Evaluation of the prothrombin fragment 1.2 in patients with coronavirus disease 2019 (COVID-19)

Hanny Al-Samkari1,2 | Fei Song2,3 | Elizabeth M. Van Cott2,4 | David J. Kuter1,2 | Rachel Rosovsky1,2

1Division of Hematology, Massachusetts General Hospital, Boston, Massachusetts
2Harvard Medical School, Boston, Massachusetts
3Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
4Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts

Correspondence
Hanny Al-Samkari, Division of Hematology Oncology, Massachusetts General Hospital, Zero Emerson Place Suite 118 Office 112, Boston, MA 02114, USA.
Email: hal-samkari@mgh.harvard.edu

Abstract
Coronavirus disease 2019 (COVID-19) may cause a hypercoagulable state. The D-dimer is frequently elevated in COVID-19, but other markers of coagulation activation, including the prothrombin fragment 1.2 (PF1.2) are poorly described. We studied hospitalized adults with COVID-19 and PF1.2 measurements performed at any time during hospitalization. We evaluated the relationship between PF1.2 and synchronously measured D-dimer. We utilized receiver operating characteristic (ROC) analysis to evaluate optimal thresholds for diagnosing thrombosis and multivariable logistic regression to evaluate association with thrombosis. A total of 115 patients were included [110 (95.7%) critically ill]. Both PF1.2 and D-dimer were moderately positively correlated (r = 0.542, P < .001) but significant discordance was observed in elevation of each marker above the laboratory reference range (59.0% elevated PF1.2 vs 98.5% elevated D-dimer). Median PF1.2 levels were higher in patients with thrombosis than those without (611 vs 374 pmol/L, P = .006). In ROC analysis, PF1.2 had superior specificity and conferred a higher positive likelihood ratio in identifying patients with thrombosis than D-dimer (PF1.2 threshold of >523 pmol/L: 69.2% sensitivity, 67.7% specificity; >924 pmol/L: 37.9% sensitivity, 87.8% specificity). In multivariable analysis, a PF1.2 >500 pmol/L was significantly associated with VTE [adjusted odds ratio (OR) 4.26, 95% CI, 1.12-16.21, P = .034] and any thrombotic manifestation (adjusted OR 3.85, 95% CI, 1.39-10.65, P = .010); conversely, synchronously measured D-dimer was not significantly associated with thrombosis. 90.6% of patients with a non-elevated PF1.2 result did not develop VTE. So, PF1.2 may be a useful assay, and potentially more discriminant than D-dimer, in identifying thrombotic manifestations in hospitalized patients with COVID-19.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is associated with a hypercoagulable state, and coagulation-related complications have been associated with considerable morbidity and mortality in critically ill patients with COVID-19.1,2 Numerous studies have reported elevated rates of venous thromboembolism (VTE)2-4 and other thrombotic complications1,2 in critically ill patients with COVID-19 as well as an association of elevated plasma D-dimer concentrations with critical illness and mortality.5,7,8 Autopsy studies have reported fibrin thrombi within distended small vessels and capillaries9 as well as a high rate of occult pulmonary vessel thrombosis.10

The etiology of the near-universal D-dimer elevation in critically ill patients with COVID-19 remains unclear. Given the elevated rates of thrombotic complications observed in these patients, the assumption can be made that elevated D-dimer levels are secondary to increased and pathologic thrombin generation and fibrin clot formation. However, many patients with COVID-19 have dramatic D-dimer
elevations in the absence of clinical or radiographic evidence of thrombosis or laboratory evidence of disseminated intravascular coagulation (DIC). The contribution of other potential causes of D-dimer elevation, such as hyperfibrinolysis, direct lung injury, or reduced D-dimer clearance in patients with COVID-19 is not known.

Little is known about other serological markers of coagulation activation in COVID-19. One such marker, the prothrombin fragment 1.2 (PF1.2), is released from prothrombin by the catalytic action of the prothrombinase complex. It is a well-described marker of coagulation activation that is elevated in individuals with acute thrombosis and individuals with hypercoagulable states. Additionally, it has been demonstrated to be a useful biomarker for prediction of venous thromboembolism in certain patient populations. For example, in a prospective cohort study of 821 patients with cancer, an elevated PF1.2 (above 358 pmol/L) was associated with elevated risk of VTE compared with patients with a normal PF1.2 (HR 2.2, 95% CI, 1.3-3.6, \( P = .003 \)). In another study of 631 patients with a wide diversity of medical conditions, of whom 116 had a thrombotic complication and 515 did not, a PF1.2 of >300 pmol/L had a sensitivity of 86.2% and specificity of 80.6% for the diagnosis of a thrombotic complication.

Therefore, following reports of high VTE rates, hematology leadership at the Massachusetts General Hospital began advising medical ICUs in our hospital to consider measuring PF1.2 levels in patients with COVID-19. This was both as an additional data point for clinical decision-making in addition to the D-dimer, and to evaluate the relationship of PF1.2 and D-dimer levels given the near universal and frequently dramatic D-dimer elevations being observed. Therefore, the goal of this study was to evaluate the PF1.2 in patients with COVID-19, describing rates of elevation, relation to synchronously measured D-dimer, and association with thrombosis.

2 METHODS

2.1 Patients and data collection

This study was approved by the Institutional Review Board of Partners Healthcare (approval PHS/2020P000994). All patients with a prothrombin fragment F1.2 assay drawn at the Massachusetts General Hospital from 1 April 2020 to 6 May 2020 (inclusive of the peak of the pandemic in Massachusetts) were identified using the hospital laboratory information system. The data cutoff date was May 27, 2020. Manual chart review was used to identify hospitalized patients with a PF1.2 drawn during this span who also had a diagnosis of COVID-19, defined as either a positive SARS-CoV2 reverse-transcriptase polymerase chain reaction (RT-PCR) test by nasopharyngeal/oropharyngeal swab, sputum specimen or a clinical diagnosis satisfying all three of the following criteria: (a) consistent cross-sectional lung imaging, (b) assignment of the diagnosis by an infectious disease specialist, and (c) no alternative diagnosis under serious clinical consideration. The following data was obtained on patients meeting inclusion criteria: demographics, need for intensive care unit admission and endotracheal intubation, hospital length of stay, completion of hospitalization (hospital discharge and death), radiographically-proven venous and arterial thrombotic events, clinically significant non-vessel thrombotic complications, anticoagulation (including agent and dose) at the time of PF1.2 assay, results of PF1.2 and D-dimer assays, known pre-existing thrombophilias, and thrombosis history prior to hospitalization. Patients with synchronously diagnosed DVT and PE were considered to have a single VTE event.

Clinically significant non-vessel thrombotic complications were defined as central venous catheter or arterial line clotting necessitating line replacement to a new site or two or more occurrences of clotting of the continuous veno-venous hemofiltration (CVVH) circuit in a 24-hour period in patients requiring renal replacement therapy that was deemed sufficiently problematic to initiate therapeutic systemic anticoagulation.

2.2 Laboratory assays

Plasma D-dimer levels were measured using the VIDAS enzyme-linked immunosorbent assay (bioMérieux), with a reference range of <500 ng/mL FEU. Plasma PF1.2 levels were measured using an enzyme immunoassay (Quest Diagnostics) with a reference range of 41-372 pmol/L.

2.3 Data analysis

All analyses comparing PF1.2 and D-dimer measurements compared those obtained on the same day for each patient (synchronous measurements). The relationship between PF1.2 and D-dimer levels for the study population was evaluated graphically and via calculation of Spearman correlation coefficients. Median PF1.2 and D-dimer levels in those patients with and without VTE or thrombotic complications were compared using the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was performed and PF1.2 and D-dimer thresholds for optimal discrimination between those who developed thrombotic complications and those who did not develop thrombotic complications were obtained via calculation of Youden’s J statistic. Additionally, the specificity of each test in identifying patients with thrombotic manifestations was further evaluated by specifying an optimal specificity threshold of the ROC curve, defined as the highest specificity that maintained a sensitivity of at least 30%. Multivariable logistic regression controlling for age, sex, and body mass index (BMI) was performed to assess the association of PF1.2 and D-dimer with VTE and any thrombotic manifestation, as well as the association of PF1.2 with mortality. Thresholds for PF1.2 and D-dimer used in multivariable regression were derived from thresholds specified by the Youden’s J statistic in ROC analyses. Given the known suppression of these markers by anticoagulation and to avoid confounding on this basis, patients receiving therapeutic anticoagulation at the time of the assay measurement were excluded from all of the above analyses. For patients
with multiple PF1.2 assays performed, the first value was used for the above analyses.

In patients with multiple PF1.2 assays drawn longitudinally over time who had a radiographically-confirmed VTE within 4 days of one of the PF1.2 assays, the trend of the PF1.2 and D-dimer in relation to the VTE and initiation of therapeutic anticoagulation was examined graphically.

Statistical analysis was performed and graphs for figures were prepared using GraphPad Prism 7 (GraphPad, Inc., San Diego, CA), and Microsoft Excel 360 (Microsoft Corp., Seattle, WA). Missing data was not imputed. Any results above the upper limit of the assay were entered as one unit higher than the assay upper limit value for all analyses using continuous variables.

3 | RESULTS

3.1 | Patient characteristics and thrombotic events

Among 141 patients with a PF1.2 assay performed, 115 were hospitalized patients with COVID-19 (26 were excluded: 24 were outpatients and two were inpatients without COVID-19). The median age was 61 years (interquartile range [IQR], 53-70 years) and 29.6% were female. The median duration of hospitalization at the time of PF1.2 measurement was 7 days (range, 0-28 days). A group of 110 patients (95.7%) developed critical illness and were admitted to the ICU, 107 patients (93.0%) underwent endotracheal intubation and mechanical ventilation, 38 patients (33.0%) received renal replacement therapy with CVVH, and one patient (0.9%) received treatment with extracorporeal membrane oxygenation. COVID-19 was molecularly-confirmed in 109 patients (94.8%). The study included a total of 3318 patient-days (474 patient-weeks) analyzed for thrombotic and critical illness complications. At the data cutoff date, 74 patients (64.3%) had been hospitalized for a median of 44 (range, 30-62) days.

Over a median follow-up of 29 (range, 2-62) hospital days, 26 patients developed radiographically-confirmed VTE (22.6%, a rate of 5.49 per 100 patient-weeks), including nine with proximal DVT, one with distal DVT, seven with lobar or segmental PE, three with subsegmental PE, and six with superficial venous thrombosis alone. One patient had radiographically-proven arterial thrombosis (multiple aortic thrombi). Of 38 patients receiving CVVH, 27 (71.1%) developed recurrent circuit thrombosis. A total of 22 patients (19.1%) developed arterial catheter or central venous catheter thrombosis necessitating catheter replacement. Including any of the above thrombotic complications, 56 patients (48.7%) developed a thrombotic complication.

At the time of PF1.2 and synchronous D-dimer measurement, 37 patients (32.1%) were receiving therapeutic anticoagulation, 77 patients (67.0%) were receiving prophylactic anticoagulation, and one patient (0.9%) was not receiving pharmacologic thromboprophylaxis. All synchronously drawn D-dimer assays were drawn on the same day as PF1.2 measurement and most (56%) were drawn during the same blood draw.

3.2 | Association of prothrombin fragment 1.2 with hypercoagulability

The PF1.2 and D-dimer levels were higher in patients with venous thromboembolism or any thrombotic manifestation than those without (Table 1, Figure 1). Therapeutic anticoagulation suppressed median PF1.2 levels: median (IQR) PF1.2 in patients with VTE not receiving therapeutic anticoagulation (N = 13) was 611 pmol/L (331-1335 pmol/L), significantly higher than the median (IQR) PF1.2 in patients with VTE receiving therapeutic anticoagulation (N = 13) of 333 pmol/L (231-455 pmol/L), P = .026. The same was true for those with any thrombotic manifestation: median (IQR) PF1.2 in patients not receiving therapeutic anticoagulation (N = 29) was 611 pmol/L (333-1148 pmol/L), significantly higher than the median (IQR) PF1.2 in patients receiving therapeutic anticoagulation (N = 27) of 347 pmol/L (195-506 pmol/L), P = .002. These findings, consistent with prior studies of the PF1.2, confirmed the suitability of excluding patients who had the PF1.2 drawn while on therapeutic anticoagulation from the remaining analyses.

3.3 | Association of prothrombin fragment 1.2 with D-dimer

Both PF1.2 and D-dimer were moderately positively correlated (r = 0.542, P < .001, Figure 2). Using the upper limit of the laboratory reference range as a threshold, considerable discordance was observed between synchronously obtained PF1.2 and D-dimer measurements. Of the 78 patients not receiving therapeutic anticoagulation at the time of PF1.2 measurement, 46 (59.0%) had a PF1.2 result above the upper limit of the reference range (>372 pmol/L) and 20 (25.6%) had a result greater than two times the upper limit of the reference range (>744 pmol/L). A total of 66 of the 78 patients had a D-dimer drawn on the same day: 65 (98.5%) had a D-dimer result above the upper limit of the reference range (>500 ng/mL) and 59 (89.4%) had a result greater than two times the upper limit of the reference range (>1000 ng/mL).

3.4 | Receiver operating characteristic and multivariable logistic regression analyses

In ROC analysis, the optimal threshold for a randomly-drawn PF1.2 to identify patients who developed either VTE alone or any thrombotic manifestation during hospitalization was >523 pmol/L (69.2% specificity and 67.7% specificity for VTE alone, 62.1% sensitivity and 75.5% specificity for any thrombotic manifestation, Figure 3). The optimal specificity thresholds of the PF1.2 to identify patients who developed VTE or any thrombotic manifestation were >1156 pmol/L...
(38.5% sensitivity and 90.8% specificity) and >924 pmol/L (37.9% sensitivity and 87.8% specificity), respectively, Figure 3. Note, PF1.2 had higher positive likelihood ratios and superior specificity to D-dimer in identifying patients with VTE or any thrombotic manifestation regardless of analysis (Figure 3B).

In multivariable logistic regression analyses controlling for age, sex, and BMI, a PF1.2 >500 pmol/L was significantly associated with VTE [odds ratio (OR) 4.26, 95% CI, 1.12-16.21, \( P = .034 \)] and any thrombotic manifestation (OR 3.85, 95% CI, 1.39-10.65, \( P = .010 \)). Conversely, a D-dimer >2500 ng/mL was not significantly associated with VTE (OR 5.91, 95% CI, 0.69-50.56, \( P = .11 \)) or any thrombotic manifestation (OR 2.47, 95% CI, 0.78-7.78, \( P = .12 \)). Additionally, PF1.2 >500 pmol/L was not significantly associated with mortality (OR 4.04, 95% CI, 0.64-25.8, \( P = .14 \)).

Of the 32 patients with a PF1.2 result within the reference range (41-372 pmol/L) not receiving therapeutic anticoagulation at the time of measurement, 29 patients (90.6%) did not develop VTE and 24 patients (75.0%) did not develop any thrombotic complication.

### TABLE 1

| Population                           | PF1.2 (pmol/L), median (IQR) | \( P \) value\(^a\) | D-dimer (ng/mL), median (IQR) | \( P \) value\(^a\) |
|--------------------------------------|------------------------------|----------------------|-----------------------------|----------------------|
| All patients (N = 115)               | 397 (260-611)                | -                    | 3179 (1950-6133)            | -                    |
| Not on therapeutic AC (N = 78)       | 429 (263-894)                | -                    | 2996 (1978-5555)            | -                    |
| VTE (N = 13)                         | 611 (331-1335)               | .082                 | 4359 (3309-8323)            | .027                 |
| No VTE (N = 65)                      | 402 (263-679)                | .006                 | 2849 (1832-5555)            | .049                 |
| Thrombotic manifestations (N = 29)   | 611 (333-1148)               | -                    | 3901 (2474-6414)            | -                    |
| No thrombotic manifestations (N = 49) | 374 (230-542)                | -                    | 2639 (1622-5118)            | -                    |

Abbreviations: AC, anticoagulation; IQR, interquartile range; PF1.2, prothrombin fragment 1.2; VTE, venous thromboembolism.

\( ^a \)For VTE or thrombotic manifestations vs no VTE or thrombotic manifestations, by Mann-Whitney \( U \) test.

### FIGURE 1

Distribution of A, prothrombin fragment 1.2 measurements and B, D-dimer measurements in the study population by thrombosis status. Outliers defined by the Tukey method for all plots (one outlier each in "No VTE" plot and "No TM" plot in A, not shown to preserve figure resolution). VTE, venous thromboembolism; TM, any thrombotic manifestation; PF1.2, prothrombin fragment 1.2, FEU, fibrinogen-equivalent units [Color figure can be viewed at wileyonlinelibrary.com]

### 3.5 Longitudinal analysis of PF1.2 and D-dimer in patients with venous thromboembolism

Four patients with radiographically-confirmed VTE had multiple PF1.2 values obtained temporally close to the VTE event (Figure 4). An upward trend in PF1.2 in the days leading up to the diagnosis of the VTE can be seen (Figure 4A-C). Upon initiation of anticoagulation, the elevated PF1.2 values rapidly normalized (Figure 4B-D); D-dimer values declined but did not normalize.

### 4 DISCUSSION

In this study of 115 patients with COVID-19 who had measurements of the PF1.2 during hospitalization, we report the PF1.2 levels, the relationship between the PF1.2 and D-dimer, and association of PF1.2 with thrombosis. In patients not receiving therapeutic anticoagulation at the time of testing, although the PF1.2 and D-dimer were moderately positively correlated (\( r = +0.542 \), Figure 2), there was considerable
discordance between synchronous PF1.2 and D-dimer measurements at the individual patient level, with elevation of the D-dimer in 98.5% compared with elevation of the PF1.2 in just 59.0%. The distribution of measurements between patients with and without thrombosis appears more discriminant with the PF1.2 than the D-dimer (Figure 1). Optimal thresholds of the PF1.2 obtained via ROC analysis demonstrated superior specificity and improved likelihood ratios of the PF1.2 in identifying patients with VTE or thrombotic manifestations overall as compared with synchronously measured D-dimer (Figure 3). Consistent with this, multivariable logistic regression analyses demonstrated statistically significant associations between PF1.2 elevation and thrombosis but did not demonstrate a significant association between D-dimer elevation and thrombosis. Lastly, 90.6% of patients who had a PF1.2 measurement within the normal reference range (in the absence of the confounding effect of therapeutic anticoagulation) did not develop VTE over the course of their hospitalization.

**FIGURE 2** Relationship of prothrombin fragment 1.2 with synchronously measured D-dimer. Linear regression trendline (solid line) shown with 95% confidence interval (dotted lines). PF1.2, prothrombin fragment 1.2, FEU, fibrinogen-equivalent units.

**FIGURE 3** Receiver operating characteristic analysis. A, ROC curves shown with Youden’s J statistic (blue) and optimal specificity threshold (green) highlighted. B, Sensitivity, specificity, and likelihood ratios for each specified threshold. VTE, venous thromboembolism; TM, any thrombotic manifestation; PF1.2, prothrombin fragment 1.2, FEU, fibrinogen-equivalent units. AUC, area under the curve, LR, likelihood ratio, 95% CI, 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]
While the D-dimer can reflect activation of coagulation with clot formation, it may also be elevated due to other causes. The PF1.2 assay is a more direct measurement of coagulation activation. The superior ability of randomly-drawn PF1.2 measurements as compared with D-dimer measurements (drawn synchronously with the PF1.2 measurements) to identify patients who developed thrombosis during hospitalization suggests the possibility of biological "noise" impacting the D-dimer to a greater degree than the PF1.2. This could take the form of hyperfibrinolysis, which has been postulated in SARS coronavirus infection\textsuperscript{11} or some other mechanism, such as plasmin-independent degradation of fibrin and fibrinogen. The latter has been demonstrated in a mouse model of SARS-CoV-1 infection due to the action of pulmonary macrophages.\textsuperscript{22} Alternatively, the reason fewer patients have elevated PF1.2 might relate to the shorter half-life of PF1.2 (1.5 hours) compared to D-dimer (8 hours). Given the present findings, as well as our prior findings that D-dimer measurements at initial presentation are predictive of thrombosis during hospitalization in patients with COVID-19,\textsuperscript{1} the PF1.2 drawn at initial presentation may have similar or improved predictive value in predicting thrombotic complications as the D-dimer, and this merits further study. Similarly, in patients not receiving therapeutic anticoagulation, trending the PF1.2 in patients at high risk of thrombosis may be clinically useful (Figure 4).

While our study was the first to evaluate the PF1.2 in COVID-19 and did so in a large number of predominantly critically ill patients over a long period of follow-up, it has limitations. The most important limitation is the random timing of PF1.2 measurement, which may have occurred at any point along a patient’s hospital course. Our findings that the PF1.2 may be more discriminant than synchronously measured D-dimer at identifying patients with COVID-19 who experience thrombosis requires confirmation in a study in which PF1.2 assays are drawn at a common point along the course of illness, such as initial presentation or ICU admission. Additionally, it bears mention that the PF1.2 assay is not currently typically performed in-house by most hospitals, although it is readily available as a send-out test in major reference laboratories (such as LabCorp or Quest Diagnostics in the United States).

In conclusion, we observed that the PF1.2 was elevated in most critically ill patients with COVID-19, but to a lesser extent than the D-dimer. The D-dimer was almost universally elevated, and frequently to much a greater degree than PF1.2. The PF1.2 was more specific than synchronously measured D-dimer in identifying patients who experienced thrombosis and was significantly associated with thrombotic manifestations in multivariable analyses while the D-dimer was not. Further investigation into the clinical utility of the PF1.2 in identifying patients with thrombosis and predicting those at high risk for thrombotic complications is warranted.
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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Hanny Al-Samkari wrote the first draft of the manuscript and contributed to concept and design, data collection, data analysis, creation of tables and figures, critical revision of the manuscript, and final approval; Fei Song contributed to concept and design, data collection, data analysis, critical revision of the manuscript, and final approval; Elizabeth Van Cott contributed to data collection, critical revision of the manuscript, and final approval; David J. Kuter contributed to concept and design, critical revision of the manuscript and final approval; Rachel Rosovsky contributed to concept and design, data collection, critical revision of the manuscript, and final approval.

DATA AVAILABILITY STATEMENT
For data requests, please contact hal-samkari@mgh.harvard.edu.

ORCID
Hanny Al-Samkari https://orcid.org/0000-0001-6175-1383
David J. Kuter https://orcid.org/0000-0003-2084-8810

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