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RESEARCH ARTICLE

Validation of an admission coagulation panel for risk stratification of COVID-19 patients

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Abstract

Background

There is limited data on the markers of coagulation and hemostatic activation (MOCHA) profile in Coronavirus disease 2019 (COVID-19) and its ability to identify COVID-19 patients at risk for thrombotic events and other complications.

Methods

Hospitalized patients with confirmed SARS-COV-2 from four Atlanta hospitals were included in this observational cohort study and underwent admission testing of MOCHA parameters (plasma d-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex, fibrin monomer). Clinical outcomes included deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, access line thrombosis, ICU admission, intubation and mortality.

Main results

Of 276 patients (mean age 59 ± 6.4 years, 47% female, 62% African American), 45 (16%) had a thrombotic endpoint. Each MOCHA parameter was independently associated with a thrombotic event ($p<0.05$) and $\geq$ 2 abnormalities was associated with thrombotic endpoints (OR 3.3, 95% CI 1.2–8.8) as were admission D-dimer $\geq$ 2000 ng/mL (OR 3.1, 95% CI 1.5–6.6) and $\geq$ 3000 ng/mL (OR 3.6, 95% CI 1.6–7.9). However, only $\geq$ 2 MOCHA abnormalities were associated with ICU admission (OR 3.0, 95% CI 1.7–5.2) and intubation (OR 3.2, 95% CI 1.6–6.4). MOCHA and D-dimer cutoffs were not associated with mortality. MOCHA with

activation. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

<2 abnormalities (26% of the cohort) had 89% sensitivity and 93% negative predictive value for a thrombotic endpoint.

Conclusions

An admission MOCHA profile is useful to risk-stratify COVID-19 patients for thrombotic complications and more effective than isolated d-dimer for predicting risk of ICU admission and intubation.

Introduction

Coronavirus disease 2019 (COVID-19) has been widely associated with the development of a systemic coagulopathy that is likely multifactorial in etiology [1]. COVID-19-associated coagulopathy exhibits the classic components of Virchow's triad, and there are ongoing efforts to better characterize the underlying pathophysiology of the hypercoagulable state in the setting of COVID-19 infection [2]. Elevated levels of fibrin degradation products, particularly D-dimer, have been used to predict venous thromboembolic events (VTE) and hypercoagulable states in various disease states [3, 4]. Plasma D-dimer in COVID-19 patients was found to be a useful predictor of VTE [5, 6] and thresholds of 2000 ng/mL or 3000 ng/mL have been suggested as indicators of disease severity [7, 8].

A biomarker panel called the markers of coagulation and hemostatic activation (MOCHA), which includes plasma D-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex and fibrin monomer levels, has been shown to predict subsequent diagnosis of new malignancy, VTE, and other hypercoagulable states in patients with cryptogenic stroke [9, 10]. A previous study has also demonstrated that a MOCHA profile with < 2 marker abnormalities can effectively rule out hypercoagulable states in patients with embolic stroke of undetermined source [11]. One study suggested that the presence of multiple abnormal coagulation parameters could predict ICU admission and poor outcomes in COVID-19 patients [12].

The objective of this study was to validate whether the admission MOCHA profile in hospitalized COVID-19 patients could aid in risk stratification by identifying those patients at low versus high risk of thrombotic events, ICU admission, intubation and clinical outcome more effectively than D-dimer alone.

Methods

Study design and setting

This is an observational cohort study of patients identified from an admission census list that identified all COVID-19 patients admitted to four hospitals in Emory Healthcare, an urban, academic, tertiary healthcare system in Atlanta, Georgia who had a MOCHA profile ordered on admission as part of a standardized COVID-19 orderset from April 3, 2020 through July 31, 2020. Expert consensus of a multidisciplinary working group recommended obtaining a MOCHA profile on all patients admitted with a diagnosis of COVID-19. All patients were 18 years of age or older with diagnosis of COVID-19 confirmed by PCR and had a MOCHA profile drawn within 72 hours of hospitalization. For this analysis we excluded patients on outpatient anticoagulation therapy prior to hospitalization due to the effect of anticoagulation on the MOCHA profile [10] and pregnant patients due to the lack of validated reference ranges. Patients received prophylactic anticoagulation therapy upon admission, per the Emory VTE

prophylaxis guidelines [8]. Prophylactic anticoagulation therapy was not shown to have a significant influence on the MOCHA profile [9]. Electronic medical records were retrospectively reviewed from admission through discharge or until the censor date of September 14, 2020 to identify venous and arterial thrombotic events. This study was approved by the Emory University Institutional Review Board. Data was analyzed anonymously and did not require consent.

Patient demographics including age, sex, race, body mass index (BMI), and a history of comorbidities including smoking, diabetes, hypertension, asthma, chronic obstructive pulmonary disorder (COPD), human immunodeficiency virus (HIV) infection, end stage renal disease, atrial fibrillation, prior VTE, coronary artery disease (CAD), stroke, and known active cancer were collected. Total length of stay, length of intensive care unit (ICU) admission, length of intubation, and final disposition were additionally recorded. Prespecified venous and arterial endpoints monitored during hospitalization included deep vein thromboses (DVT), pulmonary embolus (PE), myocardial infarction (MI), ischemic stroke, and dialysis or central line clots. DVT was confirmed by duplex ultrasound and PE by CT, CT angiography or ventilation/perfusion scans. MI was diagnosed as a troponin elevation and confirmation by a board-certified cardiologist. Ischemic stroke was diagnosed by CT or MRI and confirmation by a board-certified neurologist. Central access and renal replacement therapy circuit thrombosis were determined based on chart documentation.

Laboratory testing

Admission MOCHA profiles were obtained within 72 hours of hospitalization and included plasma levels of D-dimer (reference value <574 ng/mL), prothrombin fragment 1.2 (reference range 65–288 pmol/L), thrombin-antithrombin complex (reference range 1.0–5.5 μg/L), and fibrin monomer (reference value <7 μg/mL). All assays were performed in the hospital clinical laboratories using 3.2% citrated plasma specimens. D-dimer levels were measured with high-sensitivity latex dimer assay (Instrumentation Laboratories, Bedford, MA). Both prothrombin fragment 1.2 and thrombin-antithrombin complexes were measured with the Enzygnost ELISA kit (Siemens Healthcare, Tarrytown, NY). Soluble fibrin monomer levels were measured by latex immunoassay (Stago, Parsippany, NJ).

Statistical analysis

Descriptive statistics were used to summarize the data with results reported as percentages for categorical variables. Means with standard deviations or medians with interquartile ranges were reported for normally distributed and skewed variables, respectively. Comparisons between means or medians of continuous variables were assessed with independent T-tests (two-tailed) or by the Mann-Whitney U non-parametric test, respectively. Categorical variables were compared with Pearson's chi-square and Fisher Exact tests. Significance for all descriptive analyses was set at $p<0.05$. Univariable analyses were conducted using binary logistic regression for binary outcome variables (thrombotic endpoint, VTE, ICU admission, intubation and mortality). Statistically significant predictors of these outcomes ($p<0.10$) were then considered in multivariable binary logistic regression analyses to identify independent outcome predictors (adjusted $p<0.05$). The association with thrombotic events within 14 days of admission was additionally examined.

The frequency of D-dimer and MOCHA profile abnormalities were recorded and subsequently analyzed in specific patient subsets, including those with ICU admission and intubation. The four parameters of the MOCHA profile were independently assessed using receiver operator characteristic (ROC) curve analysis in order to determine the area under the curve (AUC) as a measure of discriminative power. Patients were stratified based on the number of

elevated MOCHA markers on admission. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated at different MOCHA and D-dimer cutoffs. This was used to identify optimal thresholds for predicting thrombotic endpoints and to compare the performance of admission MOCHA with admission D-dimer alone. Statistical analyses and figures were generated using SPSS version 26 software.

Results and discussion

Descriptive data

A total of 297 confirmed COVID-19 patients were hospitalized during the study period and had MOCHA profile within 72 hours of admission. After exclusion of 18 patients on outpatient anticoagulation therapy and three pregnant patients, the analysis cohort included 276 patients. The mean age of the cohort was 59 ± 6 years, 130 (47%) were female, and 160 (62%) were African American. Median BMI was 30 (IQR: 26–37) kg/m^2 (Table 1). Common comorbidities included hypertension (59%), obesity (n = 140, 51%) and diabetes (n = 108, 39%). The median duration of hospitalization was 10 days (IQR: 6–19) including 159 patients (58%) admitted to the ICU during their hospitalization, 90 (33%) who were intubated. Amongst the cohort, 241 (87%) patients were discharged, 31 (11%) died and 4 (1%) remained hospitalized as of the censor date.

Frequency of thrombotic events

Thrombotic events were diagnosed in 45 patients (16%) (Table 2). Median number of days to diagnosis of a thrombotic event was 7 days (IQR: 2–15) from admission, with 32 (71%) of these events occurring within the first two weeks of hospitalization. DVT occurred in 24 (8.7%) patients, PE in 8 (2.9%), MI in 4 (1.5%), ischemic stroke in 5 (1.8%) and central or dialysis line thrombosis in 7 (2.5%) patients, wherein 6 (2.2%) developed renal replacement therapy thrombosis, and 1 (0.4%) patient developed an extracorporeal membrane oxygenation circuit thrombosis. Three patients (1%) developed more than one of these complications.

Overall, 7 (2.5%) patients had no MOCHA abnormalities on admission, 66 (24%) had one abnormality, 62 (23%) had two abnormalities, 69 (25%) had three abnormalities, and 72 (26.1%) had abnormalities in all four MOCHA; 217 patients (79%) had an abnormal D-dimer on admission, 51 (19%) had an admission D-dimer greater than 2000 ng/mL, and 40 (15%) had an admission D-dimer greater than 3000 ng/mL. There were 115 (42%) patients who had an elevated prothrombin fragment 1.2 level, 185 (67%) with an elevated thrombin-antithrombin complex level, and 167 (61%) with elevated fibrin monomer levels. The frequency of thrombotic events, ICU admission and intubation rates progressively increased with the number of MOCHA abnormalities (Fig 1).

Association of admission MOCHA and D-dimer with thrombotic events

In univariable analysis admission MOCHA $\geq$ 2 abnormalities, D-dimer $\geq$ 2000 ng/mL, D-dimer $\geq$ 3000 ng/mL, BMI, and CAD were significantly associated with thrombotic events. However, in multivariable analysis only MOCHA $\geq$ 2 (OR 3.3, 95% CI 1.2–8.8; p = .02), BMI (OR 1.04, 95% CI 1.0–1.1; p = .03), D-dimer $\geq$ 2000 ng/mL (OR 3.1, 95% CI 1.5–6.6; p = .003), and D-dimer $\geq$ 3000 ng/mL (OR 3.6, 95% CI 1.6–7.9; p = .002) were significant. In multivariable analysis, factors associated with thrombotic events within 14 days of admission included male sex (OR 2.2, 95% CI 1.0–5.0; p = .049), MOCHA $\geq$ 2 abnormalities (OR 6.4, 95% CI 1.5–27.6; p = .013) and D-dimer $\geq$ 2000 ng/mL (OR 2.5, 95% CI 1.1–5.9; p = .03).

Table 1. Patient characteristics and outcomes.

Characteristic	Cohort (n = 276)
Demographics	
Age mean (SD)	59 (6.4)
Female, n (%)	130 (47)
Race, n (%)	
African American	160 (58)
Caucasian	45 (16)
Hispanic	44 (16)
Asian	9 (3)
Unspecified	18 (6.5)
Median BMI (IQR)	30 (26–37)
Hospitalization Details	
Median Length of Stay (IQR)	10 (6–19)
Intubation, n (%)	90 (33)
ICU Admission, n (%)	158 (57)
Discharge Disposition, n (%)	
Home	182 (67)
LTAC	16 (5.9)
Acute/Inpatient Rehab	8 (2.9)
Subacute Rehab	8 (2.9)
Nursing Home/ALF	27 (9.9)
Death	31 (11)
Comorbidities	
Smoker, ever, n (%)	60 (24)
Obese, n (%)	140 (51)
Diabetes, n (%)	108 (39)
Hypertension, n (%)	163 (59)
History of VTE, n (%)	3 (1.1)
Asthma, n (%)	25 (9.1)
COPD, n (%)	23 (8.3)
HIV, n (%)	4 (1.4)
ESRD on HD, n (%)	15 (5.4)
Atrial Fibrillation, n (%)	9 (3.3)
CAD, n (%)	25 (9.1)
Stroke, n (%)	19 (6.9)
Active Cancer, n (%)	8 (2.9)

Abbreviations: Body mass index (BMI). Intensive Care Unit (ICU). Long-term acute care (LTAC). Assisted living facility (ALF).

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Association of admission MOCHA and D-dimer with ICU admission, intubation and mortality

In univariable analysis, admission MOCHA $\geq$ 2 abnormalities and a history of stroke were significantly associated with ICU admission. However, in multivariable analysis, only admission MOCHA $\geq$ 2 abnormalities was a significant predictor of ICU admission (OR 3.0, 95% CI 1.7–5.2; p = .0001).

With regards to the risk of respiratory deterioration and intubation, BMI, history of hypertension, and MOCHA $\geq$ 2 abnormalities were associated with intubation in univariable

Table 2. Frequency of outcomes.

	Frequency*	
Outcomes	**Entire Hospitalization**	**Within 14 Days**
DVT, n (%)	24 (8.7)	17 (6.2)
PE, n (%)	8 (2.9)	7 (2.5)
MI, n (%)	4 (1.5)	4 (1.5)
Ischemic Stroke, n (%)	5 (1.8)	2 (0.7)
Line Clot, n (%)	7 (2.5)	5 (1.8)
Total Thrombotic Endpoints, n (%)	45 (16.3)	32 (11.6)

* 3 patients developed more than one vascular endpoint.

DVT = deep vein thrombosis; PE = pulmonary embolus; MI = myocardial infarction.

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analysis. In multivariable analysis, MOCHA ≥ 2 abnormalities (OR 3.2, 95% CI 1.6–6.4; p = .001) and BMI (OR 1.04, 95% CI 1.0–1.1; p = .017) remained significant. D-dimer was not significantly associated with either ICU admission or intubation.

In univariable analysis, admission MOCHA ≥ 2 abnormalities, history of stroke, hypertension, diabetes and BMI were significantly associated with mortality. In multivariable analysis, only BMI remained a significant predictor of mortality (OR 1.04, 95% CI 1.01–1.08; p = 0.02).

Value of admission MOCHA and D-dimer in predicting thrombotic events, VTE, ICU admission, and intubation

Sensitivity, specificity, PPV, and NPV at different MOCHA and D-dimer cutoffs are shown in Table 3. A MOCHA profile with ≥ 2 abnormalities had a sensitivity of 89% (NPV 93%) for a

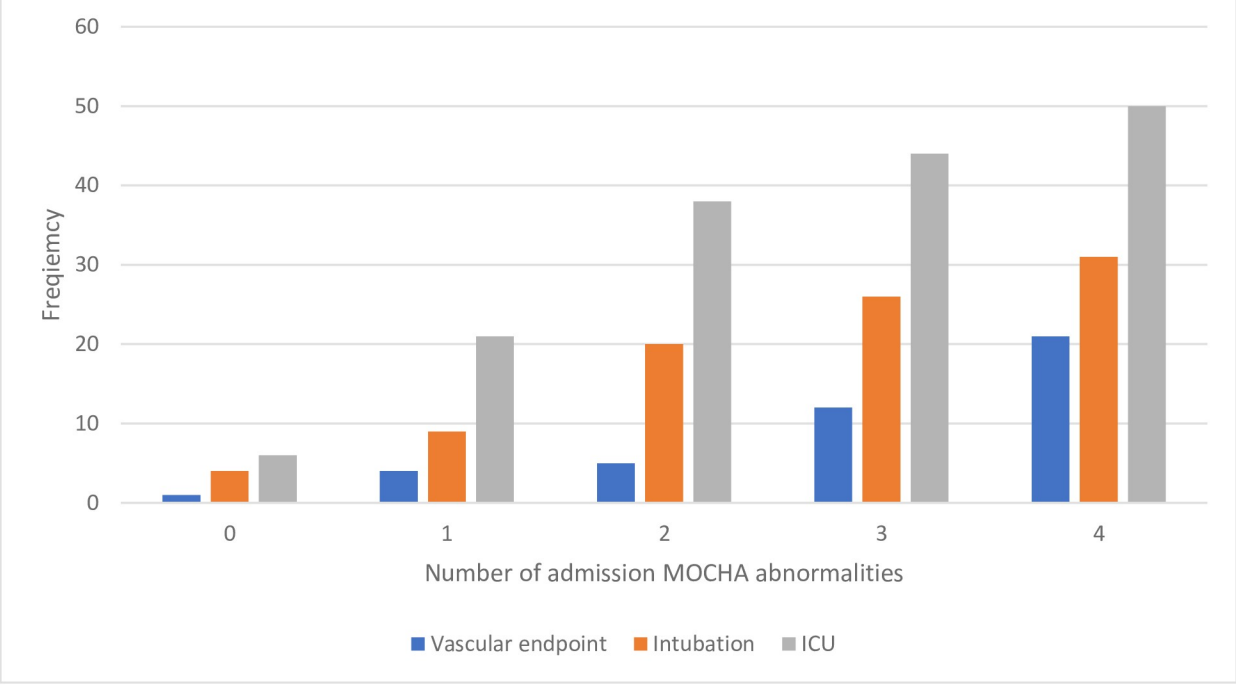

Fig 1. Frequency of MOCHA abnormalities in patients with thrombotic endpoints, intubation and ICU admission.

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Table 3. Sensitivity, specificity, positive predictive value and negative predictive value for (A) admission MOCHA and (B) D-dimer cutoffs with thrombotic endpoints.

A. Admission MOCHA abnormalities

1. Total thrombotic endpoints (n = 45)

Threshold	Sensitivity	Specificity	PPV	NPV
≥0	100	0	16	
≥1	98	2.6	16	86
≥2	89	29	20	93
≥3	78	54	25	93
4	47	78	29	88

2. Thrombotic endpoints <14 days from admission (n = 32)

Threshold	Sensitivity	Specificity	PPV	NPV
≥0	100	0	12	
≥1	100	2.9	12	100
≥2	94	29	15	97
≥3	81	53	18	96
4	41	76	18	91

3. Total VTE (n = 31)

Threshold	Sensitivity	Specificity	PPV	NPV
≥0	100	0	11	
≥1	97	2.4	11	86
≥2	87	28	13	94
≥3	77	52	17	95
4	45	76	19	92

4. VTE <14 days from admission (n = 23)

Threshold	Sensitivity	Specificity	PPV	NPV
≥0	100	0	8.3	
≥1	100	2.8	8.6	100
≥2	96	28	11	99
≥3	87	52	14	98
4	48	76	15	94

B. Admission D-dimer (ng/mL)

1. Total thrombotic endpoints (n = 45)

Threshold	Sensitivity	Specificity	PPV	NPV
≥2000 ng/mL	33	84	29	87
≥3000 ng/mL	29	88	33	86

2. Thrombotic endpoints <14 days from admission (n = 32)

Threshold	Sensitivity	Specificity	PPV	NPV
≥2000 ng/mL	31	83	20	90
≥3000 ng/mL	25	87	20	90

3. Total VTE (n = 31)

Threshold	Sensitivity	Specificity	PPV	NPV
≥2000 ng/mL	39	84	24	92
≥3000 ng/mL	32	88	25	91

4. VTE <14 days from admission (n = 23)

Threshold	Sensitivity	Specificity	PPV	NPV
≥2000 ng/mL	44	84	20	94
≥3000 ng/mL	35	87	20	94

MOCHA = markers of coagulation and hemostatic activation; PPV = positive predictive value; NPV = negative predictive value; VTE = venous thromboembolism.

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thrombotic event through total hospitalization, 94% (NPV 97%) for a thrombotic event within two weeks of admission, and 96% (NPV 99%) for VTE within two weeks of admission. D-dimer level $\geq$ 2000 ng/mL on admission had a sensitivity of 33% (NPV 87%) for a thrombotic event through total hospitalization, sensitivity of 31% (NPV 90%) for a thrombotic event within two weeks of admission and a sensitivity of 43% (NPV 94%) for VTE within two weeks.

ROC curve analysis showed that all four MOCHA parameters were independent predictors of any thrombotic endpoint ($p < .01$). However, the discriminative power for MOCHA was highest for VTE within the first two weeks of admission, during which time D-dimer and thrombin-antithrombin complex both had AUC 0.74, prothrombin fragment 1.2 had AUC 0.68 and fibrin monomer AUC 0.62.

Our study provides systematic assessment of the admission MOCHA profile in hospitalized COVID-19 patients and its association with thrombotic events. While the frequency of elevated D-dimer and prothrombin fragment 1.2 is similar to those reported in recent studies [7, 13], our study is the first to report the frequency of admission thrombin-antithrombin complex and fibrin monomer levels in hospitalized COVID-19 patients. While $\geq$ 2 abnormalities in the admission MOCHA profile and D-dimer cutoffs were significantly associated with thrombotic events only the admission MOCHA profile was associated with subsequent ICU admission and intubation whereas D-dimer cutoffs of $\geq$ 2000 ng/mL and $\geq$ 3000 ng/mL were not. Our results validate a previous small study showing that the combination of coagulation markers is able to identify patients at risk for ICU admission [12].

We assessed these four markers of coagulation and hemostatic activation given their prior association with thrombotic events [9–11]. D-dimer is a marker of fibrinolysis as a byproduct of fibrin degradation. Prothrombin fragment 1.2 is a marker of coagulation activation and released during conversion of prothrombin to thrombin. Thrombin-antithrombin complex is a marker of coagulation activation and a complex formed during thrombin formation. Fibrin monomer (soluble fibrin) is a marker of coagulation activation and a byproduct of fibrinogen conversion to fibrin [14].

We found no association between admission MOCHA profile or admission D-dimer and mortality, contrary to early studies from China which suggested that D-dimer was a predictor of mortality in pooled analysis [14]. There are several factors which may contribute to this difference: 1) our patients were all placed on prophylactic or therapeutic doses of anticoagulation therapy according to our local guidelines which may have influenced overall mortality rates and were lower in our cohort than other studies in the pooled analysis [8]; 2) the Chinese studies in this pooled analysis were all retrospective cohorts and excluded patients who were still hospitalized at the end of the study period contributing to a high risk of bias [15].

Given current recommendations on the use of anticoagulation therapy in COVID-19 patients [16], we also sought to identify whether the MOCHA profile could identify a COVID-19 patient subgroup that was at low risk for thrombotic events. In our cohort, 26% of patients on admission had 0 or 1 MOCHA abnormality with NPV of 93% for thrombotic events and NPV of 95% for VTE. These data suggest that this patient subgroup is at low risk for subsequent thrombotic complications.

This study had several limitations. As the data was collected from a single academic healthcare system, the generalizability of these findings needs to be studied in other settings. The severity of COVID-19 infection and the degree of lung involvement were not assessed, and the association between infection severity and increased VTE risk was not studied. Screening for DVT and PE was at the discretion of individual providers, which may have had an influence on the frequency of these diagnoses. Our study focused on admission coagulation markers to aid in early risk stratification for COVID-19 patients however it is unknown whether serial measurements and changes in values across time may be better predictors. Lastly, our study

did not assess whether the MOCHA profile could be used to guide anticoagulation therapy and how that may impact overall thrombotic events and clinical outcome.

In summary, the admission MOCHA profile of hospitalized COVID-19 patients is useful in identifying hospitalized patients who are at increased risk for subsequent arterial and venous thrombotic events and more effectively identifies patients requiring ICU admission and intubation than admission D-dimer levels alone. Further investigation is needed to determine the utility of the MOCHA profile to guide anticoagulation therapy.

Supporting information

S1 Dataset.
(PDF)

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Mr. Alabyad has nothing to disclose.

Dr. Rangaraju has nothing to disclose.

Dr. Liu has nothing to disclose.

Dr. Kempton has nothing to disclose.

Dr. Sharifpour has nothing to disclose.

Dr. Auld has nothing to disclose.

Dr. Gaddh has nothing to disclose.

Dr. Sniecinski has nothing to disclose.

Dr. Maier has nothing to disclose.

Dr. Guarner has nothing to disclose.

Dr. Duncan has nothing to disclose.

Dr. Nahab has United States Patent Application 20200147125on the detection of high risk arterial thromboembolic diseases by markers of coagulation and hemostatic activation. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Author Contributions

Conceptualization: Cheryl L. Maier, Jeannette Guarner, Alexander Duncan, Fadi Nahab.

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Investigation: Roman Sniecinski.

Methodology: Srikant Rangaraju, Rajeel Imran, Christine L. Kempton, Milad Sharifpour, Sara C. Auld, Manila Gaddh, Cheryl L. Maier, Fadi Nahab.

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Writing – review & editing: Srikant Rangaraju, Michael Liu, Rajeel Imran, Christine L. Kempton, Milad Sharifpour, Sara C. Auld, Manila Gaddh, Roman Sniecinski, Cheryl L. Maier, Jeannette Guarner, Alexander Duncan, Fadi Nahab.

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