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Pulmonary Embolism in Patients with COVID-19: Comparison between Different Care Settings

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Abstract

The clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) who develop pulmonary embolism (PE) in the full spectrum of patient care settings need to be elucidated. The aim of this study was to compare the clinical characteristics, treatment, and 90-day outcomes in patients diagnosed with PE while recovering from COVID-19 in the outpatient setting versus those who were diagnosed with PE while being hospitalized with COVID-19. Data from the international Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry were used. The major study outcomes were all-cause death, major bleeding, and venous thromboembolism (VTE) recurrences during the first 90 days after PE. From March 2020 to March 2021, 737 patients with COVID-19 experienced acute PE. Of these, 340 (46%) were recovering from COVID-19 as outpatients (267 patients who had been treated at home for COVID-19 and 73 discharged after being hospitalized with COVID-19). Compared with inpatients with COVID-19, those recovering in the outpatient setting upon PE were less likely to be men (odds ratio [OR]: 0.54; 95% confidence interval [CI]: 0.40–0.72) and less likely to have hypertension (OR: 0.55; 95% CI: 0.41–0.74) or diabetes (OR: 0.51; 95% CI: 0.33–0.76). At 90-day follow-up, eight patients (none recovering from COVID-19 as outpatient vs. 2.4% of inpatients with COVID-19) developed recurrent VTE, 34 (1.9 vs. 7.9%) had major bleeding, and 128 (10 vs. 24%) died. On multivariable analysis, inpatients with COVID-19 were at a higher risk of major bleeding (adjusted

Keywords
- COVID-19
- pulmonary embolism
- outpatient
- RIETE registry

* *Full list of RIETE investigators is provided in the* ►**Appendix**.

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hazard ratio [HR]: 6.80; 95% CI: 1.52–30.4) or death (adjusted HR: 2.24; 95% CI: 1.40–3.58). In conclusion, using a large multinational registry of patients with COVID-19 who experienced PE, thromboembolic episodes occurring in those recovering from COVID-19 as outpatients were associated with less ominous outcomes than inpatients with COVID-19.

Coronavirus disease 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Several studies found several hemostatic abnormalities in hospitalized patients with COVID-19.[1,2] Additionally, critical illness and immobility predispose these patients to develop venous thromboembolism (VTE), including pulmonary embolism (PE).[3–5] In recent meta-analysis, the overall incidence of PE in hospitalized patients with COVID-19 was estimated at 7.1%,[6,7] and the incidence of major bleeding was 3.9%,[7] with a very high degree of between-study heterogeneity.[6] Multiple ongoing randomized controlled trials are currently evaluating the role of a group of antithrombotic regimens in hospitalized patients with COVID-19.[8,9] In most trials, the intensity of antithrombotic therapy is proportional to the expected VTE rates. More intensive therapies (including parenteral intermediate-dose or fully-therapeutic doses of anticoagulants) have been considered in trials of hospitalized patients.[10–13] However, patients with COVID-19 may also develop VTE outside the hospital, either in those who did not require hospitalization during the period of acute infection or in the post-hospital discharge period.[14–16] So far, some information has been provided on VTE rates and clinical characteristics in patients with COVID-19 attending emergency departments before hospitalization,[17,18] or discharged after hospitalization for COVID-19.[19,20] Nonetheless, in these subsets of patients, the clinical characteristics, time course, severity of VTE, use of VTE prophylaxis, ideal therapy, and outcomes during the course of anticoagulant therapy have not been yet reported in a large series. Moreover, the existing reports are limited to studies with relatively small number of patients with incident VTE and cannot generate insights into distinctions between different settings of patients with COVID-19 who develop VTE.[19,20] From a theoretical point of view, patients who develop VTE in hospital may potentially benefit from more timely diagnosis and earlier treatment than those who develop VTE in outpatient settings. However, inpatients are often older, sicker, and more likely to have concomitant disorders. Therefore, whether clinical outcomes may be influenced by the setting in which VTE occurred is unclear.

PE, in particular, would be a challenging complication in COVID-19. PE may add insult to an already compromised respiratory status, and may potentially lead into fatal complications, or bleeding, or be associated with subsequent VTE events.[21,22] The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) registry is an ongoing, multicenter, international registry, designed to gather data on the clinical characteristics, treatment patterns and outcome in consecutive patients with objectively confirmed, acute VTE.[23] In the current study, we aimed to compare the clinical characteristics, treatment, and 90-day outcomes in different settings of patients with COVID-19 who were diagnosed with PE while recovering in the outpatient setting and in whom a PE was detected during hospitalization.

Patients and Methods

Study Design

The methodology and design features of the RIETE registry have been described previously (ClinicalTrials.gov identifier: NCT02832245).[23] The aim of the current study was to compare the clinical characteristics, time course of PE, use of VTE prophylaxis, treatment, and 90-day outcomes in patients with COVID-19 who were diagnosed with PE outside the hospital or on hospital admission (i.e., patients recovering from COVID-19 as outpatients) versus those in whom a PE was detected while being hospitalized with COVID-19 (i.e., inpatients with COVID-19). The first group was further subdivided depending on whether or not patients were hospitalized with COVID-19 in the previous 60 days. Patients hospitalized upon PE were subdivided according to the site where they were diagnosed with PE (intensive care unit [ICU] or medical ward). All patients provided informed consent to their participation in the registry, according to the requirements of the ethics committee within each hospital. The study coordinating center assigns patients with a unique identification number to maintain patient confidentiality and is responsible for all data management. Data quality is regularly monitored electronically, including checks to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals by contract research organizations that compare medical records with the submitted data.

Inclusion Criteria

Consecutive patients with confirmed COVID-19 infection and symptomatic, acute PE, confirmed by objective tests (pulmonary angiography, lung scintigraphy, or helical computed tomography (CT) scan), were enrolled in RIETE. The diagnosis of COVID-19 infection was confirmed by positive polymerase chain reaction testing of a nasopharyngeal sample or from tracheal aspirate in intubated patients. Patients were excluded if they were participating in a therapeutic clinical trial taking a blind medication at the time of screening.

Outcomes

The major study outcomes were all-cause death (primary outcome), major bleeding, and VTE recurrences during the first 90 days from PE diagnosis. Bleeding was classified as

"major" if it was fatal, retroperitoneal, spinal or intracranial, or if it required a transfusion of at least 2 units of blood. This definition is closely related to that of the International Society on Thrombosis and Haemostasis.[23,24] Fatal bleeding was considered in patients who died within the first 10 days after a major bleed, in the absence of any alternative cause. Study outcomes were adjudicated by the attending physicians. In case of doubt (i.e., absence of objective confirmation of the cause of death) the cause of death was adjudicated by the RIETE Adjudication Committee.

Patients were managed according to each participating hospital clinical practice, and there were no standardization or recommendation of treatment. All participants were followed up for at least 90 days. All episodes of clinically suspected symptomatic VTE recurrences were investigated by repeat compression ultrasonography, contrast venography, ventilation-perfusion lung scan, or by helical CT scan.

Other Study Variables and Definitions

The following parameters are routinely recorded in RIETE: baseline clinical characteristics and coexisting or underlying conditions, additional risk factors for PE, signs and symptoms, the treatment received upon PE diagnosis, and the outcome during the first 90 days after VTE diagnosis. At the time of PE diagnosis, a blood sample is collected and laboratory parameters are recorded. The neutrophil and lymphocyte counts are evaluated in peripheral blood collected using a Coulter counter method, and the neutrophil to lymphocyte ratio (NLR) is calculated.

Active cancer was defined as newly diagnosed cancer or any cancer receiving antineoplastic treatment of any type. Immobilized patients were defined as nonsurgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for $\geq$4 days in the 2-month period prior to PE diagnosis. In the outpatient setting, the presence of immobility and the use of prophylactic anticoagulation prior to incident PE were assessed by patient survey. Surgical patients were defined as those who underwent a surgical intervention in the 2 months prior to PE. Recent bleeding was defined as a major bleeding episode <30 days prior to PE.

Follow-Up

Patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. After PE diagnosis, all patients were followed-up for 90 days. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was documented by repeat compression ultrasonography, venography, lung scanning, helical CT scan, or pulmonary angiography.

Statistical Analysis

The study reported categorical data as proportions and continuous data as mean and standard error of the mean or median (interquartile range) days. We used unpaired two-tailed *t*-tests or the Mann–Whitney *U* test (for those variables found not to follow a normal distribution) for comparisons in the distributions of continuous variables, and chi-squared or Fisher's exact tests to compare the categorical data between groups. We compared demographics, concomitant disorders, initial PE presentation, pharmacological VTE prophylaxis, and treatment during the first 90 days, according to different clinical settings at the time of PE diagnosis.

Then, we performed a multivariable analysis through a Cox model trying to identify the predictors for all-cause death within the first 90 days. We also used competing risk models (Fine-Gray) to identify predictors for major bleeding, with mortality not due to bleeding as the competing risk. Covariates entering into the models were selected by a significance level of $p < 0.10$ on bivariate analysis or by a well-known association reported in the literature and selected by the study investigators. We conducted statistical analyses using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A *p*-value <0.05 was considered significant for comparison of the association between clinical settings at the time of PE diagnosis and 90-day all-cause mortality. No adjustment for multiplicity was performed and other *p*-values should be considered exploratory.

Results

Patient Characteristics

From March 2020 to March 2021, 737 patients with COVID-19 and acute PE were included. Of these, 340 (46%) were diagnosed with PE while recovering from COVID-19 in the outpatient setting (73 discharged within the first 60 days after being hospitalized with COVID-19, 158 after immobility for COVID-19 at home, and 109 treated for COVID-19 at home, but without immobility), while 397 (54%) were diagnosed with PE while being hospitalized with COVID-19 (254 in medical wards, and 143 in the ICU; ►**Fig. 1**).

Overall, 620 patients (84%) were recruited in Spain, 79 (11%) in France, 14 (1.9%) in Italy, 5 in Switzerland, 4 in Israel, and 2 in Ireland. The median time elapsed from COVID-19 diagnosis to PE was shorter in patients recovering from COVID-19 as outpatients than inpatients with COVID-19 (8 vs. 10 days, respectively; $p < 0.01$), and significantly longer in patients with PE diagnosed after hospital discharge than in those who had been treated at home for COVID-19 (14 vs. 5 days, respectively; $p < 0.01$).

Compared with inpatients with COVID-19, those recovering as outpatients upon PE were less likely to be men (odds ratio [OR]: 0.54; 95% confidence interval [CI]: 0.40–0.72) and less likely to have had recent immobility (OR: 0.62; 95% CI: 0.45–0.85), hypertension (OR: 0.55; 95% CI: 0.41–0.74), diabetes (OR: 0.51; 95% CI: 0.33–0.76), or anemia (OR: 0.19; 95% CI: 0.14–0.27).

There were no significant differences in the patients' age (62 ± 1.0 vs. 65 ± 0.7 years; $p = 0.015$) nor in the proportion of patients with cancer, chronic heart failure, chronic lung disease, or renal insufficiency. At baseline, patients recovering from COVID-19 as outpatients had lower neutrophil counts and higher lymphocyte counts than inpatients with COVID-19. Thus, the NLR was much lower in the former (6.0 ± 0.4 vs. 12.1 ± 0.8, respectively; $p < 0.001$).

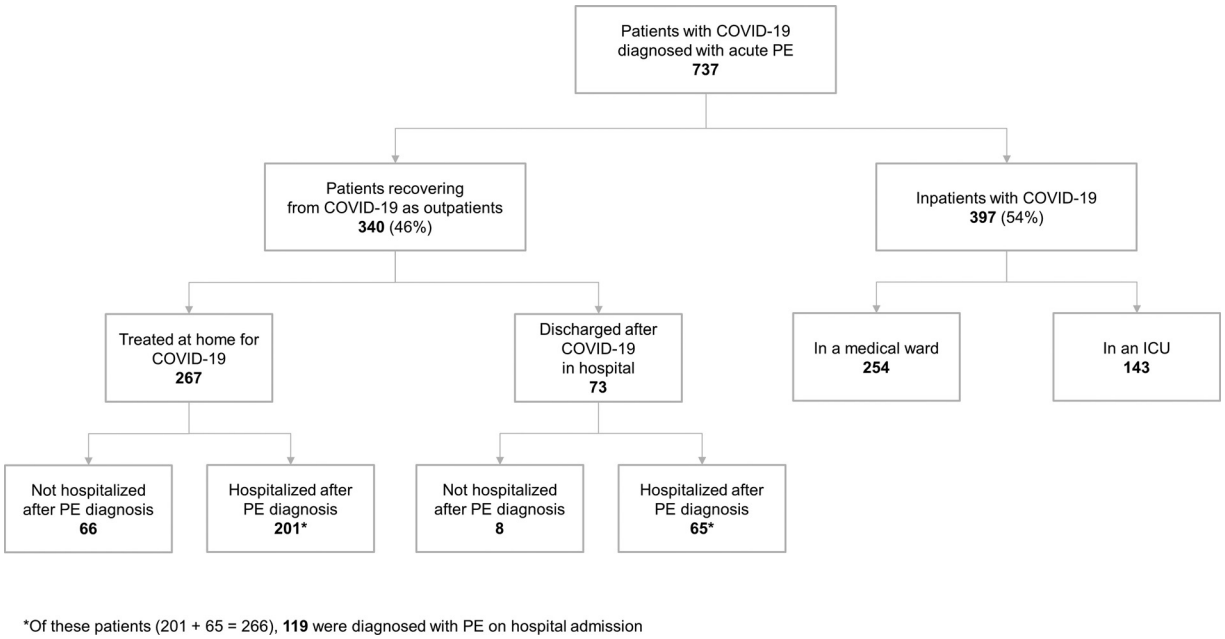


Fig. 1 Flow diagram of included patients. PE, pulmonary embolism.

Compared with patients with PE diagnosed after hospital discharge, those who had been treated at home for COVID-19 were younger and less likely to have recent immobility and anemia, whereas ICU patients displayed higher body mass index and NLR values, as well as increased prevalence of diabetes, hypertension, and anemia compared with patients hospitalized in medical wards, as shown in ►**Table 1**.

Two in every three patients (64 vs. 66%, patients recovering from COVID-19 as outpatients vs. inpatients with COVID-19, respectively) had only subsegmental and/or segmental arteries involved. Compared with the former, inpatients with COVID-19 had lower involvement of main pulmonary arteries. However, there were no major differences in the proportion of patients with hemodynamic instability, hypoxemia, or tachycardia between groups of patients (►**Table 2**).

Thromboprophylaxis

Overall, the use of prophylactic anticoagulation prior to incident PE was less frequent in patients recovering from COVID-19 as outpatients than inpatients with COVID-19 (17 vs. 64%, respectively; OR: 0.11; 95% CI: 0.08–0.15). Most (48 of 73; 71%) of the first who received VTE prophylaxis were recently discharged from hospital, while rates of VTE prophylaxis were low in patients who had been treated at home for COVID-19, despite recent immobilization because of acute illness (11 of 158; 7%).

Overall, 89 patients were on antiplatelet therapy, 81 of whom (91%) being of acetylsalicylate in monotherapy. Rates of antiplatelet therapy were not significantly different between groups.

Treatment

The majority (266 of 340; 78%) of the patients recovering from COVID-19 as outpatients required hospital admission following PE diagnosis (►**Table 3**). Among those, 119 were diagnosed with PE on hospital admission (►**Fig. 1**).

Most patients recovering from COVID-19 as outpatients and inpatients with COVID-19 (81 vs. 84%, respectively) received initial therapy with low-molecular-weight heparin (LMWH) or biosimilars of enoxaparin. The use of the direct oral anticoagulants (DOACs) was more common among the former, and particularly in those who had been treated at home for COVID-19, whereas the use of thrombolytic drugs, vasopressors, or extracorporeal membrane oxygenation was more likely in inpatients with COVID-19 (particularly in those admitted in the ICU).

As for long-term therapy, LMWH was the main anticoagulant used in both inpatient settings (44 vs. 41%, medical ward vs. ICU, respectively), whereas DOACs were mainly prescribed to patients recovering from COVID-19 as outpatients (48 vs. 41%, treated at home vs. discharged after being hospitalized with COVID-19, respectively).

Clinical Outcomes

Within the first 90 days of follow-up, 8 patients developed VTE recurrences (none recovering from COVID-19 as outpatient vs. 2.4% of inpatients with COVID-19, respectively), 34 (1.9 vs. 7.9%) had major bleeding, and 128 (10 vs. 24%) died. Among the latter, five patients had fatal bleeding (►**Table 4**). The vast majority of these outcomes appeared within the first 30 days (►**Figs. 2** and **3**).

Rates of VTE recurrence, major bleeding, and all-cause death including fatal bleeding were highest in ICU patients with COVID-19. Compared with patients treated at home for COVID-19, patients with PE diagnosed after hospital discharge displayed increased rates of major bleeding (5.5 vs. 0.7%, respectively), whereas VTE recurrence and death rates were similar in the two groups of patients, as shown in ►**Table 4**.

Table 1 Clinical characteristics of patients, according to the different care settings

	Patients recovering from COVID-19 as outpatients				Inpatients with COVID-19			
	Treated at home for COVID-19		Discharged after COVID-19 in hospital		In a medical ward		In an ICU	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
Patients, *n*	267		73		254		143	
Clinical characteristics								
Male sex	137 (51%)	45–57%	40 (55%)	43–66%	158 (62%)*	56–68%	108 (76%)‡	68–83%
Age (mean years ± SEM)	60.4 ± 1.1		68.1 ± 1.9†		66.4 ± 0.9‡		62.5 ± 0.9	
BMI (mean kg/m^2 ± SEM)	27.3 ± 0.3		28.4 ± 0.6		27.7 ± 0.3		29.4 ± 0.6†	
Time from COVID-19 to PE								
Median days (IQR)	5 (0–36)		14 (1–26)†		9 (3–15)		12 (6–19)†	
Risk factors for VTE								
Recent immobility ≥4 days	158 (59%)	53–65%	68 (93%)‡	87–99%	195 (77%)†	72–82%	108 (76%)	68–83%
VTE prophylaxis	11 (7%)	3–11%	48 (71%)‡	60–81%	158 (81%)‡	76–87%	97 (90%)‡	84–96%
Recent surgery	0	0–0%	5 (6.8%)‡	1–13%	12 (4.7%)*	2.1–7.3%	6 (4.2%)	0.9–7.5%
VTE prophylaxis	0	0–0%	2 (40%)	0–88%	8 (67%)	39–95%	4 (67%)	25–100%
Active cancer	14 (5.2%)	2.6–7.9%	3 (4.1%)	0–8.7%	19 (7.5%)	4.2–11%	3 (2.1%)	0–4.5%
Estrogens use	12 (4.5%)	2–7%	0	0–0%	4 (1.6%)	0–3.1%	0	
Pregnancy/postpartum	2 (0.7%)	0–1.8%	1 (1.4%)	0–4.1%	3 (1.2%)	0–2.5%	1 (0.7%)	0–2.1%
None of the above	96 (36%)	30–42%	0	0–0%	40 (16%)‡	11–20%	29 (20%)	14–27%
Prior VTE	12 (4.5%)	2–7%	5 (6.8%)	1–13%	9 (3.5%)	1.3–5.8%	5 (3.5%)	0.5–6.5%
Underlying diseases								
Chronic lung disease	23 (8.6%)	5.2–12%	12 (16%)	7.9–25%	23 (9.1%)	5.5–13%	9 (6.3%)	2.3–10%
Chronic heart failure	11 (4.1%)	1.7–6.5%	4 (5.5%)	0.2–11%	15 (5.9%)	3–8.8%	6 (4.2%)	0.9–7.5%
Arterial hypertension	88 (33%)	27–39%	27 (37%)	26–48%	121 (48%)‡	41–54%	70 (49%)†	41–57%
Diabetes	30 (11%)	7.4–15%	9 (12%)	4.7–20%	42 (17%)	12–21%	39 (27%)‡	20–35%
Laboratory levels								
Anemia	44 (16%)	12–21%	20 (27%)*	17–38%	104 (41%)‡	35–47%	110 (77%)‡	70–84%
Neutrophil count (mean ± SEM)	7.1 ± 0.5		7.0 ± 0.4		7.3 ± 0.3		10.8 ± 0.6‡	
Lymphocyte count (mean ± SEM)	2.4 ± 0.4		1.6 ± 0.2		1.5 ± 0.2*		1.1 ± 0.1‡	
Platelet count (mean ± SEM)	256 ± 5.6		251 ± 13.8		295 ± 7.6‡		259 ± 9.1	
NLR	5.76 ± 0.39		6.9 ± 0.89		10.1 ± 0.82‡		16.2 ± 1.73‡	
NLR >5.0	100 (40%)	34–46%	30 (42%)	31–54%	124 (55%)‡	49–62%	97 (79%)‡	72–86%
CrCl levels <60 mL/min	57 (21%)	16–26%	21 (29%)	18–39%	47 (19%)	14–23%	31 (22%)	15–28%

Abbreviations: BMI, body mass index; CI, confidence intervals; COVID-19, coronavirus disease 2019; CrCl, creatinine clearance; ICU, intensive care unit; NLR, neutrophil to lymphocyte ratio; PE, pulmonary embolism; SEM, standard error of the mean; VTE, venous thromboembolism.
Notes: Comparisons between outpatients treated at home for COVID-19 and the other subgroups: *p <0.05; †p <0.01; ‡p < 0.001.

Overall, inpatients with COVID-19 had a much higher rate of major bleeding (hazard ratio [HR]: 4.10; 95% CI: 1.71–9.87) or death (OR: 2.59; 95% CI: 1.68–4.00) than patients treated at home for COVID-19. The multivariable analysis confirmed that inpatients with COVID-19 were at a higher risk of major bleeding (adjusted HR: 6.80; 95% CI: 1.52–30.4) or all-cause death (adjusted HR: 2.24; 95%CI: 1.40–3.58), while patients who had been recently discharged after being hospitalized with COVID-19 were at no significant increased risk of both. Further predictors of all-cause death were the presence of active cancer, NLR ≥5, and creatinine clearance levels <60 mL/min, while patients with anemia or low creatinine clearance levels were at an increased risk of major bleeding. No drug administered as initial therapy was associated with an increased or decreased risk of bleeding or death, using LMWH as a reference (►**Table 5**).

Discussion

Our findings, obtained from a large series of consecutive patients with COVID-19 who developed incident PE, reveal that almost half of them (46%) were detected outside the

Table 2 Symptoms and signs of PE at initial presentation

	Patients recovering from COVID-19 as outpatients				Inpatients with COVID-19			
	Treated at home for COVID-19		Discharged after COVID-19 in hospital		In a medical ward		In an ICU	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
Patients, *n*	267		73		254		143	
Signs and symptoms								
SBP levels <90 mm Hg	7 (2.6%)	0.7–4.5%	1 (1.4%)	0–4.1%	6 (2.4%)	0.5–4.3%	9 (6.5%)	2.4–11%
Heart rate (mean bpm ± SEM)	90 ± 1.2		90.1 ± 2.0		86.7 ± 1.1*		93.7 ± 2.1	
Heart rate >110 bpm	39 (15%)	10–19%	9 (12%)	4.7–20%	23 (9.3%)	5.7–13%	22 (17%)	11–24%
Sat O_2 levels (mean % ± SEM)	93.6 ± 0.4		93.5 ± 0.8		89.9 ± 1.1†		92.0 ± 0.8	
Sat O_2 levels <90% ($n = 375$)	27 (16%)	10–21%	8 (22%)	8.2–35%	30 (32%)†	22–41%	14 (25%)	16–34%
sPESI <1 point	145 (54%)	48–60%	28 (38%)*	27–50%	124 (49%)	43–55%	79 (55%)	47–63%
Concomitant DVT	22 (8.2%)	4.9–12%	10 (14%)	5.8–22%	20 (7.9%)	4.6–11%	17 (12%)	6.6–17%
Burden of PE on CT scan	242		64		226		101	
Main arteries	10 (4.1%)	1.6–6.6%	4 (6.3%)	0.3–12%	3 (1.3%)*	0–2.8%	2 (2.0%)	0–4.7%
Lobar arteries	66 (27%)	22–33%	12 (19%)	9.1–28%	66 (29%)	23–35%	30 (30%)	21–39%
Segmental arteries	81 (33%)	28–39%	27 (42%)	30–54%	104 (46%)†	40–53%	45 (45%)	35–54%
Subsegmental arteries	43 (18%)	13–23%	11 (17%)	7.9–27%	36 (16%)	11–21%	15 (15%)	7.9–22%
No information available	25 (9.4%)	5.9–13%	9 (12%)	4.7–20%	28 (11%)	7.2–15%	42 (29%)‡	22–37%

Abbreviations: bpm, beats per minute; CI, confidence intervals; COVID-19, coronavirus disease 2019; CT, computed tomography; DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; SBP, systolic blood pressure; SEM, standard error of the mean; sPESI, simplified pulmonary embolism severity index.
Note: Comparisons between outpatients treated at home for COVID-19 and the other subgroups:*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

hospital or on hospital admission. No significant difference was found between patients recovering from COVID-19 as outpatients and inpatients with COVID-19 in terms of age and severity of the initial presentation of PE, though the former were younger, less likely to be male, to have hypertension, diabetes, or anemia.

Overall, these data are consistent with the evidence that inpatients with COVID-19, and particularly those hospitalized in the ICU, are usually sicker, with a more severe systemic inflammatory response compared with subjects receiving care in the outpatient setting.[25]

Time elapsed from COVID-19 to VTE showed great variability in both patients recovering from COVID-19 as outpatients and inpatients with COVID-19 but was rather shorter among the former, especially comparing outpatients treated at home for COVID-19 to ICU inpatients. Although we do not have a clear explanation for this finding, it is possible that outpatients had a delayed diagnosis of COVID-19 compared with inpatients, since many hospitals have implemented screening for COVID-19 on admission so far. Moreover, outpatients with COVID-19-related symptoms may have been encouraged to quarantine themselves without testing, especially early in the pandemic, so they may have had symptoms longer before PE diagnosis.

During follow-up, inpatients with COVID-19 in our cohort had a fourfold higher rate of major bleeding and a twofold higher mortality rate than patients who have been treated at home for COVID-19 before PE diagnosis, with results remaining consistent in multivariable analyses. In addition, no patient recovering from COVID-19 as outpatient developed VTE recurrences during the first 90 days, as compared with 2.4% of inpatients with COVID-19. Although patients who had been recently discharged displayed higher rates of major bleeding than those treated at home for COVID-19, the rates of VTE recurrence and death were similar between groups. Thus, the 90-day rates of adverse events in patients diagnosed with PE while recovering from COVID-19 in the outpatient setting were overall milder than in inpatients with COVID-19. Intriguingly, the great majority of the included outcomes occurred within the first 30 days in both subgroups, thus suggesting that special attention should be focused during the early period. The low rate of VTE recurrences in both inpatients with COVID-19 and patients recovering as outpatients during the first 90 days may have potential implications for decisions about duration of anticoagulation in patients with COVID-19. Long-term follow-up of these patients is ongoing and will be of additional help in this regard.

Death rates among patients diagnosed with PE while being hospitalized with COVID-19 were consistent with previous observations on inpatients with COVID-19.[26–28] Scarce information is available in the outpatient setting, and 90-day death rate has never been described in large cohorts, to our knowledge, in patients with COVID-19 who developed incident PE. Although not negligible (up to 10% in our population), 90-day death rates were less than half of those of inpatients with COVID-19, and less than one-third compared with patients admitted to ICU. In the outpatient

Table 3 Treatment strategies

	Patients recovering from COVID-19 as outpatients				Inpatients with COVID-19			
	Treated at home for COVID-19		Discharged after COVID-19 in hospital		In a medical ward		In an ICU	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
Patients, *n*	267		73		254		143	
Required hospital admission	201 (75%)	70–80%	65 (89%)*	82–96%	–	–	–	–
Initial therapy								
Low-molecular-weight heparin	190 (71%)	66–77%	54 (74%)	64–84%	207 (81%)†	77–86%	93 (65%)	57–73%
Unfractionated heparin	5 (1.9%)	0.2–3.5%	1 (1.4%)	0–4.1%	4 (1.6%)	0–3.1%	32 (22%)‡	16–29%
Direct oral anticoagulants	49 (18%)	14–23%	4 (5.5%)†	0.2–11%	12 (4.7%)‡	2.1–7.3%	2 (1.4%)‡	0–3.3%
Biosimilars of enoxaparin	16 (6.0%)	3.1–8.8%	11 (15%)*	6.8–23%	28 (11%)	7.2–15%	5 (3.5%)	0.5–6.5%
Thrombolytics	2 (0.7%)	0–1.8%	1 (1.4%)	0–4.1%	1 (0.4%)	0–1.2%	9 (6.3%)†	2.3–10%
Required vasopressors	4 (1.8%)	0–3.6%	0	0–0%	3 (1.5%)	0–3.3%	36 (31%)‡	23–39%
ECMO	0	0–0%	0	0–0%	1 (0.5%)	0–1.5%	10 (8.7%)‡	3.5–14%
Inferior vena cava filter	4 (1.5%)	0–3%	1 (1.4%)	0–4.1%	1 (0.4%)	0–1.2%	5 (3.5%)	0.5–6.5%
Long-term therapy								
Low-molecular-weight heparin	81 (30%)	25–36%	27 (37%)	26–48%	113 (44%)†	38–51%	59 (41%)*	33–49%
Direct oral anticoagulants	128 (48%)	42–54%	30 (41%)	30–52%	74 (29%)‡	24–35%	18 (13%)‡	7.1–18%
Vitamin K antagonists	30 (11%)	7.4–15%	6 (8.2%)	1.9–15%	25 (9.8%)	6.2–14%	3 (2.1%)‡	0–4.5%
Biosimilars of enoxaparin	7 (2.6%)	0.7–4.5%	2 (2.7%)	0–6.5%	7 (2.8%)	0.7–4.8%	1 (0.7%)	0–2.1%
Concomitant therapies								
Antiplatelets	26 (10%)	6.5–14%	11 (15%)	7–24%	35 (15%)	11–20%	17 (13%)	7.1–18%
NSAIDs	15 (5.9%)	3–8.8%	1 (1.4%)	0–4.2%	21 (9.3%)	5.5–13%	8 (6.1%)	2–10%
Corticosteroids	12 (4.7%)	2.1–7.3%	8 (11%)	3.9–19%	70 (31%)‡	25–37%	49 (37%)‡	29–45%
Statins	65 (25%)	20–30%	22 (31%)	20–41%	59 (24%)	19–29%	31 (22%)	15–29%

Abbreviations: CI, confidence intervals; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IU, International units; LMWH, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs.
Note: Comparisons between outpatients treated at home for COVID-19 and the other subgroups: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

setting, rates were not significantly different between patients treated at home and previously hospitalized for COVID-19.

Besides "inpatient with COVID-19" status, other clinical features like the presence of cancer or renal insufficiency were associated with an increased risk of death, while patients with transient risk factors or renal insufficiency were at an increased risk of major bleeding on multivariable analysis. Interestingly, our findings also confirm the prognostic value of the NLR in patients with acute PE developing after COVID-19, since those with a ratio over 5.0 at the time of PE diagnosis had an over threefold higher risk of death and an over twofold higher risk of major bleeding. Several pathophysiological mechanisms have been suggested to explain the COVID-19-associated coagulopathy, including the activation of monocytes and complement cascade, as well as the release of monocyte-derived extracellular vesicles, neutrophil extracellular traps, and neutrophil elastase, resulting in the so-called immunothrombosis.[29] NLR was found to increase significantly in patients with severe COVID-19,[30] and emerged as an independent risk factor for mortality in hospitalized patients with COVID-19.[31] Furthermore, a threshold of >6.11 at hospital admission was found in a previous study to discriminate a higher risk of death.[32] Our findings support the potential importance of this inflammatory marker in the prognostic stratification of patients with COVID-19 and PE, whose utilization should be probably implemented both in the in- and outpatient settings.

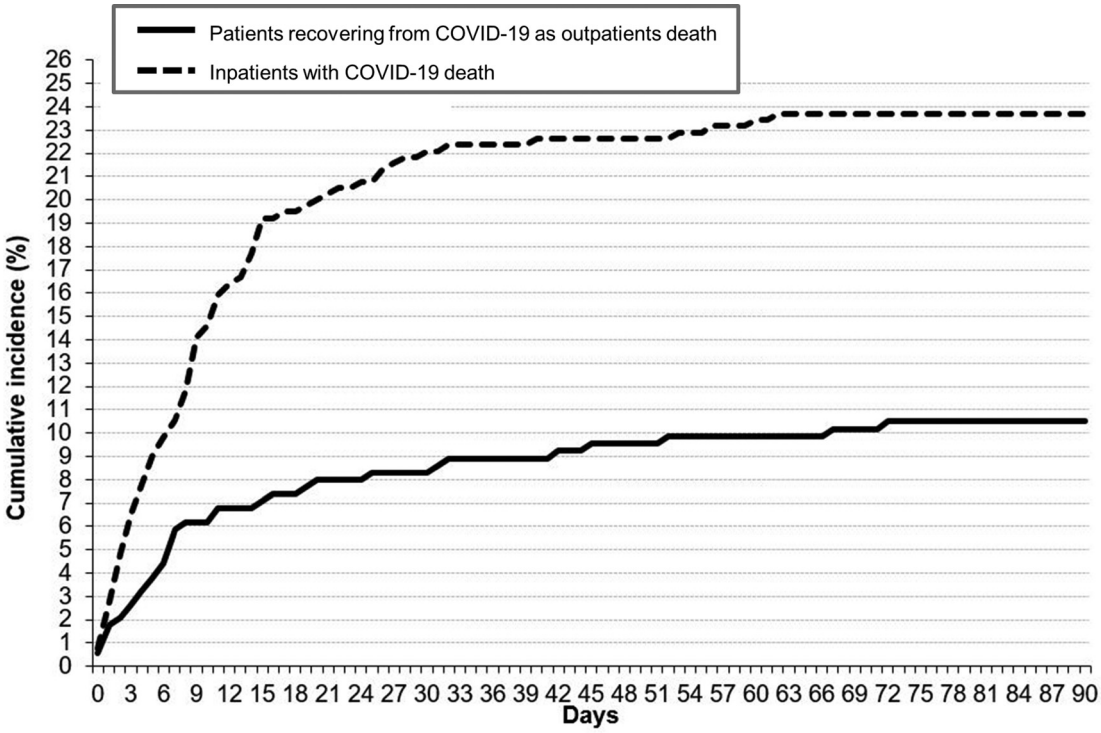
To date, the risk of a first episode of VTE has been reported to be higher in men than in women without reproductive risk factors, and the risk of recurrent VTE risk is also higher in men.[33] In our cohort, the proportion of men was around 60%, and higher percentages were found among inpatients with COVID-19, particularly in those admitted in the ICUs. Although multivariable analysis did not confirm a significantly higher risk of death or major bleeding in male patients in our cohort, the progressive increase in the proportion of men across the increasing levels of intensity of care is consistent with prior studies revealing a higher severity of COVID-19 infection in men than in women.[28]

In addition to their effect on coagulation, some antithrombotic drugs have an immunomodulatory effect, and several beneficial effects of heparins on the inflammatory response or the virus itself have been proposed so far.[34] Moreover, recent evidence suggests that statins and antiplatelets use may be associated with decreased VTE or

Table 4 Clinical outcomes during the first 90 days of therapy

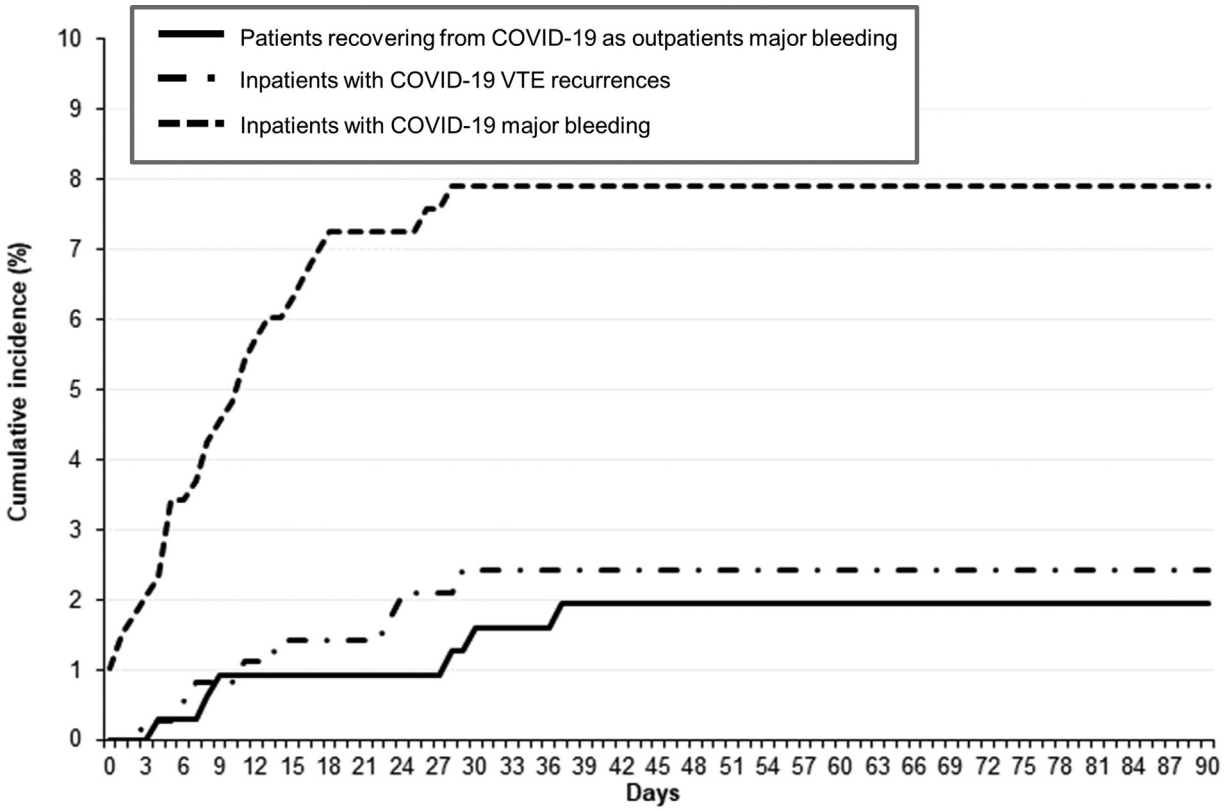
	Patients recovering from COVID-19 as outpatients				Inpatients with COVID-19			
	Treated at home for COVID-19		Discharged after COVID-19 in hospital		In a medical ward		In an ICU	
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
PE, *n*	267		73		254		143	
PE recurrences	0	–	0	–	1 (0.4%)	0–1.2%	2 (1.4%)	0–3.3%
DVT recurrences	0	–	0	–	1 (0.4%)	0–1.2%	4 (2.8%)†	0.1–5.5%
Major bleeding	2 (0.7%)	0–1.8%	4 (5.5%)*	0.2–11%	9 (3.5%)	1.3–5.8%	19 (13%)‡	7.7–19%
Hematoma	1 (0.4%)	0–1.1%	2 (2.7%)	0–6.5%	3 (1.2%)	0–2.5%	3 (2.1%)	0–4.5%
Gastrointestinal	1 (0.4%)	0–1.1%	1 (1.4%)	0–4.1%	2 (0.8%)	0–1.9%	3 (2.1%)	0–4.5%
Intracranial	0	–	1 (1.4%)	0–4.1%	2 (0.8%)	0–1.9%	3 (2.1%)	0–4.5%
Retroperitoneal	0	–	0	–	1 (0.4%)	0–1.2%	5 (3.5%)†	0.5–6.5%
Death	26 (9.7%)	6.2–13%	9 (12%)	4.7–20%	41 (16%)*	12–21%	52 (36%)‡	28–44%
Causes of death,[a]								
Fatal bleeding	0	–	1 (1.4%)	0–4.1%	0	–	4 (2.8%)*	0.1–5.5%

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolism.
Note: Comparisons between outpatients treated at home for COVID-19 and the other subgroups: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
[a]Although in RIETE other causes of death are frequently reported by the sites with prespecified definitions, in the absence of autopsy, ascertainment of nonhemorrhagic causes of death is difficult in patients with COVID-19. Therefore, it was prespecified not to explore site-reported presumed causes of death, other than fatal bleeding.



	Setting	10 days	30 days	60 days	90 days
Death	Patients recovering from COVID-19 as outpatients	21 (6.2%)	28 (8.3%)	33 (9.9%)	35 (10%)
	Inpatients with COVID-19	58 (15%)	87 (22%)	92 (23%)	93 (24%)

Fig. 2 Cumulative mortality rates in the different clinical settings.



	Setting	10 days	30 days	60 days	90 days
VTE recurrences	Patients recovering from COVID-19 as outpatients	0	0	0	0
	Inpatients with COVID-19	3 (0.8%)	8 (2.4%)	8 (2.4%)	8 (2.4%)
Major bleeding	Patients recovering from COVID-19 as outpatients	3 (0.9%)	5 (1.6%)	6 (1.9%)	6 (1.9%)
	Inpatients with COVID-19	18 (4.8%)	28 (7.9%)	28 (7.9%)	28 (7.9%)

Fig. 3 Cumulative rates of venous thromboembolism (VTE) recurrences and major bleeding in the different clinical settings.

mortality.[35] In our study, no such impact on 90-day outcomes was confirmed on multivariate analysis, stressing the need for more insight in patients with COVID-19 who develop VTE.

Our study has several limitations worth noting. First, since the RIETE registry only enrolls patients with confirmed PE, we could not evaluate the incidence of PE among patients with COVID-19 in different settings. Moreover, in the absence of a systematic screening or a standardized protocol for testing for PE, patients' characteristics and outcomes may have been influenced by discretionary decisions to test and diagnose PE. However, our sites included both large referral hospitals and smaller community-based hospitals in several countries, and reflect PE diagnosis in routine practice, as well as treatment patterns and patient's outcomes.

A second limitation is that the contribution of PE to 90-day death is not assessable in our study. Although in RIETE causes of death are frequently reported by sites with prespecified definitions, in the absence of autopsy, ascertainment of nonhemorrhagic causes of death is difficult in patients with COVID-19. Therefore, presumed causes of death reported by sites other than fatal hemorrhage were prespecified not to be explored.

Third, compared with all-cause death, the relatively low number of major bleeding episodes in our population may have limited the precision of the multivariable analysis for association of predictors with major bleeding.

The distinction between clinical settings deserves another, separate discussion. Although inpatients with COVID-19 were defined based on a diagnosis of PE during hospitalization, several subjects may have had PE on admission.[36] On the other hand, we cannot exclude that among patients recently discharged after being hospitalized with COVID-19, PE had already occurred during the

Table 5 Uni- and multivariable analyses for major bleeding and for all-cause death during the first 90 days. Data are presented as hazard ratios and 95% confidence intervals

	All-cause death		Major bleeding	
	Univariable	Multivariable	Univariable	Multivariable
Clinical characteristics				
Male sex	1.24 (0.87–1.79)	1.16 (0.79–1.70)	2.18 (0.99–4.81)	1.71 (0.69–4.29)
Age ≥65 y	2.57 (1.76–3.76)‡	1.39 (0.90–2.15)	1.63 (0.82–3.25)	0.96 (0.44–2.1)
Patients recovering as outpatients (treated at home for COVID-19)	Ref.	Ref.	Ref.	Ref.
Patients recovering as outpatients (discharged after COVID-19 in hospital)	1.28 (0.60–2.73)	1.19 (0.55–2.59)	1.22 (0.43–3.45)	3.50 (0.78–15.3)
Inpatients with COVID-19	2.59 (1.68–4.00)‡	2.24 (1.40–3.58)‡	4.10 (1.71–9.87)†	6.80 (1.52–30.4)*
Time from COVID-19 to PE, >10 days	1.48 (1.04–2.11)*	1.18 (0.81–1.71)	1.02 (0.52–1.99)	–
Active cancer	3.29 (1.86–5.82)‡	2.49 (1.48–4.20)‡	0.53 (0.07–3.75)	1.13 (0.07–18.5)
Prior VTE	1.34 (0.62–2.87)	–	–	–
Concomitant disorders				
Chronic lung disease	1.53 (0.90–2.58)	1.43 (0.83–2.46)	–	–
Chronic heart failure	2.21 (1.22–4.01)†	1.21 (0.65–2.25)	–	–
Arterial hypertension	–	–	1.25 (0.64–2.45)	–
Diabetes	1.40 (0.92–2.14)	1.05 (0.68–1.63)	1.11 (0.46–2.67)	–
Blood tests				
Anemia	2.09 (1.48–2.96)‡	1.14 (0.77–1.69)	4.11 (1.96–8.54)‡	2.36 (1.06–5.25)*
NLR ≥5.0	4.94 (3.21–7.60)‡	3.74 (2.40–5.82)‡	3.15 (1.47–6.73)†	1.99 (0.84–4.72)
CrCl levels <60 mL/min	3.60 (2.54–5.10)‡	2.57 (1.73–3.84)‡	4.42 (2.26–8.64)‡	4.55 (2.22–9.36)‡
Initial therapy,				
Thrombolytic drugs	–	–	1.74 (0.23–13.1)	0.91 (0.1–8.31)
Concomitant therapies				
Corticosteroids	1.75 (1.18–2.58)	1.18 (0.79–1.77)	1.54 (0.72–3.27)	–
Statins	1.22 (0.82–1.79)	–	0.98 (0.44–2.16)	–

Abbreviations: COVID-19, coronavirus disease 2019; CrCl, creatinine clearance; NLR, neutrophil to lymphocyte ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; VTE, venous thromboembolism.
*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.

hospital stay in some cases. Furthermore, although about half of the patients in our study were diagnosed with PE while recovering as outpatients, it must be noted that most of them were later hospitalized because of PE. In these patients, some of the clinical features that followed PE diagnosis may therefore be similar of those found in patients who were hospitalized with COVID-19 and developed in-hospital PE. This is particularly the case of initial treatment strategies for PE in patients diagnosed with PE on hospital admission, which could explain, for instance, the high rates of LMWH in patients recovering from COVID-19 as outpatients. However, we believe that the interpretability of our results is affected to a limited extent overall. In fact, the aim of our study was not to delve into the pathophysiology of PE in the different clinical settings, but to evaluate the clinical characteristics and outcomes of patients with PE diagnosed in different outpatient and inpatient settings, thus helping the clinician in the management of these patients.

Beyond these aspects, our study has strengths. To our knowledge, this is among the first studies to provide information on the clinical characteristics and 90-days outcomes of patients with VTE during COVID-19 in different inpatient and outpatient settings, and to identify predictors of major outcomes, including overall mortality and major bleeding. Further research is needed to clarify the incidence of PE in outpatients with COVID-19, identify the optimal strategies for VTE prevention and diagnosis, and mitigate the outcomes once PE occurs in the different settings.

Conclusions

In this study from a large multinational prospective registry of patients with COVID-19 who experienced PE,

thromboembolic episodes detected in patients recovering from COVID-19 as outpatients were associated with less ominous outcomes than inpatients with COVID-19. Several clinical and laboratory features, including high level of NLR, were significantly associated with adverse outcomes at 90 days, and could be thus implemented in the initial clinical evaluation of these patients.

Notes

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Conflict of Interest

B.B. reported being a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of inferior vena cava filters. M.M. reported honoraria for lectures from Sanofi, Pfizer, Rovi, and Alfa sigma, support for meetings from Sanofi, and he participated in advisory meetings with Sanofi and Leo Pharma. The other coauthors have nothing to disclose.

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APPENDIX

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