

# High Risk of Secondary Infections Following Thrombotic Complications in Patients With COVID-19

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**Background.** This study's primary aim was to evaluate the impact of thrombotic complications on the development of secondary infections. The secondary aim was to compare the etiology of secondary infections in patients with and without thrombotic complications.

**Methods.** This was a cohort study (NCT04318366) of coronavirus disease 2019 (COVID-19) patients hospitalized at IRCCS San Raffaele Hospital between February 25 and June 30, 2020. Incidence rates (IRs) were calculated by univariable Poisson regression as the number of cases per 1000 person-days of follow-up (PDFU) with 95% confidence intervals. The cumulative incidence functions of secondary infections according to thrombotic complications were compared with Gray's method accounting for competing risk of death. A multivariable Fine-Gray model was applied to assess factors associated with risk of secondary infections.

**Results.** Overall, 109/904 patients had 176 secondary infections (IR, 10.0; 95% CI, 8.8–11.5; per 1000-PDFU). The IRs of secondary infections among patients with or without thrombotic complications were 15.0 (95% CI, 10.7–21.0) and 9.3 (95% CI, 7.9–11.0) per 1000-PDFU, respectively ( $P = .017$ ). At multivariable analysis, thrombotic complications were associated with the development of secondary infections (subdistribution hazard ratio, 1.788; 95% CI, 1.018–3.140;  $P = .043$ ). The etiology of secondary infections was similar in patients with and without thrombotic complications.

**Conclusions.** In patients with COVID-19, thrombotic complications were associated with a high risk of secondary infections.

**Keywords.** thrombosis; bacteria; coronavirus; infections; pulmonary embolism.

Coronavirus disease 2019 (COVID-19)-associated coagulopathy leading to venous and arterial thrombotic complications is frequent and potentially life-threatening in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1–3]. Indeed, COVID-19 has been associated with a dysregulated inflammatory response [4] and a hypercoagulable state [5], with studies reporting thrombotic events in up to 30% of patients [6]. Therefore, several approaches have been proposed regarding the best management of anticoagulation in patients with

COVID-19, albeit without reaching a definitive conclusion [7, 8]. Another critical issue in hospitalized COVID-19 patients is represented by the high frequency of secondary infections, especially in patients with need of intensive care [9–12].

Interestingly, several studies have shown that immune activation during COVID-19 is frequently accompanied by immune exhaustion [13, 14]. Together with lymphopenia [15], this state of immune dysregulation may also lead to suppression of the immune response and, possibly, development of secondary infections [16]. Moreover, while systemic infections are a known risk factor for thrombotic complications [17], thrombotic lesions are known to be at risk of bacterial colonization and subsequent development of infection, as exemplified by infective endocarditis [18]. Given the possible shared pathophysiological pathway between coagulation disorders, derangement of the immune system, and infectious complications, we aimed at evaluating the impact of thrombotic complications on the development of secondary infections. Furthermore, we compared the etiology of secondary infections in patients with and without thrombotic complications.

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## METHODS

### Study Population

Patients considered in this analysis are part of the COVID-19 prospective institutional cohort (COVID-BioB) at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Hospital, a 1350-bed tertiary care hospital in Milan, Italy. We included all patients hospitalized with COVID-19 between February 25 and June 30, 2020.

COVID-19 was defined as a positive real-time reverse transcriptase polymerase chain reaction for SARS-CoV-2 from a nasopharyngeal swab or bronchoalveolar lavage associated with suggestive signs, symptoms, and/or radiological findings. Patients were managed according to internal institutional guidelines and the available evidence at the time of admission. Antithrombotic prophylaxis or treatment was not universally administered but was introduced on a case-by-case basis according to the treating physician.

Thrombotic complications (superficial, deep venous and arterial thrombosis [SVT, DVT, AT], pulmonary thrombosis/thromboembolism [PT]) were considered to precede secondary infections if diagnosed before or <48 hours after microbiological evidence of infection. All thrombotic complications had to be documented by either contrast-enhanced computed tomography (CT) scan or doppler ultrasonography (US); scans were requested at the treating physician's discretion. Heparin use included either prophylactic or full-dose anticoagulation.

Secondary infections (either bloodstream infections [BSIs] or lower respiratory tract infections [LRTIs]) were included in the analysis only if occurring at least 48 hours after hospital admission in order to differentiate them from coinfections.

BSIs were defined as a single positive blood culture for a likely pathogen or 2 or more positive blood cultures for common skin colonizers (ie, coagulase-negative staphylococci, diphtheroids, *Bacillus* spp., *Cutibacterium* spp., viridans group streptococci), without a concomitant microbiologically documented lower respiratory tract infection due to the same pathogen. Patients who had >1 positive blood culture within 7 days from the first positive blood culture were considered to have a single episode of BSI with multiple isolates.

LRTIs were defined as positive cultures of potentially pathogenic organisms from respiratory specimens obtained with invasive techniques (bronchoscopy-guided bronchoalveolar lavage [BAL] or, when not available, bronchial aspirate [BRASP]), excluding *Candida* spp. COVID-19-associated pulmonary aspergillosis was defined according to the ECMM/ISHAM consensus criteria [19].

Both blood and respiratory cultures were requested by the attending physicians in patients with suspected secondary infections because of the clinical and/or respiratory deterioration associated with suggestive laboratory or radiological findings. BAL and BRASP were not routinely collected for surveillance.

Patients for whom no microbiology specimens were requested were considered not to have secondary infections.

### Microbiological Methods

Blood culture samples were processed using the bioMérieux Virtuo BacT/Alert system, respiratory samples were inoculated in specific growth media (according to site protocol) and identified using Matrix Assisted Laser Desorption/Ionisation Time-Of-Flight Mass Spectrometry (MALDI-TOF MS; VITEK-MS, bioMérieux). The Platelia *Aspergillus* immuno-enzymatic assay was used to detect galactomannan.

### Statistical Analysis

Results of continuous variables were described by median (quartiles), while categorical variables were described by frequency (%).

The characteristics of patients with or without at least 1 secondary infection during hospitalization were compared with the chi-square or Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The distribution of microbial etiology of secondary infections among patients with or without thrombotic complications was compared with the chi-square test.

As previously described [20], quartiles of ferritin, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), D-dimer, and prothrombin time were calculated in order to determine (i) a composite inflammation score (number of elevated biomarkers of inflammation, ie,  $\geq 75$ th percentile threshold of ferritin and CRP); (ii) a composite cytolysis score (number of elevated biomarkers of cytolysis, ie,  $\geq 75$ th percentile threshold of AST, ALT, LDH); (iii) a composite coagulation score (number of elevated biomarkers of coagulation, ie,  $\geq 75$ th percentile threshold of D-dimer and prothrombin time). The 3 scores were thus defined as the number of laboratory parameters with markedly elevated values (values at or above the 75th percentile), ranging from 0 to 2 (in case of inflammation and coagulation) or 3 (in case of cytolysis score).

Incidence rates of secondary infections and thrombotic complications were calculated by univariable Poisson regression and reported as number of cases per 1000 person-days of follow-up (PDFUs).

The cumulative incidence function (CIF) of 1 or more secondary infections was calculated in the overall cohort and according to the presence of thrombotic complications with Gray's method [21]; 95% confidence intervals for survival probabilities and cumulative incidence were calculated accounting for competing risks of death.

A multivariable Fine-Gray model was applied to assess factors associated with the risk of secondary infections, including all variables deemed to be clinically significant or with a *P* value <.200 at univariate analysis, along with the 3 previously

described scores based on laboratory parameters. Moreover, a sensitivity analysis including use of heparin before the diagnosis of secondary infections was performed.

All statistical tests were 2-sided at the 5% level and were performed using SAS 9.4 (Statistical Analyses System Inc, Cary, NC, USA).

#### Patient Consent

Written informed consent was obtained according to institutional review board guidelines. The study is part of the institutional clinical–biological cohort assessing patients with COVID-19 (COVID-BioB, ClinicalTrials.gov NCT04318366), which was approved by the Institutional Review Board of IRCCS San Raffaele Hospital (protocol number 34/int/2020).

## RESULTS

#### Patients' Characteristics

Overall, 904 patients were included in the study. Patients' characteristics and baseline (hospital admission) laboratory parameters are described in [Table 1](#). All-cause in-hospital mortality was 22% (199/904 patients), with a median time to death since hospital admission (interquartile range [IQR]) of 13 (7–22) days. The median duration of hospital stay (IQR) was 14 (8–25) days.

#### Thrombotic Complications

Thrombotic complications were documented in 72/904 patients (8.0%), who developed 87 events (9 SVT, 18 DVT, 5 AT, 55 PT), for an overall incidence rate of 4.94 (3.98–6.07) per 1000-PDFUs. Eleven out of 72 patients had thrombotic complications >48 hours after diagnosis of secondary infection. The 61/904 patients (6.7%) with a thrombotic complication diagnosed before or <48 hours after the diagnosis of a secondary infection developed 75 events (7 SVT, 17 DVT, 4 AT, 47 PT), with a median time since hospital admission (IQR) of 7 (2–13) days. Data regarding heparin use were available for 599 patients; among them, 308 (51.4%) received heparin. Characteristics of patients according to the diagnosis of thrombotic complications are detailed in [Supplementary Table 1](#).

#### Secondary Infections

Secondary infections were documented in 109/904 patients (12.1%), who developed 176 events, with a median time since hospital admission (IQR) of 12 (8–18) days. Multiple secondary infections were diagnosed in 35 patients (3.9%). Characteristics of patients according to the diagnosis of secondary infections are shown in [Table 1](#). The incidence rate of secondary infections was 10.0 (8.5–11.5) per 1000-PDFUs. Overall, 147 BSIs were documented in 97/904 patients (10.7%), while 48 LRTIs were diagnosed in 40 (4.4%) subjects, with a median time since hospital admission (IQR) of 12 (8–18) and 20 (9–34) days,

respectively. The microbial etiology of BSIs and LRTIs is detailed in [Supplementary Table 2](#). Among patients with BSIs, gram-positive microorganisms predominated (138/219 isolates, 63.0%), particularly coagulase-negative staphylococci (83/138, 60.1%), while gram-negative bacteria were 25.0% of the total (55/219). Multiple isolates were found in 49/147 events (33.3%). On the contrary, gram-negative microorganisms predominated among LRTIs (36/53 isolates, 67.9%), followed by *Aspergillus* spp. (15/53, 28.3%).

The distribution of microbial etiology of BSIs and LRTIs among patients with and without thrombotic complications was similar ([Figure 1](#); [Supplementary Tables 3 and 4](#)), as was the frequency of polymicrobial infections.

#### Impact of Thrombotic Complications on the Development of Secondary Infections

Secondary infections were observed at or after thrombotic complication diagnosis in 19/61 patients (31.1%), while 90/843 subjects (10.7%) without thrombotic complications developed a secondary infection ( $P < .0001$ ). The incidence rate of secondary infections among patients with and without thrombotic complications was 15.0 (10.7–21.0) vs 9.3 (7.9–11.0) per 1000-PDFUs ( $P = .017$ ). Specifically, the incidence rate of BSIs was 12.8 (8.9–18.4) vs 7.7 (6.4–9.2) per 1000-PDFUs ( $P = .021$ ), while the incidence rate of LRTIs was 3.5 (1.5–7.0) vs 2.7 (1.9–3.6) per 1000-PDFUs ( $P = .469$ ). Heparin use between patients with and without secondary infections was similar (40.9% vs 52.6%;  $P = .085$ ); 24/25 patients with secondary infections received heparin before the diagnosis of the infectious complication.

The cumulative incidence function of secondary infections according to occurrence of thrombotic complications is shown in [Figure 2](#).

At multivariable analysis ([Table 2](#)), along with intensive care unit (ICU) admission within 48 hours from hospital admission and partial pressure of oxygen in the arterial blood/fraction of inspired oxygen, thrombotic complications were associated with development of secondary infections (subdistribution hazard ratio [sHR], 1.788; 95% CI, 1.018–3.140;  $P = .043$ ). This finding was explored in a sensitivity analysis including use of heparin before diagnosis of secondary infections, where the association was confirmed, albeit without reaching statistical significance, possibly due to the limited number of included patients (sHR, 2.037; 95% CI, 0.979–4.238;  $P = .057$ ) ([Supplementary Table 5](#)).

## DISCUSSION

In our cohort, patients hospitalized with COVID-19 complicated by thrombotic events had a high risk of secondary infections.

Thrombotic complications were diagnosed in 8.0% of patients, with an overall incidence rate of 4.94 (3.98–6.07) per

**Table 1. Patients' Characteristics and Baseline Laboratory Parameters**

Characteristics	Category	Overall (n = 904)	With Secondary Infections (n = 109)	Without Secondary Infections (n = 795)	P Value <sup>a</sup>
Age, y	...	64 (55–76)	63 (56–71)	65 (54–76)	.902
Sex, female	...	297 (32.9%)	22 (20.2%)	275 (34.6%)	<b>.002</b>
Arterial hypertension	...	400 (45.4%)	38 (39.6%)	362 (46.1%)	.234
Coronary artery disease	...	226 (25.7%)	20 (20.8%)	206 (26.2%)	.268
Diabetes mellitus	...	158 (17.9%)	21 (21.6%)	137 (17.5%)	.326
Chronic obstructive pulmonary disease	...	64 (7.3%)	3 (3.1%)	61 (7.8%)	.100
Chronic kidney disease	...	87 (9.9%)	8 (8.2%)	79 (10.1%)	.718
Malignancy	...	133 (15.1%)	7 (7.3%)	126 (16.1%)	<b>.022</b>
Liver disease	...	17 (2.9%)	3 (6.5%)	14 (2.6%)	.143
No. of comorbidities	...	1 (0–2)	1 (0–2)	1 (0–2)	.122
Days from symptom onset to hospital admission	...	7 (3–10)	7 (3–9)	7 (3–10)	.503
ICU admission	...	123 (13.6%)	75 (68.8%)	48 (6%)	<b>&lt;.0001</b>
ICU admission within 48 h of hospital admission	...	61 (6.7%)	29 (26.6%)	32 (4%)	<b>&lt;.0001</b>
PaO <sub>2</sub> /FiO <sub>2</sub>	...	224 (100–305)	109 (100–229)	238 (100–311)	<b>&lt;.0001</b>
	>200	384 (42.5%)	29 (26.6%)	355 (44.7%)	<b>&lt;.0001</b>
	<200	311 (34.4%)	63 (57.8%)	248 (31.2%)	
	Unknown	209 (23.1%)	17 (15.6%)	192 (24.2%)	
Use of biological immunosuppressive drugs	...	149 (16.5%)	26 (23.9%)	123 (15.5%)	<b>.038</b>
Use of corticosteroids (available in n = 599)	...	139 (23.2%)	13 (21.3%)	126 (23.4%)	.873
Use of remdesivir	...	32 (3.5%)	2 (1.8%)	30 (3.8%)	.414
Use of heparin (available in n = 599)	...	308 (51.4%)	25 (40.9%) <sup>b</sup>	283 (52.6%)	.085
Hemoglobin, g/dL	...	13.5 (12–14.7)	13.8 (12–15)	13.4 (12–14.6)	.300
Platelets, per 10 <sup>9</sup> /L	...	207 (155–272)	220 (147–316)	206 (156–269)	.331
White blood cells, per 10 <sup>9</sup> /L	...	6.9 (5–9.9)	7.8 (5.4–12)	6.8 (4.9–9.7)	<b>.003</b>
Neutrophils, per 10 <sup>9</sup> /L	...	4.9 (3.4–7.7)	6 (4–9.7)	4.9 (3.3–7.4)	<b>.001</b>
Lymphocytes, per 10 <sup>9</sup> /L	...	1 (0.7–1.3)	0.8 (0.6–1.1)	1 (0.7–1.4)	<b>.017</b>
Creatinine, mg/dL	...	0.98 (0.8–1.23)	0.99 (0.85–1.28)	0.97 (0.79–1.23)	.301
ALT, U/L	...	35 (23–56)	41 (26–68)	34 (22–55)	<b>.010</b>
AST, U/L	...	44 (31–66)	49 (35–87)	44 (30–63)	<b>.003</b>
LDH, U/L	...	363 (274–468)	431 (339–597)	355 (268–456)	<b>&lt;.0001</b>
Ferritin (available in n = 54), ng/mL	...	926 (480–1684)	1524 (1002–3097)	888.5 (474–1499.5)	.134
CRP, mg/L	...	70.9 (29.1–132.5)	117.2 (48.9–211.8)	67.75 (26.9–123.7)	<b>&lt;.0001</b>
D-dimer (available in n = 204), µg/mL	...	0.98 (0.53–2.46)	1.32 (0.99–3.15)	0.9 (0.5–2.37)	<b>.010</b>
Prothrombin time, sec	...	13.9 (13.1–15.3)	14.2 (13.3–15.6)	13.8 (13.1–15.3)	.265
Cytolysis score	...	...	...	...	<b>&lt;.0001</b>
	0	527 (59.6%)	54 (50.5%)	473 (60.9%)	
	1	157 (17.8%)	14 (13.1%)	143 (18.4%)	
	2	127 (14.4%)	15 (14%)	112 (14.4%)	
	3	73 (8.3%)	24 (22.4%)	49 (6.3%)	
Inflammation score	...	...	...	...	<b>&lt;.0001</b>
	0	665 (75.5%)	56 (53.3%)	609 (78.5%)	
	1	214 (24.3%)	48 (45.7%)	166 (21.4%)	
	2	2 (0.2%)	1 (1%)	1 (0.1%)	
Coagulation score	...	...	...	...	.191
	0	554 (70.8%)	68 (65.4%)	486 (71.6%)	
	1	209 (26.7%)	31 (29.8%)	178 (26.2%)	
	2	20 (2.6%)	5 (4.8%)	15 (2.2%)	

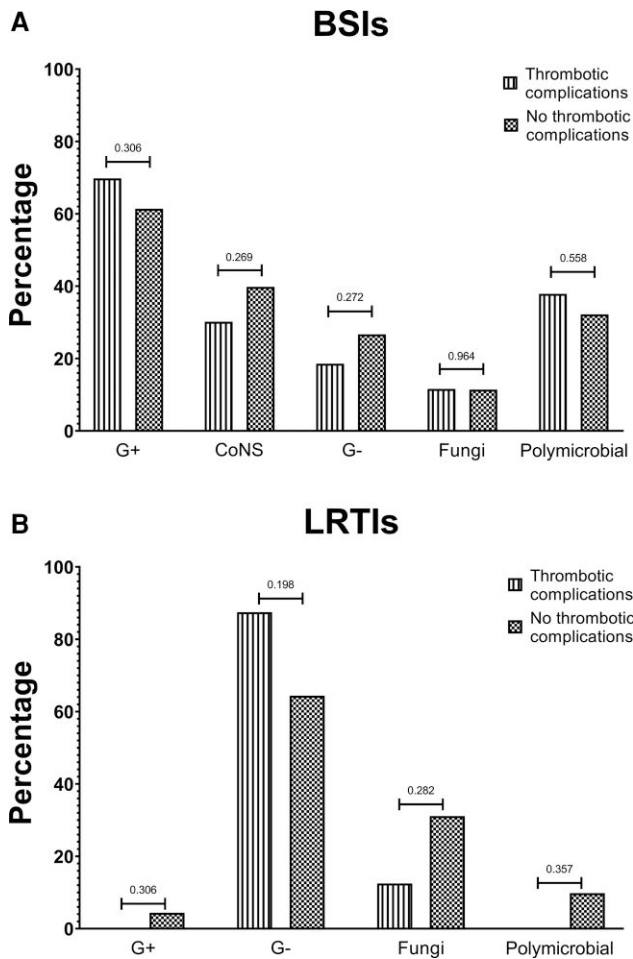
Results are reported as median (IQR) or frequency (%). P-value < .05 are reported in bold. For variables with >10% missing values, actual numbers of observations are reported. Cytolysis score included alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase. Inflammation score included ferritin and C-reactive protein. Coagulation score included D-dimer and prothrombin time. The 3 scores had a range of 0–2 or –3, with 0 corresponding to no abnormalities in inflammatory parameter levels and 2 or 3 corresponding to patients with markedly elevated values for all the considered laboratory parameters.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; PaO<sub>2</sub>/FiO<sub>2</sub>, partial pressure of oxygen in the arterial blood/fraction of inspired oxygen.

<sup>a</sup>By chi-square or Fisher's exact test (categorical variables) or Wilcoxon rank-sum test (continuous variables).

<sup>b</sup>Twenty-four of 25 patients with secondary infections received heparin before the diagnosis of the infectious complication.





**Figure 1.** Microbial etiology of infectious complications. *A*, BSIs. *B*, LRTIs. Abbreviations: BSIs, bloodstream infections; CoNS, coagulase-negative staphylococci; G+, gram-positive; G-, gram-negative; LRTIs, lower respiratory tract infections.

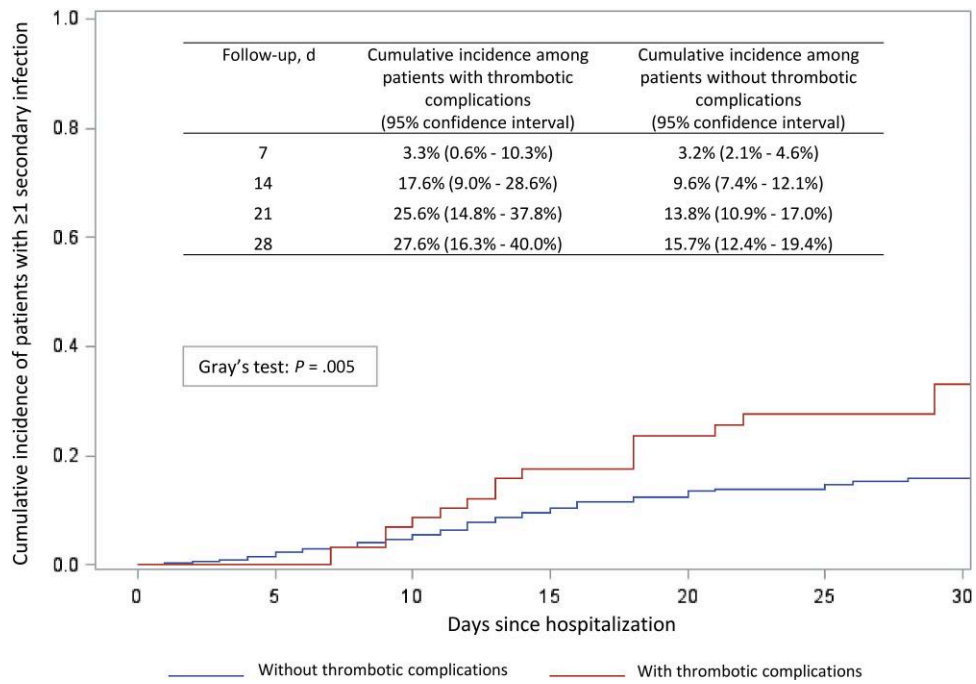
1000-PDFUs; the majority of patients developed pulmonary thrombosis/thromboembolism. The incidence of thrombotic complications among patients with COVID-19 reported in the literature varies depending on the severity of illness, the use of prophylactic/therapeutic anticoagulation, and the presence of preexisting risk factors (up to 65% of non-ICU hospitalized patients and up to 85% of ICU patients in settings where systematic screening was applied) [22–25]. Indeed, the actual proportion of patients with thrombotic complications is likely higher than reported in the literature, as systematic screening for thrombosis has shown that the majority of patients do not have a suggestive clinical picture [26].

Secondary infections were documented in 12.1% of patients, with an incidence rate of 10.0 (8.5–11.5) per 1000-PDFUs. Our results are in line with available reports [9–11], highlighting the non-negligible proportion of hospitalized COVID-19 patients with infectious complications. The majority of patients had

BSIs (10.0%), while LRTIs were diagnosed in 4.4% of subjects. Nevertheless, as only patients with microbiologically documented infections were considered in the analysis, the actual number of LRTIs would likely be higher than reported due to the limited number of patients who underwent invasive diagnostic procedures during the COVID-19 pandemic. Notably, microbial etiology was significantly different between patients with BSIs and LRTIs, with gram-positives as the main cause of secondary bloodstream infections and a prevalence of gram-negatives among pulmonary infections. As previously reported [19], COVID-19-associated pulmonary aspergillosis was documented in a significant proportion of patients, mainly in the ICU.

The incidence of secondary infections was significantly higher in patients with thrombotic complications (15.0 [10.7–21.0] vs 9.3 [7.9–11.0] per 1000-PDFUs;  $P = .017$ ), especially when considering BSIs (12.8 [8.9–18.4] vs 7.7 [6.4–9.2] per 1000-PDFUs;  $P = .021$ ). The association between thrombotic complications and secondary infections was confirmed at multivariable analysis, as patients with thrombotic events were shown to have about 1.8 times the risk of developing infectious complications compared with patients without thromboses (sHR, 1.788; 95% CI, 1.018–3.140;  $P = .043$ ). Although patients with thrombotic events are likely to present with a severe or critical clinical picture, the finding of an independent association between thrombosis and secondary infections possibly reflects a shared pathophysiologic background. Indeed, the inflammation and cytolysis scores, both associated with secondary infections, were significantly higher in patients with thrombotic complications compared with those without. On the other hand, while the coagulation score was significantly higher in patients with thrombotic events, no significant differences were found between patients with and without secondary infections, suggesting that thrombotic events, irrespective of nonspecific alterations in the coagulation parameters, may be associated with subsequent infectious complications.

The high incidence of thrombotic events in patients with COVID-19 has already been linked to a series of processes collectively defined as immunothrombosis [1], but the pathogenic mechanisms underlying the possible relationship between thrombosis and predisposition to secondary infections have yet to be fully elucidated. Interestingly, along with the several mechanisms by which SARS-CoV-2 infection may lead to immune dysregulation (among others, T-cell functional exhaustion, inhibition of IFN signaling, and pathogen clearance due to phagocytes) [16], platelet activation during COVID-19 has been suggested to be associated with a state of immunosuppression [27]. It is possible to speculate that patients with a prominent immune activation leading to immunothrombosis may also be prone to paradoxical immunosuppression, leading to a heightened risk of secondary infections. In this context,



**Figure 2.** Cumulative incidence of patients with at least 1 secondary infection.

**Table 2. Multivariable Analysis on the Risk of Secondary Infections in Patients Hospitalized With Coronavirus Disease 19 (COVID-19)**

Characteristics (n = 745)	Subdistribution Hazard Ratio	95% CI		P Value <sup>a</sup>	
Age, per 1 y older	0.993	0.974	1.011	.429	
Sex, male vs female	1.404	0.815	2.417	.221	
No. of comorbidities, per 1-point increase	0.876	0.680	1.128	.305	
ICU admission within 48 h of hospital admission	2.661	1.540	4.598	<b>.001</b>	
PaO <sub>2</sub> /FiO <sub>2</sub>	>200	...	...	Reference	
	<200	1.653	1.008	2.710	<b>.046</b>
	Unknown	0.863	0.417	1.788	.692
Use of biological immunosuppressive drugs, yes vs no	1.141	0.687	1.894	.611	
Cytolysis score, per 1-point increase	1.156	0.944	1.414	.160	
Inflammation score, per 1-point increase	1.488	0.961	2.304	.075	
Coagulation score, per 1-point increase	0.861	0.577	1.283	.461	
Thrombotic complications, yes vs no	1.788	1.018	3.140	<b>.043</b>	

<sup>a</sup>P-value < .05 are reported in bold. Abbreviations: ICU, intensive care unit; PaO<sub>2</sub>/FiO<sub>2</sub>, partial pressure of oxygen in the arterial blood/fraction of inspired oxygen.

more than a risk factor per se, thrombotic events may serve as a proxy of an impaired immune system. The finding of a similar microbial etiology of secondary infections in patients with and without thrombotic events may further support this hypothesis, as gram-positive pathogens (frequently seen in patients with septic thrombosis, especially if catheter-related [28]) were not predominant in patients with thrombosis.

The possible pathophysiological relationship between thrombosis and secondary infections in patients with COVID-19 seems attractive, as intervention aimed at dampening the immune dysregulation typical of SARS-CoV-2 infection may help reduce the incidence of thrombotic events and

infectious complications. To our knowledge, there is a paucity of data regarding the impact of corticosteroids or other immune suppressors on development of thrombotic complications, while secondary infections do not seem to be more frequent in patients receiving these drugs [29]. This somewhat unexpected finding may indeed be related to the favorable impact of immune suppressors on COVID-19-associated immune dysregulation.

This study has some limitations. First, the study had a monocentric retrospective nature. Second, patients were enrolled during the first wave of the pandemic, and the clinical management of patients with COVID-19 changed thereafter with the

widespread use of corticosteroids (and other immunosuppressors) and antithrombotic prophylaxis or treatment. Therefore, the results may not be generalizable to other epidemiological contexts. Third, a systematic assessment of infectious and thrombotic complications was not performed, possibly leading to underestimation of infectious and thrombotic events. Fourth, no data were available regarding the presence of intravascular catheters, which may have influenced the incidence of venous thrombosis. Finally, the main multivariable analysis did not include heparin use as a variable, given the reduced number of patients for whom this information was available; nevertheless, the sensitivity analysis including heparin confirmed the results of the main model.

In our cohort of COVID-19 hospitalized patients, thrombotic complications were associated with a high risk of secondary infections. The etiology of secondary infections was similar among patients with and without thrombotic complications.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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