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BRIEF REPORT

Placental growth factor level in plasma predicts COVID-19 severity and in-hospital mortality

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a respiratory disease associated with vascular inflammation and endothelial injury.

Objectives: To correlate circulating angiogenic markers vascular endothelial growth factor A (VEGF-A), placental growth factor (PlGF), and fibroblast growth factor 2 (FGF-2) to in-hospital mortality in COVID-19 adult patients.

Methods: Consecutive ambulatory and hospitalized patients with COVID-19 infection were enrolled. VEGF-A, PlGF, and FGF-2 were measured in each patient ≤48 h following admission.

Results: The study enrolled 237 patients with suspected COVID-19: 208 patients had a positive diagnostic for COVID-19, of whom 23 were mild outpatients and 185 patients hospitalized after admission. Levels of VEGF-A, PlGF, and FGF-2 significantly increase with the severity of the disease ($P < .001$). Using a logistic regression model, we found a significant association between the increase of FGF-2 or PlGF and mortality (odds ratio [OR] 1.11, 95% confidence interval [CI; 1.07–1.16], $P < .001$ for FGF-2 and OR 1.07 95% CI [1.04–1.10], $P < .001$ for PlGF) while no association were found for VEGF-A levels. Receiver operating characteristic curve analysis was performed and we identified PlGF above 30 pg/ml as the best predictor of in-hospital mortality in COVID-19 patients. Survival analysis for PlGF confirmed its interest for in-hospital mortality prediction, by using a Kaplan-Meier survival curve ($P = .001$) and a Cox proportional hazard model adjusted to age, body mass index, D-dimer, and C-reactive protein (3.23 95% CI [1.29–8.11], $P = .001$).

Conclusion: Angiogenic factor PlGF is a relevant predictive factor for in-hospital mortality in COVID-19 patients. More than a biomarker, we hypothesize that PlGF blocking strategies could be a new interesting therapeutic approach in COVID-19.

KEYWORDS
angiogenesis, COVID-19, FGF-2, mortality, placental growth factor, PlGF

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) mortality is related to respiratory failure characterized by interstitial pneumonia progressing into a life-threatening acute respiratory distress syndrome with a potential evolution in fibrosis.[1] The pathogenic pathways involved in the local lung fibrogenesis, in particular in idiopathic pulmonary fibrosis (IPF), are still elusive. However, lung parenchymal lesions are consistently associated with major vascular remodeling processes,[2] microvascular alterations,[3] and changes in endothelial phenotype.[4–6] Mechanisms underlying this vascular remodeling are yet to be elucidated. We previously proposed a deregulation of circulating angiogenic factors as a potential origin of endothelial dysfunction in IPF.[7]

Autopsy findings and circulating markers of endotheliopathy in COVID-19 have accumulated.[8–12] This endothelial injury is probably mostly the result of cytokine release and complement-system activation.[11,13] Moreover, we recently described an association between several biomarkers of endothelial activation and intensive care unit (ICU) referral or in-hospital mortality.[14,15] Moreover, more than endothelial lesion, increased vessel growth, through a mechanism of intussusceptive angiogenesis has been reported in the lungs of patients who died from COVID-19[16] in contrast to patients who died

from influenza virus. This abnormal angiogenesis was associated with a dysregulated expression of numerous angiogenesis-related genes.[16] However, the association of circulating angiogenic marker levels with disease severity and mortality has still not been established in large cohorts.

The objective of the present study was to assess if major angiogenic biomarkers vascular endothelial growth factor (VEGF)-A, fibroblast growth factor (FGF)-2 and placental growth factor (PlGF) measured at admission were predictive of in-hospital mortality in a large cohort of 208 adult COVID-19–positive patients.

2 | PATIENTS AND METHODS

2.1 | Patient description

We performed a bi-centric cross-sectional study of adult (≥18 years old) COVID-19 hospitalized and ambulatory patients in two French hospitals (European Georges Pompidou Hospital and Cochin-Hotel Dieu Hospital, Paris, France) between March 13 and June 26, 2020. The study was performed in accordance with the Declaration of Helsinki and a written consent form was signed by

all patients included or their trusted relatives at the time of enroll-ment (SARCODO 2020-A01048-31A, NCT04624997). All included patients, hospitalized or not, presented a confirmed diagnosis of COVID-19, using a reverse transcriptase–polymerase chain reac-tion (RT-PCR) assay on nasopharyngeal swab samples as previously described.[15]

Patients were classified according to World Health Organization guidance (WHO) as non-critical (median oxygen requirement 3 L/min; WHO score range 4–6) or critical (requiring mechanical ventilation, WHO score range 7–9) in the first 48 h following admission for clin-ically suspected COVID-19. Outpatients were COVID-19 patients who did not meet hospitalization criteria and returned home imme-diately after RT-PCR testing for COVID-19. None of the outpatients required supplemental oxygen, were later hospitalized, or died in the month following COVID-19 diagnosis. Finally, we also included 29 non-COVID-19 non-hospitalized individuals who served as con-trols. These patients had suspected COVID-19, but with mild clinical presentation and a negative RT-PCR result. Patient characteristics including age, sex, comorbidities, medical history, and treatment at admission were recorded. The primary outcome was COVID-19 in-hospital mortality.

2.2 | Laboratory tests

Routine laboratory tests and sampling for angiogenic biomarkers were all performed at hospital admission, that is, in the first 48 h following the admission for suspected COVID-19. Venous blood was collected from patients and controls and processed according to standard laboratory techniques. Routine laboratory tests were plasma creatinine, C-reactive protein (CRP), and high-sensitivity cardiac Troponin I (Hs-TnI). Regarding coagulation assays and an-giogenic biomarker measurements, blood was collected in 0.129 M trisodium citrate tubes (9NC BD Vacutainer). Platelet-poor plasma (PPP) was obtained after centrifugation twice at 2500 g for 15 min and stored at −80°C until analysis. Measurement of D-dimer was performed using the Vidas D-dimers® assay (bioMérieux) accord-ing to the manufacturer's instruction. The plasma concentrations of VEGF-A, FGF-2, and PlGF were quantified in PPP using a Human Magnetic Luminex Assay (R&D Systems). Data were assessed with the Bio-Plex 200 using the Bio-Plex Manager 5.0 software (Bio-Rad).

2.3 | Statistical analysis

Continuous data were expressed as median (interquartile range [IQR]) and categorical data as frequencies and proportions. The association between levels of angiogenic biomarkers and COVID-19 severity was assessed using the Kruskal-Wallis test followed by Dunn's post-test for multiple group comparisons with median reported. Clinical char-acteristics and outcomes (categorical variables) were compared ac-cording to the COVID-19 severity using the Cochran-Armitage trend test. Spearman rank coefficient correlation was used to determine

the correlation between angiogenic biomarkers (VEGF-A, PLGF, and FGF-2) and biomarkers of multiorgan dysfunction (creatinine, Hs-TnI, D-dimer, and CRP). In order to estimate the ability of PlGF to predict in-hospital mortality, we used receiver operating character-istic (ROC) analysis. We estimated the area under the curve (AUC) and its 95% confidence interval (CI) and selected the optimal cut-off that illustrated the prognostic ability of PlGF. For the survival analysis among patients hospitalized for COVID-19, the start of the study was triggered by the diagnosis of SARS-CoV-2 infection. The end of the study was defined either by patient's death during their hospitalization or by discharge alive from the hospital. We used the Kaplan-Meier curve to estimate the survival function from diagnosis to in-hospital death according to the optimal cutoff of PlGF. Survival curves were compared using the log-rank test. We used the Cox proportional hazard model adjusted for age, body mass index (BMI), D-dimer, and CRP levels to investigate the relationships between the increase in PlGF (over the calculated cut-off value) and in-hospital mortality. In sensitivity analysis, to adjust for bias due to nonrandom allocation of potential covariates among COVID-19 patients, we applied propensity score-matching methods. For each angiogenic biomarker, we estimated the propensity score by running a logistic regression model in which the outcome variable is a binary variable indicating biomarkers levels status (< or > threshold). We included any covariate that is related to both biomarkers and potential out-comes such as age, sex, and BMI. Then a 1:1 match was performed using Greedy matching techniques. Based on the matched dataset, we compare patients' characteristics and outcomes according to the threshold of angiogenic biomarkers (< or > threshold). All analyses were two-sided and a P-value of <.05 was considered statistically significant. Statistical analysis was performed using R studio soft-ware (R Foundation for Statistical Computing).

3 | RESULTS AND DISCUSSION

A total of 208 COVID-19 adult patients comprising 23 outpatients and 185 hospitalized patients were included (Table 1). Patients were significantly older (P < .001) and included a higher propor-tion of males (P < .001) than non-COVID-19 patients. Among the patients included, 129 (62.0%) were male. The non-COVID-19 con-trol group comprised 17 (58.6%) females and 12 (41.4%) males. The median age was 39 [IQR 32.0–46.0] in the non-COVID-19 group and 62 [50.0–72.0] in COVID-19 patients. Compared to the non-COVID-19 group, cardiovascular comorbidities were more frequent in COVID-19 patients. Moreover, hospitalized and in particular criti-cal patients had high D-dimer, creatinine, and CRP levels. Levels of VEGF-A, PlGF, and FGF-2 increased significantly with the severity of the disease (P < .001; Figure 1A). We evaluated the correlation between VEGF-A, PlGF, and FGF-2 and biomarkers of multiorgan dysfunction. Because Hs-TnI, D-dimer, CRP, and creatinine at admis-sion were associated to severity,[9,17] we analyzed the association of angiogenic factors with these four markers (Figure 1D–O). While a significant association was found between CRP, D-dimer, and the

TABLE 1 Demographic, clinical and biological characteristics of COVID-19 and non-COVID-19 patients at admission

		COVID−19 patients (n = 208)			
	Non-COVID−19 (n = 29)	Outpatients (n = 23)	Non-critical (n = 96)	Critical (n = 89)	P-value
Male sex – n (%)	12 (41.4)	9 (39.1)	55 (57.3)	65 (73.0)	.002
Age – years median [IQR]	39.0 [32.0–46.0]	40.0 [34.0–46.5]	65.5 [55.0–76.0]	62.0 [51.0–71.0]	<.001
Comorbidities					
Obesity – n (%)	5 (17.2)	0 (0.0)	18 (18.8)	33 (37.1)	<.001
Hypertension – n (%)	4 (13.8)	2 (8.7)	53 (55.2)	50 (56.2)	<.001
Hyperlipidaemia – n (%)	0 (0.0)	2 (8.7)	21 (21.9)	30 (33.7)	<.001
Diabetes – n (%)	1 (3.4)	0 (0.0)	23 (24.0)	31 (34.8)	<.001
Chronic kidney disease – n (%)	1 (3.4)	0 (0.0)	9 (9.4)	13 (14.6)	.10
Biological parameters					
D-dimer – ng/ml median [IQR]	214 [172–291]	295 [140–438]	1089 [798–1889]	4186 [2498–7292]	<.001
CRP – mg/L median [IQR]	NA	28.0 [14.8–33.4]	63.6 [32.0–117.9]	189.1 [121.5–259.9]	<.001
Plasma creatinine – μmol/L median [IQR]	NA	64.00 [64.0–64.0]	68.0 [56.5–83.5]	102.0 [72.6–214.3]	<.001
Outcomes					
In-hospital mortality – n (%)	0 (0.0)	0 (0.0)	2 (2.1)	39 (43.8)	<.001

Note: Obesity was defined as body mass index >30 Kg/m^2.

Abbreviations: CRP, C-reactive protein; IQR, interquartile range.

three angiogenic biomarkers studied (all with *P*-value < .001), no association existed with creatinine, Hs-TnI, and VEGF-A (*P* = .16 for VEGF-A and creatinine; *P* = .07 for Hs-TnI and VEGF-A). In contrast, FGF-2 and PlGF were both associated to creatinine and Hs-TnI (with *P* < .001 for FGF-2 and both creatinine and Hs-TnI; *P* < .01 for PlGF and creatinine, and *P* < .001 for PlGF and Hs-TnI).

ROC curve analysis was performed to define an optimal cut-off of VEGF-A, FGF-2, and PlGF level to predict in-hospital mortality. We identified that VEGF-A level above 44.2 pg/ml, FGF-2 level above 18 pg/ml, and a PlGF level above 30 pg/ml could predict in-hospital mortality in COVID-19 patients (AUC 51.8, 95% CI [40.7–62.8] for VEGF-A; AUC 77.0, 95% CI [69.2–84.8] for FGF-2; and AUC 77.2%, 95% CI [68.8–85.6] for PlGF).

Because VEGF-A and PlGF are both ligand for VEGF family receptors, we wanted to verify potential interactions between them. First, among patients with high VEGF-A (>44.2 pg/ml), only 41.7% had a high PlGF (>30 pg/ml). In the same way, among patients with high PlGF, only 28.9% had a high VEGF. Among the entire population, only 8.4% patients had both VEGF-A and PlGF at high levels. Moreover, there was no significant association between VEGF-A and PlGF (r = .12, *P* = .07). Taken together, these results are not in line with a relationship between VEGF-A and PlGF.

Moreover, we performed a propensity-matched score for VEGF-A, PlGF, and FGF-2 adjusted on age, sex, and BMI. As demonstrated in Table 2, clinical characteristics were the same between patients with high and low levels of VEGF-A, PlGF, and

FGF-2. Moreover, in terms of outcomes, ICU admission and endotracheal intubation were significantly different between high and low levels of the three angiogenic factors studied. In-hospital mortality rate was significantly increased only in patients with high levels of FGF-2 and PlGF (*P*-value = .632 for VEGF-A, *P* < .001 for FGF-2 and PlGF). Using a logistic regression model, we found a significant association between both FGF-2 and PlGF levels with in-hospital mortality (OR 1.11, 95% CI [1.07–1.16], *P* < .001 for FGF-2 and OR 1.07 95% CI [1.04–1.10], *P* < .001 for PlGF) while no association were found for VEGF-A levels (OR 1.01 95% CI [0.99–1.02], *P* = .358) in univariate analysis. Time between hospitalization and death in our population spread from 2 to 57 days, with a median of 14 days. We compared level of VEGF-A, FGF-2, and PlGF in patients who died before and after 14 days of hospitalization and found no significant association between time and in-hospital mortality (data not shown).

Because PlGF provided the best prognostic value (higher AUC, sensitivity, specificity, and negative predictive value), we performed the survival analysis for PlGF confirming its usefulness for in-hospital mortality prediction, using a Kaplan-Meier survival curves (*P* = .001; Figure 2B) and a Cox proportional hazard model adjusted for age, BMI, D-dimer, and CRP (HR: 3.23, 95% CI [1.29–8.11], *P* = .001, Figure 2C). Because CRP and D-dimer are significantly associated (Spearman's correlation coefficient: r = .35; *P* < .001), we tested an interaction term to a regression model to expand understanding of the relationship between CRP and D-dimer in the model with in-hospital mortality. The interaction
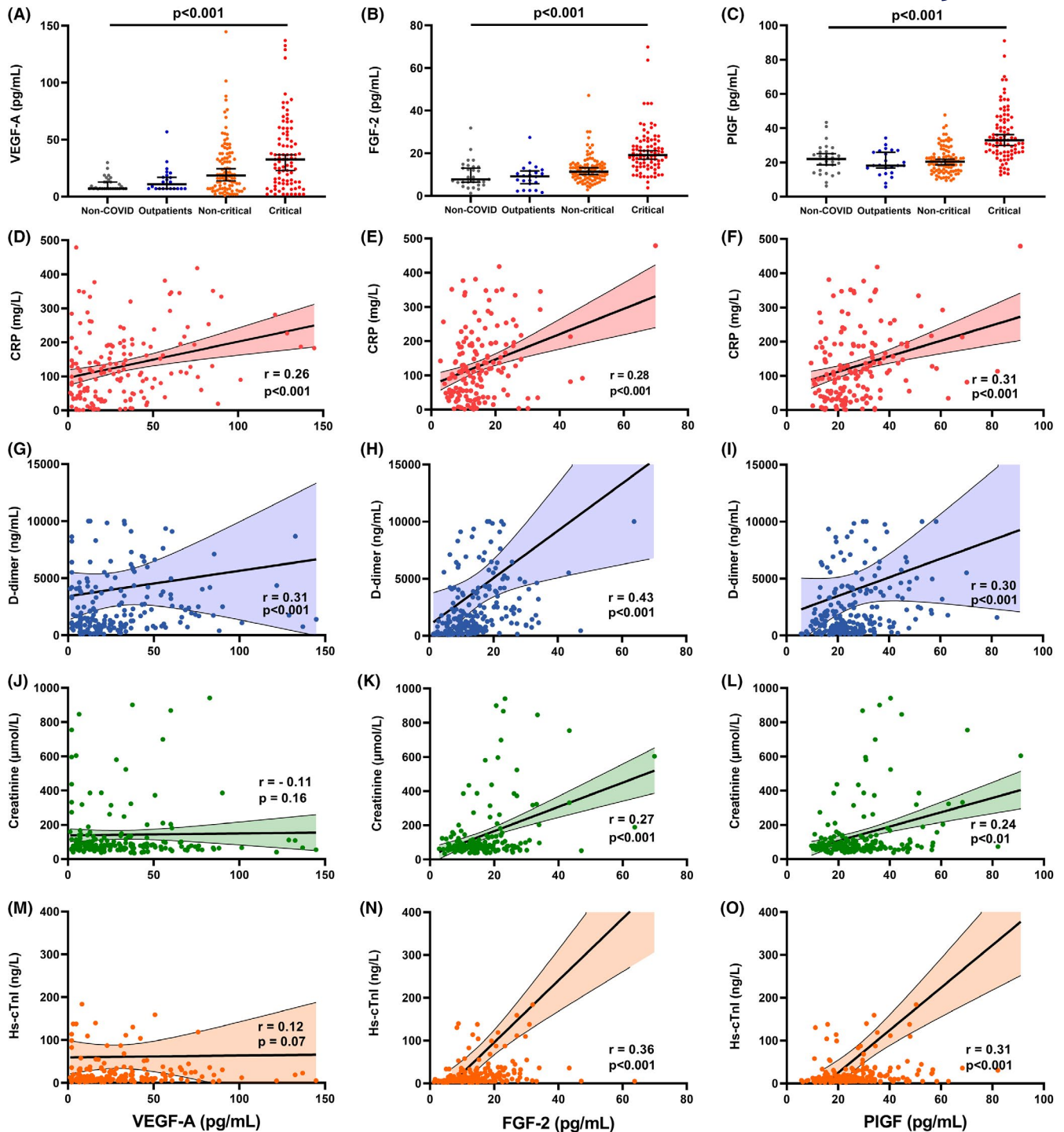
FIGURE 1 Involvement of angiogenic biomarker plasma levels in COVID-19 severity. A–B–C, Boxplot of plasma level (pg/ml) of each circulating angiogenic biomarkers (fibroblast growth factor 2 [FGF-2], placental growth factor [PlGF], and vascular endothelial growth factor A [VEGF-A]) according to COVID-19 severity (control, outpatients, non-critical, and critical). Data points represent individual measurements, whereas horizontal bars represent the means with standard deviations. We compared the level of angiogenic biomarkers among the four groups (control, outpatients, non-critical, and critical) using the Kruskal-Wallis test. D–O, Scatter plots showing the correlations between VEGF-A, FGF-2, and PlGF and biomarkers of multiorgan failure (C-reactive protein [CRP], D-dimer, creatinine, and high-sensitivity cardiac Troponin I [Hs-TnI]). Data points represent individual measurements. The black bold line indicates line of best fit and the lightly colored area 95% confidence interval. r for Kendall rank correlation coefficient

term between CRP and D-dimer was not significant (OR univariable 2.52, 95% CI [0.08–78.1], *P* = .552; OR multivariable 3.65, 95% CI [0.1–121.1], *P* = .419). Absence of significant interaction indicates that effect of CRP (or D-dimer) on the outcome (in-hospital mortality) is not different at different values of the other predictor variables.

TABLE 2 Patients' characteristics and outcomes according to the propensity matching analysis for VEGF-A, FGF-2, and PlGF

	VEGF-A			FGF-2			PlGF		
	<44.2 pg/ml	>44.2 pg/ml	p-value	<18 pg/ml	>18 pg/ml	p-value	<30 pg/ml	>30 pg/ml	p-value
Matched population on age, sex and BMI	48	48		66	66		69	69	
Clinical severity									
Non-COVID-19	5 (10.4)	0 (0.0)	.002	9 (13.6)	2 (3.0)	<.001	5 (7.2)	3 4.3	<.001
Outpatients	5 (10.4)	1 (2.1)		5 (7.6)	1 (1.5)		3 (4.3)	1 (1.4)	
Non-critical	24 (50.0)	17 (35.4)		32 (48.5)	11 (16.7)		37 (53.6)	13 (18.8)	
Critical	14 (29.2)	30 (62.5)		20 (30.3)	52 (78.8)		24 (34.8)	52 (75.4)	
Clinical characteristics									
Male sex – n (%)	32 (66.7)	33 (68.8)	1.00	48 (72.7)	50 (75.8)	.84	49 (71.0)	47 (68.1)	.85
Age – years, median [IQR]	62.0 [51.5–74.3]	63.5 [54.0–73.0]	.96	59.0 [44.0–67.0]	57.0 [49.3–70.8]	.65	61.0 [49.0–72.00]	59.0 [50.0–69.0]	.8
BMI, median [IQR]	25.7 [23.9–30.4]	27.1 [24.4–30.0]	.64	27.8 [25.6–32.7]	27.9 [26.1–33.5]	.71	27.8 [25.6 31.6]	28.6 [25.7–33.7]	.50
Hypertension – n (%)	22 (45.8)	27 (56.2)	.41	32 (48.5)	34 (51.5)	.86	39 (56.5)	35 (50.7)	.61
Hyperlipidaemia – n (%)	13 (27.1)	15 (31.2)	.82	14 (21.2)	22 (33.3)	.17	13 (18.8)	22 (31.9)	.12
Diabetes – n (%)	13 (27.1)	15 (31.2)	.82	20 (30.3)	21 (31.8)	1.00	21 (30.4)	27 (39.1)	.37
Chronic kidney disease – n (%)	3 (6.2)	8 (16.7)	.20	4 (6.1)	10 (15.2)	.16	8 (11.6)	8 (11.6)	1.00
Outcomes									
ICU admission, n(%)	21 (43.8)	34 (70.8)	.013	33 (50.0)	55 (83.3)	<.001	36 (52.2)	57 (82.6)	<.001
Endotracheal Intubation, n (%)	14 (29.2)	31 (64.6)	.001	22 (33.3)	52 (78.8)	<.001	26 (37.7)	53 (76.8)	<.001
In-hospital mortality – n (%)	10 (20.8)	13 (27.1)	.63	4 (6.1)	26 (39.4)	<.001	9 (13.0)	28 (40.6)	<.001

Note: The population was matched on age, sex and BMI.

Abbreviations: BMI, body mass index; FGF-2, fibroblast growth factor 2; ICU, intensive care unit; IQR, interquartile range; PlGF, placental growth factor; VEGF-A, vascular endothelial growth factor A.
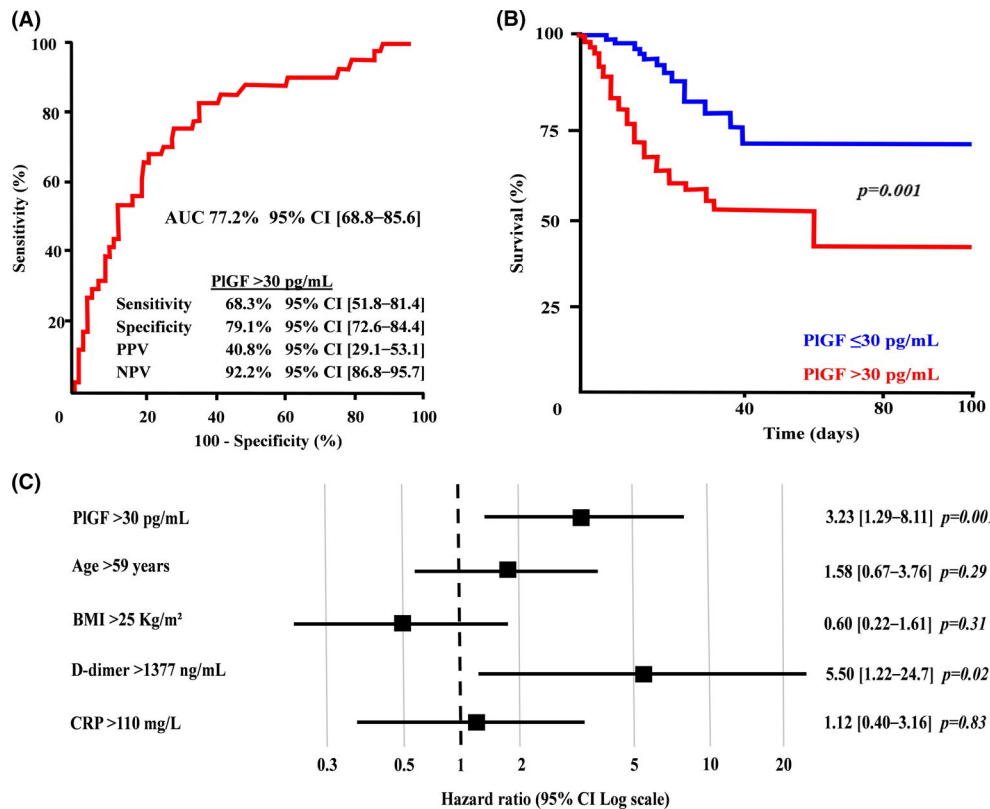
FIGURE 2 Involvement of placental growth factor (PlGF) in COVID-19 mortality. (A) Receiving operating curve (ROC) for PlGF involvement in in-hospital mortality. AUC, Area under the curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval. (B) Kaplan–Meier survival curves illustrating prognostic impact of PlGF levels (≤ or >30 pg/ml) regarding in-hospital mortality. *P*-value refers to the log rank test used to compare survival curves according to PlGF levels (≤ or >30 pg/ml). (C) Forest plot of Cox proportional hazard model. The model was adjusted on age (≤ or > 59 years old), body mass index (BMI) (≤ or > 25), D-dimer (≤ or >1377 ng/ml), and on C-reactive protein (CRP; ≤ or > 110 mg/L)

Recently, Kong et al.[18] reported a positive correlation between VEGF-D and disease severity in COVID-19 patients. As well, Rovas et al.[19] demonstrated that VEGF-A correlated positively with disease severity and acute respiratory distress syndrome development. In contrast, Pine et al. showed that VEGF-A, along with PDGF-AA and PDGF-AB/BB, was only elevated by a similar amount in COVID-19, regardless of its severity, making these biomarkers a poor predictor of in-hospital mortality.[20] However, to our knowledge, this study is the first one to examine several angiogenic-circulating biomarkers in such a range of COVID-19 severities. In this study, we demonstrated that levels of angiogenic factors were related to COVID-19 severity at admission and described PlGF as the best predictive marker of in-hospital mortality. PlGF acts through binding to VEGF receptor-1 (VEGFR-1, aka Flt-1). In animal studies, PlGF was reported to increase angiogenesis in pathological but not physiological angiogenesis.[21] PlGF stimulates angiogenesis through VEGFR-1 direct signaling and/or displacing VEGF from its binding site, and we previously described PlGF involvement in human endothelial progenitor differentiation.[22] In line with these angiogenic functions, increased PlGF plasma levels have been proposed as a biomarker of adverse outcome in patients with acute chest pain,[23] of thrombotic events risk in antiphospholipid syndrome,[24] and of poor prognosis in cancer.[25] In pregnant women, a low soluble Flt-1/PlGF ratio is used to predict

the short-term absence of preeclampsia (PE).[26] Severe COVID-19 during pregnancy can provoke a PE-like syndrome. In this setting, a normal sFLT-1/PlGF ratio might help to distinguish endothelial dysfunction caused by COVID-19 disease inflammation from true PE.[27] Increased PlGF could be involved in COVID-19 pathophysiology in leukocyte infiltration as well as in angiogenic process recently described;[16] however, there is still a lot of work to understand if high levels of angiogenic factors are a response/consequence or at the origin of angiogenic disorders observed inside lungs. Several strategies to block PlGF are in clinical development in particular in cancer and/or vascular disorders. PlGF-dependent angiogenesis and cell recruitment could be a promising new target for COVID-19 treatment.

Our results highlight the potential for plasma PlGF to discriminate COVID-19 severity and higher risk of in-hospital mortality, but also may help identify and target patients for new therapeutic approaches.

involved in the vascular medicine, internal medicine, respiratory medicine, intensive care, and hematology departments of the George Pompidou European Hospital and Cochin Hospital for their help in taking care of patients and including them in the study. We would like to acknowledge all physicians involved in the recruitment or follow-up of patients.

CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

DMS interpreted data, conceived of, and supervised the study. RC analyzed the data, supervised statistical analysis, and supervised the study. AP, OB, AB, MG, and NG performed analysis, analyzed the data, and drafted the manuscript. All other authors included patients, reviewed all patients characteristics, interpreted data, drafted and revised the manuscript, and approved the final version.

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