARS-CoV-2 by PCR and hospitalized at the Regional University Hospital of Málaga were included in the study. All patients were over 18 years of age and none had any other hemostasis disorders. Immunocompromised patients, such as oncology patients on chemotherapy or those positive for HIV were also excluded from the study. Patients with missing data were excluded from the study.

Follow-up was completed on the date of discharge or death and patients were classified according to disease severity (critical, severe and non-severe) based on World Health Organization (WHO) criteria.[17] Briefly, critical COVID-19 patients were those who presented with sepsis, septic shock or other conditions that required provision of life-sustaining therapies (mechanical ventilation or vasopressor therapy); severe were those with oxygen saturation <90% on room air or respiratory rate >30 breaths/min or with signs of severe respiratory distress including the need to use accessory muscles and the inability to formulate full sentences; and finally, the absence of any critical or severe COVID-19 criteria was considered as non-severe disease. Patients were also classified according to the presence or absence of adverse events, including the need for mechanical ventilation, development of encephalitis, thrombotic events, admission to ICU (intensive care unit) or death. The study was approved by the local ethical committee. Written informed consent was obtained from patients or legal guardians before inclusion.

Inflammatory and Procoagulant status

Citrated, EDTA and non-anticoagulated blood samples were drawn on hospital admission after confirmation of SARS-CoV-2 infection. Quantra® Hemostasis Analyzer (HemoSonics, Charlottesville, VA, USA) was used to evaluate the global viscoelastic hemostatic status of the patients. On this system, QStat® and QPlus® cartridges were used to determine the following parameters: Clot Time (CT), Heparinase Clot Time (CTH), Clot Time Ratio (CTR: CT/CTH), Clot Stiffness (CS), Fibrinogen Contribution to Clot Stiffness (FCS), Platelet Contribution to Clot Stiffness (PCS), Clot Stability to Lysis (CSL). Details of Quantra QPlus and QStat cartridges have been described previously.[18,19] Complete blood count, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), D-dimer, fibrinogen, IL-6, ferritin, lactate dehydrogenase (LDH) and C-reactive protein (CRP) were also determined.

Statistical Analysis

The statistical software "SPSS statistics" (IBM) was used for the analysis. Comparison for qualitative (Chi-square test or Fisher's Exact Test) and quantitative differences (Mann-Whitney U or Student's t test, depending on data distribution) were applied. A univariable logistic regression analysis of clinical outcome ("adverse event" or "no adverse event") was performed using the following variables at admission as predictors: age, IL-6, CRP, LDH, ferritin, PT, aPTT, platelet count, fibrinogen, D-dimer, chronic disease, CT, CTH, CS, PCS, and FCS. Variables presenting with P-values <0.05 in this univariable analysis were included in a multivariable analysis using a logistic regression model. In building the multiple logistic regression model, we will assess the multicollinearity problem. If the multicollinearity problem occurs, we will apply the stepwise regression method.

The relationship between parameters at admission and adverse events was assessed by ROC curve analysis. Optimal cutoff values, defined as the best combination of sensitivity and specificity, were determined using the Youden index.

Correlation analysis was performed using Pearson's or Spearman's coefficient depending on data distribution.

Results

Demographic and Clinical Characteristics of the Patients

Table 1 and supplementary file 1 show demographic and clinical characteristics of the patient cohort:44.9% of patients developed non-severe disease, 39.1% severe disease and 16% critical disease. Compared to non-severe patients, severe/critical patients were older, often female and had more diabetes and adverse events. A total of 26.1% of the patients had an

Table 1. Demographic and Clinical Characteristics of COVID-19 Patients With Non-Severe Disease Versus Severe/Critical Disease.

	Total (N = 69) N (%)	Non-severe (N = 31) N (%)	Severe/Critical (N = 38) N (%)	P-value (*)
Age				
>65 years	34 (49.3)	10 (32.3)	24 (63.1)	0.011
<65 years	35 (50.7)	21 (67.7)	14 (36.8)	
Sex				
Male	38 (55)	23 (74.2)	15 (39.5)	0.004
Female	31 (45)	8 (25.8)	23 (60.5)	
Past medical history				
Hypertension	32 (46.4)	11 (35.5)	21 (55.3)	0.101
Diabetes	19 (27.5)	4 (12.9)	15 (39.5)	0.014
Coronary heart disease	10 (14.5)	4 (12.9)	6 (15.8)	1.000
COPD	7 (10.1)	2 (6.5)	5 (13.2)	0.446
Adverse event	18 (26.1)	1 (3.2)	17 (44.7)	<0.001
Mechanical ventilation	13 (18.8)	0 (0)	13 (34.2)	<0.001
ICU admission	5 (7.2)	0 ()	5 (13.2)	0.060
Encephalitis	1 (1.4)	1 (3.2)	0 (0)	0.449
Thrombotic event	3 (4.3)	0 (0)	3 (7.9)	0.247
Death	4 (5.8)	0 (0)	4 (10.5)	0.122

(*) Non-severe versus severe/critical by Chi-square test and Fisher's Exact Test. COPD: chronic obstructive pulmonary disease.

Table 2. Median of Inflammation and Tissue Damage Markers, Coagulation and Quantra® Parameters in Patients With and Without Adverse Events.

	No adverse events		Adverse events		P-value (*)
	N	Median (IQR)	N	Median (IQR)	
Inflammation and tissue damage					
IL-6 (pg/mL)	38	16.7 (0–1874)	15	6.8 (0–88)	0.239
CRP (mg/L)	47	44.9 (0–236)	18	94.8 (23–174)	0.015
LDH (IU/L)	45	234 (125–404)	18	308.5 (100–1716)	0.024
Ferritin (ng/mL)	45	211 (87–847)	18	413.8 (39–1365)	0.726
Coagulation					
PT (sec)	51	11.6 (11–18)	18	12.1 (11-13)	0.897
aPTT (sec)	51	25.2 (18–30)	18	24.6 (20–27)	0.827
Fibrinogen (mg/dL)	44	554 (215–900)	15	730.7 (532–900)	0.025
Platelet count (x 10^3/μL)	51	199 (130–401)	18	238 (133–479)	0.929
D-dimer (μg/L)	50	611 (175–9915)	17	824.5 (300–3406)	0.043
Quantra®					
CT (sec)	51	137 (93–179)	18	143.5 (125–159)	0.816
CTH (sec)	50	123 (86–152)	18	129.5 (110 -160)	0.522
CS (hPa)	51	26 (11–47)	18	36.1 (19–62)	0.058
PCS (hPa)	51	22.8 (10-38)	18	30.9 (15–48)	0.063
FCS (hPa)	51	3.7 (1–12)	18	6.2 (4v14)	0.018
CSL (%)	26	98 (88–100)	11	100 (91–100)	0.169

IQR: interquartile range; (*) Mann-Whitney U or Student's t test.

adverse event during hospital admission. Except for encephalitis, all adverse events occurred in the severe/critical group.

Increased Clot Stiffness in Patients with Poor Prognosis

As shown in Table 2, patients with adverse events showed significantly higher values of CRP, LDH, fibrinogen, D-dimer and the Quantra clot stiffness parameter FCS.

Table 3 shows the proportion of elevated levels of all assessed parameters, defined as the proportion above the upper limit of normal (ULN), in the total cohort as well as in patients who did not experience an adverse event and those who did. Inflammation and tissue damage markers were elevated in at least half of the patients: IL-6 in 73.6%, CRP in 89.2%, LDH in 57.1% and ferritin in 52.4%. Regarding coagulation parameters, shortened PT and aPTT clot times, ie, below

Table 3. Markers of Inflammation and Tissue Damage, Coagulation and Quantra Parameters: Proportion Above Upper Limit of Normal (ULN) or Below the Lower Limit of normal (LLN) in COVID-19 patients With no Adverse Events Versus Those With Adverse Events. In the Case of PT, aPTT, CT and CTH, the Percentage of Patients with times Below The Lower Limit of Normal Values Was Considered.

Test	ULN/BLN	N/total (%)	No adverse events N/total (%)	Adverse events N/total (%)	P-value (*)
Inflammation and tissue damage					
IL-6 (pg/mL)	4.4	39/53 (73.6)	28/38 (73.7)	11/15 (73.3)	1.000
CRP (mg/L)	5.0	58/65 (89.2)	41/47 (87.2)	17/18 (94.4)	0.663
LDH (IU/L)	246	36/63 (57.1)	21/45 (46.7)	15/18 (83.3)	0.008
Ferritin (ng/mL)	388	33/63 (52.4)	22/45 (48.9)	11/18 (61.1)	0.380
Coagulation					
PT (sec)	10.0	0/69 (0)	0/51 (0)	0/18 (0)	1.000
aPTT (sec)	20.6	10/69 (14.5)	8/51 (15.7)	2/18 (11.1)	1.000
Platelet count (x 10^3/μL)	450	6/69 (8.7)	5/51 (9.8)	1/18 (5.6)	1.000
Fibrinogen (mg/dL)	400	48/59 (81.4)	34/44 (77.3)	14/15 (93.3)	0.259
D-dimer (μg/L)	500	45/68 (66.2)	29/50 (58)	16/18 (88.9)	0.018
Quantra®					
CT (sec)	113	6/69 (8.7)	3/51 (5.9)	2/18 (11.1)	0.600
CTH (sec)	109	10/68 (14.7)	7/50 (14)	3/18 (16.7)	0.717
CS (hPa)	33.2	24/69 (34.8)	14/51 (27.4)	10/18 (55.6)	0.031
PCS (hPa)	29.8	19/69 (27.6)	11/51 (21.6)	8/18 (44.4)	0.074
FCS (hPa)	3.7	44/69 (63.7)	28/51 (54.9)	16/18 (88.9)	0.008
CSL (%)	100	12/37 (32.4)	5/26 (19.2)	7/11 (63.6)	0.018
D-dimer (μg/L) & FCS (hPa)	500 & 3.7	32/69 (46.4)	17/51 (33.3)	15/18 (83.3)	<0.001

(*) No adverse event versus adverse event by Chi-square test and Fisher's Exact Test.

Table 4. Associations Between Clinical and Biological Variables at Admission and the Presence of any Adverse Event During Hospitalization.

	Univariate analysis		Logistic regression model	
Variable	OR [95%CI]	P value (*)	OR [95%CI]	P value (**)
Age	1.036 [0.997, 1.076]	0.072		
IL6	1.000 [0.999, 1.002]	0.391		
CRP elevated	1.009 [1.000, 1.019]	0.049	1.005 [0.984–1.025]	0.651
LDH	1.005 [0.999, 1.010]	0.082		
Ferritin	1.000 [0.999, 1.001]	0.723		
PT	0.876 [0.542, 1.417]	0.591		
aPTT	1.020 [0.860, 1.208]	0.824		
Platelet count	1.001 [0.997, 1.005]	0.663		
Fibrinogen	1.004 [1.000, 1.008]	0.031	1.001 [0.991–1.011]	0.856
D-Dimer elevated	1.000 [1.000, 1.000]	0.272		
CT	0.995 [0.965, 1.026]	0.760		
CTH	1.007 [0.976, 1.039]	0.669		
CS	1.057 [1.007, 1.109]	0.025	0.716 [0.379–1.352]	0.303
PCS	1.072 [1.006, 1.142]	0.033	1.540 [0.707–3.353]	0.277
FCS	1.197 [1.014, 1.414]	0.034		
FCS and D-dimer	10.000 [2.542, 39.334]	0.001	**13.908 [1.765–109.600]**	**0.012**
Chronic disease	3.640 [1.054, 12.571]	0.041	**8.688 [1.223–61.737]**	**0.031**

(*) No adverse event versus adverse event by univariable logistic regression analysis. (**) No adverse event versus adverse event by multivariate logistic regression analysis.

the lower limit of normal (LLN), were only observed in 0% and 14.5%, respectively. An elevated platelet count was only present in 8.7% of all patients. In contrast, fibrinogen and D-dimer were elevated in 81.4% and 66.2%, respectively. On the Quantra system, shortened CT and CTH clot times (below LLN) were only observed in 8.7% and 14.7%, respectively. Total CS was elevated in 34.8%, with an elevated PCS and FCS in 27.6% and 63.7%, respectively. A CSL value of 100% (suggesting a dampening of fibrinolysis) was observed in 32.4%. Only, LDH, D-dimer, the Quantra clot stiffness

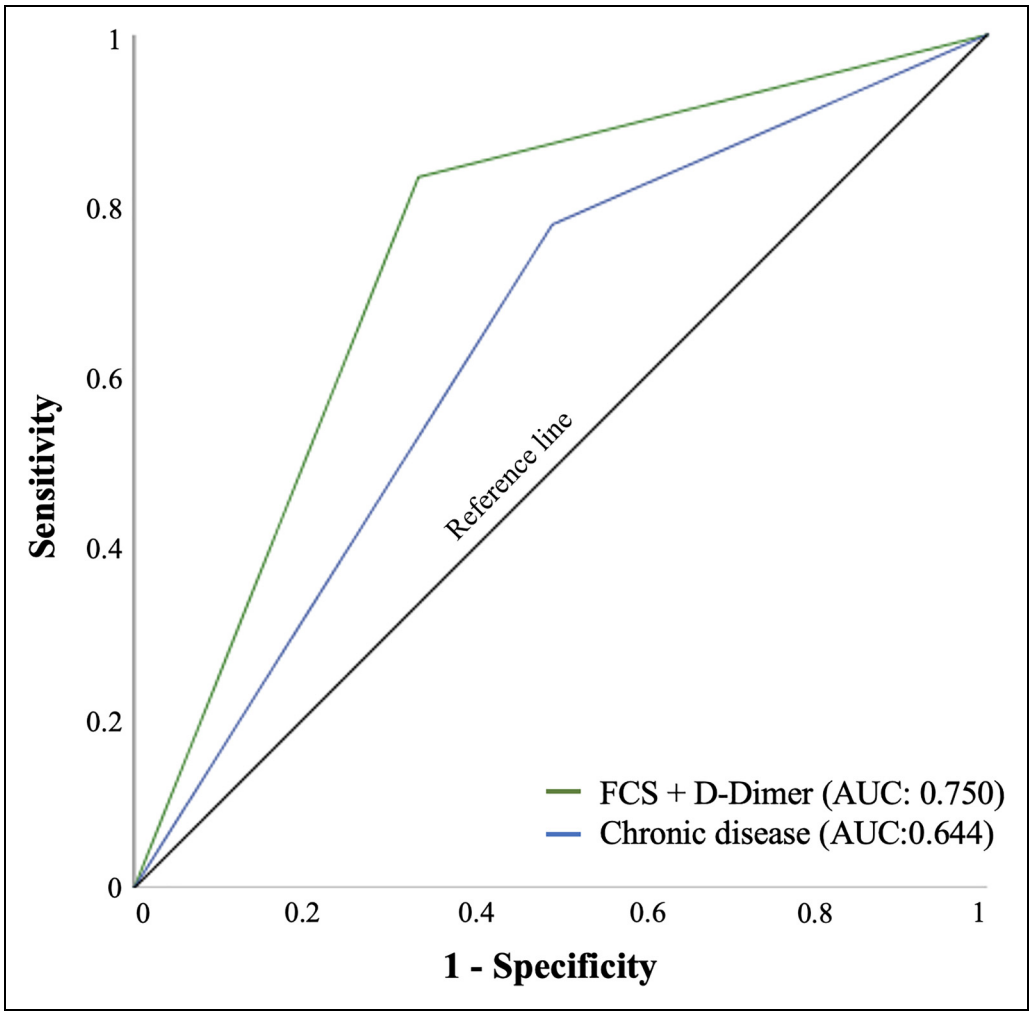

Figure 1. ROC analysis. ROC curve of FCS and D-dimer at admission versus the presence of chronic disease in predicting adverse advent.

parameters (CS and FCS) and CSL showed a significantly higher proportion of elevated values in COVID-19 patients with adverse events compared with those with no adverse events. Particularly the combination of elevated FCS and elevated D-dimer values was significantly associated with the presence of an adverse event. In fact, 83.3% of patients with an adverse event showed both parameters above the ULN, compared to 33.3% in the group of patients without an adverse event ($P < 0.001$).

Results for the univariable and multivariable analyses are presented in Table 4. In univariate analyses, CRP, fibrinogen, CS, PCS, FCS, the combination of FCS and D-dimer as a dichotomic variable, as well as other chronic diseases, such as diabetes, hypertension, coronary heart disease or Chronic obstructive pulmonary disease (COPD), were significantly associated with the presence of any adverse event during admission. Concerning the multivariable analysis, only other chronic disease (OR = 8.688 [1.223–61.737]; $P = 0.031$) and the combination of FCS and D-dimer (OR = 13.908 [1.765–109.600]; $P = 0.012$) were independently associated with the presence of any adverse event.

In predicting the severity of disease, the area under the curve (AUC) by ROC analysis was 0.644 with a 95% confidence interval of [0.500–0.787] ($P = 0.071$) for chronic disease and 0.750 [0.622–0.878] ($P = 0.002$) for the combination of FCS and D-dimer in predicting the manifestation of an adverse event (Figure 1). The optimal probability the Cutoff for FCS is found 3.7 hPa (TPR: 0.944, TNR: 0.431, YI: 0.376) and 693.815 µg/L (TPR: 0.778, TNR: 0.660, YI: 0.438) for D-dimer.

Close Interaction Between Procoagulant status and Inflammation in COVID-19 Patients

FCS values showed a strong correlation with plasma fibrinogen (r = 0.850; $P < 0.001$). In turn, both parameters showed a moderate to strong correlation with CRP values (0.699; $P < 0.001$ for FCS and 0.803; $P < 0.011$ for plasma fibrinogen). FCS and plasma fibrinogen values above ULN were significantly associated with CRP values above ULN ($P = 0.008$ and $P < 0.001$, respectively) and IL-6 values above ULN ($P = 0.028$

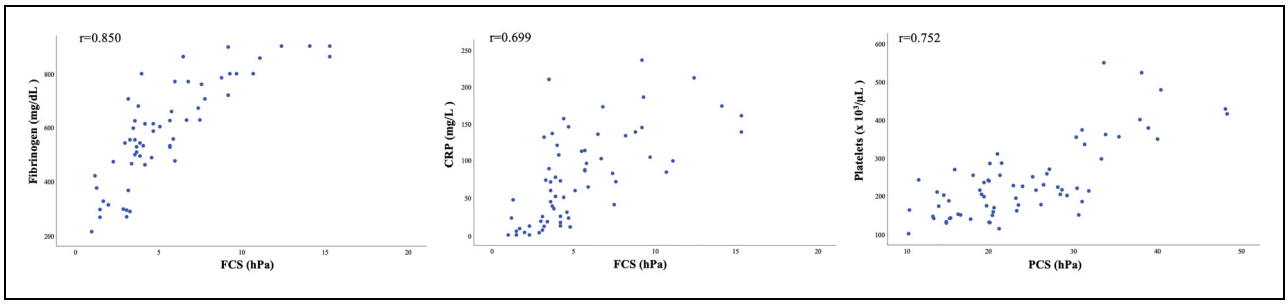

Figure 2. Scatter plots and Spearman correlation. FCS versus fibrinogen (left) and CRP (middle); PCS versus platelet count (right).

and $P < 0.001$, respectively). On the other hand, PCS correlated strongly with platelet count ($r = 0.752$; $P < 0.001$) (Figure 2).

Discussion

We present the results of a pilot study in which we evaluated the use of global viscoelastic hemostatic analysis by Sonorheometry (Quantra system) in COVID-19 patients on admission and the association of the Quantra parameters with disease severity and outcomes. Whole blood samples from 69 COVID-19 patients were analyzed using standard laboratory tests for coagulation, inflammatory and tissue damage markers, and the Quantra Hemostasis Analyzer. Global hemostatic analysis by the Quantra revealed increased clot stiffness in a high number of COVID-19 patients, especially in those who experienced an adverse event during admission, such as the need for mechanical ventilation, the development of encephalitis, thrombotic event, ICU admission or death. The combination of elevated FCS and D-dimer values appears to retain a higher predictive value of poor prognosis, potentially leading to its use in the clinical management of these patients, both in triage and in the development of new therapeutic approaches.

Of the total cohort, 55.1% were classified as having severe/critical disease according to WHO criteria.[17] As expected, all patients who experienced an adverse event belonged to this group, except for one patient in the non-severe disease group who developed encephalitis. The most occurring event was the presence of acute respiratory distress syndrome (ARDS) observed in 18.8% of patients, who required mechanical ventilation. Consistent with previous studies, we observed that an age > 65 years was indicative of a worse prognosis.[18,19] Thus, patients with advanced age were more frequently observed in the severe/critical disease group. Other comorbidities such as diabetes were also associated with a worse prognosis as previously described.[20,21]

We observed in our series a high proportion of patients with IL-6 and CRP values above the ULN. In support of our finding, these markers have been shown to be elevated in COVID-19 patients, especially in those with ARDS.[5] In fact, the group of Herold. et al demonstrated the value of these parameters as predictors of the need for mechanical ventilation. As reported by Ranucci et al and following the model of interaction between inflammation and coagulation, elevated fibrinogen levels were associated with elevated Il-6 values.[15] IL-6 is a potent proinflammatory cytokine that induces tissue factor gene expression in endothelial cells and monocytes, fibrinogen synthesis and platelet production, leading to the prothrombotic state.[22,23] A high percentage of patients in our cohort also showed LDH values above ULN, especially in those associated with worse prognosis, consistent with lung damage due to pneumonia caused by SARS-CoV-2 infection and which has been associated with increased patient mortality.[24]

Regarding coagulation parameters, COVID-19 patients showed elevated levels of fibrinogen and D-dimer, the latter being mostly observed in patients who experienced an adverse event during hospital admission. These results are also in agreement with those reported in the literature, which propose these factors as probably responsible for the thrombotic events that have been observed in COVID-19 patients.[3,4]

VET analysis has also been proposed as a powerful tool for the study of the global hemostatic status of COVID-19 patients.[25] Especially, these studies have focused on the analysis of patients with poor prognosis such as those admitted to the ICU or with ARDS, revealing that VET analysis could be established as a promising tool to predict thrombotic complications and thus optimize the diagnosis and treatment of COVID-19 patients.[26] Our results showed that a high percentage of patients had altered parameters of clot stiffness, mainly due to the contribution of fibrinogen. Alterations in these parameters were significantly more prevalent in patients with an adverse event during hospital admission. These results support previous studies suggesting that the hypercoagulability of COVID-19 patients is largely attributable to the contribution of fibrin and platelets to clot stability and stiffness.[15]

As expected, platelet count and fibrinogen levels correlated positively with PCS and FCS values, respectively. However, despite the high correlation between platelet count and PCS, an elevated platelet count was observed in only 8.7% of patients, compared to 27.6% of patients with an elevated PCS. This result supports the evidence shown by Baryshnikova et al, that PCS is not only influenced by platelet count, but also by platelet functionality.[27] Furthermore, these findings highlight that platelet hyperreactivity plays a key role in the pathogenicity of severely ill COVID-19 patients, as previous studies have shown.[28] With the Quantra QStat, based on

response in normal healthy individuals, the reference range for the CSL parameter is 93% to 100%. In our cohort tested for CSL (n = 37; 11 with adverse events), only 4 patients (1 with adverse events) showed a value below the lower limit of normal, suggesting hyperfibrinolysis. Although for the QStat CSL parameter a cut-off for hypofibrinolysis has not been determined, it is interesting to observe that the proportion with the maximum CSL value of 100% was significantly higher in the patients with an adverse event (63.6% vs 19.2%; $P = 0.018$). This finding suggests the presence of fibrinolysis resistance in support of previous findings that attributed the hypercoagulability of COVID-19 patients to this phenomenon.[29–31]

Many of these parameters, both inflammation, and coagulation, have been proposed as promising prognostic markers to help us predict the risk of more severe disease in COVID-19 patients. In particular, many studies have focused on D-dimer as an indicator of poor prognosis.[19,32] However, D-dimer has been shown a poor specificity predicting thrombotic events, as it can be elevated for other reasons, highlighting the need to identify additional powerful markers. On the other hand, increased clot stiffness has been observed especially in patients with ARDS or ICU admission, revealing a possible association between these parameters and a worse prognosis of the disease.[33] Nevertheless, the prognostic value of clot stiffness measured by VET techniques has not yet been extensively studied. Our results demonstrate that clot stiffness parameters measured by Quantra® are especially elevated in patients with a worse prognosis. Notably, only the combination of elevated FCS and D-dimer values, together with the presence of another chronic disease, remained as an independent prognostic factor for the risk of an adverse event during admission in the multivariate analysis. These results highlight the potential of using both parameters together as a predictor of the risk of a worse prognosis in COVID-19 patients.

One of the limitations of our study is, however, that patients were analyzed only at the time of diagnosis. Previous studies have shown that the predictive value of D-dimer on the risk of death is much higher when measured just before the clinical outcome compared to the time of diagnosis, suggesting the importance of dynamically monitoring D-dimer levels to detect thrombotic complications and thus reduce the mortality rate of patients.[19] The results of our study, which found that the combination of FCS and D-dimer has the highest predictive value for an adverse event, emphasize the importance of made a close follow-up of COVID-19 patients with elevated levels of both variables at admission.

Conclusion

In summary, we can conclude from this study that the use of the Quantra® sonorheometry VET technique allows a global analysis of the hemostatic status of COVID-19 patients in a rapid and efficient way, including clot stiffness parameters (CS, PCS, FCS, CSL) that are not routinely measured by standard laboratory tests. The implementation of this technique would allow for a more accurate diagnosis of patients on admission, helping in patient triage. By using this technique, we were able to detect that COVID-19 patients with higher clot stiffness showed a worse prognosis, especially due to the higher contribution of fibrinogen (FCS). Although further studies are needed to confirm these findings, the combination of elevated FCS and D-dimer, was shown to be an independent prognostic factor for the risk of an adverse event during admission among COVID-19 patients, so the close monitoring of both parameters could be of interest for the management of these patients. This finding could also contribute to the development of new therapeutic strategies thanks to the numerous anticoagulant agents currently available.

Abbreviations

aPTT	Activated partial thromboplastin time
ARSD	Acute respiratory distress syndrome
AUC	Area under the curve
COPD	Chronic obstructive pulmonary disease
CS	Clot stiffness
CSL	Clot stability to lysis
CT	Clot time
CTR	Clot time ratio
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
FCS	Fibrinogen contribution to clot stiffness
CTH	Heparinase clot time
ICU	Intensive care unit
INR	International normalized ratio
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
OR	Odd Ratio
PCS	Platelet contribution to clot stiffness
PT	Prothrombin time
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SEER	Sonic estimation of elasticity by resonance
TNR	True negative rate
TPR	True positive rate
ULN	Upper limit of normal
VET	Viscoelastic tests
WHO	World health organization
YI	Youden Index

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Author Contributions

Conceptualization, F.J.L.-J, M.I.M.-P and I.F.-B; Methodology, F.J.L.-J, I.M.-G, I.F.-B and A.M; Software, Y.T, F.J.L.-J and A.M; Validation, S.M.-T, I.F.-B and A.M; Formal analysis, F.J.L.-J, I.F.-B, Y.T and A.M; Investigation, F.J.L.-J, S.M.-T, A.D.-M,

J.M.R.-I and A.M; Data curation, A.D.-M, I.F.-B, Y.T and A.M; Writing – original draft preparation, F.J.L.-J, I.F.-B and A.M, Writing – review and editing, all authors; Visualization, all authors; Supervision; F.J.L.-J and I.F.-B; Project administration, F.J.L.-J; Funding acquisition, F.J.L.-J; All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Consent for Publication

Written informed consent was obtained from patients or legal guardians before inclusion.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Xxxxxxx.Yohannes Tesfay is an employee of Hemosonics, LLC. The rest of the authors declare that they have no conflict of interest.

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The study was approved by the local ethical committee.

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Supplemental material

Supplemental material for this article is available online.

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