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Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave

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ABSTRACT

Introduction: In the first wave, thrombotic complications were common in COVID-19 patients. It is unknown whether state-of-the-art treatment has resulted in less thrombotic complications in the second wave.
Methods: We assessed the incidence of thrombotic complications and overall mortality in COVID-19 patients admitted to eight Dutch hospitals between September 1st and November 30th 2020. Follow-up ended at discharge, transfer to another hospital, when they died, or on November 30th 2020, whichever came first. Cumulative incidences were estimated, adjusted for competing risk of death. These were compared to those observed in 579 patients admitted in the first wave, between February 24th and April 26th 2020, by means of Cox regression techniques adjusted for age, sex and weight.
Results: In total 947 patients with COVID-19 were included in this analysis, of whom 358 patients were admitted to the ICU; 144 patients died (15%). The adjusted cumulative incidence of all thrombotic complications after 10, 20 and 30 days was 12% (95% confidence interval (CI) 9.8–15%), 16% (13–19%) and 21% (17–25%), respectively. Patient characteristics between the first and second wave were comparable. The adjusted hazard ratio (HR) for overall mortality in the second wave versus the first wave was 0.53 (95%CI 0.41–0.70). The adjusted HR for any thrombotic complication in the second versus the first wave was 0.89 (95%CI 0.65–1.2).
Conclusions: Mortality was reduced by 47% in the second wave, but the thrombotic complication rate remained high, and comparable to the first wave. Careful attention to provision of adequate thromboprophylaxis is invariably warranted.

1. Introduction

COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may lead to various states of disease, from a mild flu-like illness to very severe pneumonia with profound hypoxemia requiring mechanical ventilation [1]. One of the striking features

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observed in severe COVID-19 is coagulopathy, with associated high incidences of thrombotic complications [2–4]. We and others have reported that the most frequent thrombotic phenotype is pulmonary embolism (PE) as part of venous thromboembolism (VTE), and, to a lesser extent, stroke [5–10]. Both occurred foremost in ventilated patients admitted to the Intensive Care Unit (ICU) and were associated with increased probability of death [6]. Several mechanisms involving hypercoagulability and inflammation interact resulting in thrombotic phenomena both in the microvasculature and in the larger, mostly pulmonary blood vessels [2–4,11].

Before the second wave started to roll over the world, three important developments to counteract COVID-19 and its acute sequelae became apparent. First, in response to the observed very high incidence of thrombotic complications, guidelines were rapidly adjusted to address increased awareness and proper diagnosis of VTE, and adapt dosage of low-molecular-weight heparin (LMWH) thromboprophylaxis in COVID-19 patients [12–15]. Second, remdesivir given to hospitalized patients with COVID-19 was suggested to be superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 [16]. Third, dexamethasone was demonstrated to reduce mortality in critically ill COVID-19 patients [17]. For patients on ventilators, dexamethasone was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was reduced by about one fifth [16].

With these three developments implemented in clinical care in or shortly after the first wave, we hypothesized that the overall prognosis among hospitalized COVID-19 patients would be better in the second wave than in the first, with less thrombotic complications diagnosed and a lower threshold for testing. To test this hypothesis, we evaluated the incidence of thrombotic complications and overall mortality in patients admitted to Dutch hospitals after September 1st 2020 because of COVID-19.

Table 1
Local protocols for thrombosis prophylaxis in participating hospitals for patients admitted to the general ward and intensive care unit in the second wave.

Site	Ward	ICU
Leiden University Medical Center	Nadroparin 2850 IU per day or 5700 IU per day if body weight >100 kg If coagulopathy[a] present: see ICU	Nadroparin 5700 IU per day or 5700 IU twice daily if body weight >100 kg
Erasmus University Medical Center	Nadroparin 5700 IU per day	Nadroparin 5700 IU twice daily
Amphia Hospital	Nadroparin 5700 IU per day or 5700 IU twice daily if body weight >100 kg. If noninvasive ventilation on the ward: see ICU (from 1st of October 2020)	If pulmonary embolism not yet ruled out: therapeutic dose nadroparin adjusted by body weight (86 IU per kg body weight)
Franciscus Gasthuis& Vlietland	Dalteparin 5000 IU per day	Dalteparin 5000 IU twice daily
Radboud University Medical Center	Dalteparin 5000 IU per day or 5000 IU twice daily if body weight >100 kg	Dalteparin 5000 IU per day or 5000 IU twice daily if body weight >100 kg
Maastricht University Medical Center	<70 kg: nadroparin 2850 IU per day 70–90 kg: nadroparin 3800 IU per day >90 kg: nadroparin 5700 IU per day	<70 kg: nadroparin 5700 IU per day 70–90 kg: nadroparin 7600 IU per day >90 kg: nadroparin 5700 IU twice daily
Zaans Medical Center	BMI <30: nadroparin 2850 IU per day BMI >30: nadroparin 5700 IU per day	BMI <30: nadroparin 5700 IU per day BMI >30: nadroparin 5700 IU twice daily
OLVG	<100 kg: nadroparin 5700 IU per day >100 kg: nadroparin 7600 IU per day	<100 kg: nadroparin 5700 IU per day >100 kg: nadroparin 7600 IU per day

Note: IU: international units; kg: kilograms.
[a] Defined as: spontaneous prolongation of the prothrombin time (PT) >3 s and/or activated partial thromboplastin time (APTT) >5 s.

2. Methods

2.1. Setting

In this cohort study we included all adult COVID-19 patients admitted to the wards and ICUs of four university hospitals (Leiden University Medical Center – Leiden, Erasmus Medical Center – Rotterdam, Maastricht University Medical Center – Maastricht, Radboud University Medical Center – Nijmegen) and four non-university teaching hospitals (Amphia Hospital – Breda, Franciscus Gasthuis & Vlietland – Schiedam/Rotterdam, Onze Lieve Vrouw Gasthuis – Amsterdam, Zaans Medical Center – Zaandam), all in the Netherlands, between September 1st and November 30th 2020. COVID-19 was confirmed by a positive polymerase chain reaction (PCR) test or considered positive in patients with a negative PCR but highly suggestive symptoms, typical COVID-19 abnormalities on CT scan of the chest and no alternative diagnosis. All patients received pharmacological thromboprophylaxis, according to local hospital protocols (Table 1). Remdesivir and dexamethasone were given according to Dutch guidance for patients with COVID-19: ward patients with need for supplemental oxygen received remdesivir (a loading dose of 200 mg followed by 100 mg once daily for 5 days) and dexamethasone (6 mg once daily for a maximum of 10 days), ICU patients were not treated with remdesivir [18].

The patient charts from COVID-19 patients were scrutinized for baseline characteristics and outcomes of interest, using a standardized electronic case report form (eCRF). This study was approved by the Institutional Review Board of the LUMC for observational studies and was performed on behalf of Dutch COVID & Thrombosis Coalition [19].

2.2. Objectives and outcomes

Our objectives were to assess: the incidence, timing and characteristics of thrombotic complications in hospitalized patients with COVID-19 in the second wave; how many patients received at least one diagnostic imaging test for thrombotic complications; overall mortality; and the difference between these outcomes and the results from the first wave. We performed subgroup analyses for patients that were admitted to the ICU and those that were not. The observed incidence of thrombotic complications and survival in all hospitalized COVID-19 patients in the second wave were compared to those observed in 579 COVID-19 patients hospitalized in either of three Dutch hospitals (Leiden University Medical Center – Leiden, Alrijne Hospital – Leiderdorp, Amphia Hospital – Breda) in the first wave, between February 24th and April 26th 2020 [20].

The incidence of both VTE and arterial thrombotic complications in all COVID-19 patients admitted to the participating hospitals in the study period were evaluated. Our primary composite outcome consisted of acute PE, deep-vein thrombosis (DVT), ischemic stroke, myocardial infarction and systemic arterial embolism. No VTE screening strategies at admission were applied during this study. In patients with clinically suspected thrombotic complications, appropriate diagnostic tests were applied, i.e. computed tomography pulmonary angiography (CTPA) for suspected PE and compression ultrasonography (CUS) for suspected DVT [21,22], cardiac enzymes including troponin, electrocardiogram and echocardiography for suspected acute coronary syndrome, and CT scan of the brain and CT angiography of the carotid and intracerebral arteries for suspected ischemic stroke. All diagnostic imaging tests performed during hospital admission of the included patients were collected as well, regardless of the outcome, to be able to calculate the proportion of patients with at least one diagnostic imaging test. All outcomes were adjudicated by an independent expert panel, whose members were unaware of the clinical condition of the patient, hospital admitted, and prophylactic LMWH regimen applied.

2.3. Statistical analysis

Patient characteristics were described using standard descriptive statistics. The index date was the moment of admission to the hospital. Follow-

up ended upon discharge, transfer to another hospital, when they died and/or were diagnosed with thrombotic complications (depending on the analysis), or at 30 November 2020 (the end of data collection), whichever came first. Cumulative incidences were estimated using the Kaplan-Meier method and the cumulative incidence competing risk (CICR) method, to adjust for the competing risk of death. The incidence of thrombotic complications was assessed for all patients combined and for patients admitted to the general wards and admitted to the ICU separately. Patients who were admitted to both ward and ICU were included in both analyses and followed in these analyses for the number of days spent on ICU and ward, respectively. Patients who were diagnosed with a thrombotic complication on the ward before admission to the ICU were excluded in the Kaplan-Meier analysis of thrombosis in ICU patients. Adjusted cumulative incidences were calculated for all thrombotic complications as well as for venous and arterial complications separately. To compare the incidence of the outcomes of interest between the first and second wave Cox regression analysis was performed, adjusted for relevant patient characteristics (i.e. age, sex and weight). SPSS Statistics version 25.0 and RStudio version 1.3.1056 served for data analysis.

3. Results

3.1. Patients

Between September 1st and November 30th 2020, a total of 947 patients with COVID-19 were included from the participating hospitals; 860 patients were admitted to the general wards and 358 patients to the ICU; of the latter, 271 patients were admitted to both general ward and ICU. Patient baseline characteristics are presented in Table 2. The mean age was 66 years (SD 13), 603 patients (64%) were male and a total of 127 (13%) patients used (chronic) therapeutic anticoagulation at admission. Patients presented at the hospital after a median of 7 days (IQR 4–10) after COVID-19 symptom onset.

At November 30th 2020, 50 patients (5.3%) were still in the ICU, 31 patients (3.3%) were still on the ward and 639 (67%) had been discharged. A total of 83 patients (8.8%) were transferred to another hospital, after which no information was available. A total of 144 patients (15%) died, 74 during ICU admission and 70 on the general ward. The median number of hospital admission days was 9 days (IQR 4–18), with a median of 6 days (IQR 3–11) on the ward, and 11 days (IQR 4–19) in the ICU. All patients received at least standard dose LMWH thromboprophylaxis at wards and doubled dose LMWH thromboprophylaxis at the ICU, although regimens differed between hospitals (Table 1).

3.2. Thrombotic complications and survival in the second wave

Of the 947 patients, 120 patients (13%) were diagnosed with 124 thrombotic complications (4 patients with both a VTE and ATE). Acute PE was the most often diagnosed thrombotic complication (97/124, 78%). Of the ATEs, the majority was an ischemic stroke (12/20, 60%). The adjusted cumulative incidences of all thrombotic complications after 10, 20 and 30 days were 12% (95%CI 9.8–15), 16% (95%CI 13–19) and 21% (95%CI 17–25), respectively. Thrombotic complications were diagnosed after a median of 4 days after hospital admission (IQR 1–9). A total of 144 patients died (15%) after a median of 14 days (IQR 7–22).

3.3. Thrombotic complications and survival in ward admitted COVID-19 patients in the second wave

Of the 860 ward patients, 73 patients (8.5%) were diagnosed with 75 thrombotic complications; 59 patients were diagnosed with VTE alone, of which 58 patients had a PE, and 12 patients were diagnosed with only an ATE. Two patients were diagnosed with both VTE and ATE (a combination of PE and stroke in one patient, and PE and peripheral arterial embolism in the other patient; Table 3). Of all 14 ATE events, 9 patients had ischemic strokes, 3 patients had a myocardial infarction, 1 patient had a peripheral arterial embolism, and 1 patient had a thrombosis in an endovascular aneurysm repair (EVAR). Of the thrombotic complications, 28/75 (38%) were diagnosed at presentation to the hospital (21 VTEs and 7 ATEs). All other ATEs occurred within 7 days after admission. Of the VTE diagnoses during hospital admission, 34/47 (83%) occurred within 7 days. The cumulative incidence of any thrombotic complication, adjusted for competing risk of death, was 8.6% (95%CI 6.6–11) after 10 days, 11% (95%CI 8.6–15) after 20 days, and 13% (95% CI 9.1–18) after 30 days, respectively. The VTE adjusted cumulative incidences were 7.4% (95%CI 5.6–9.7), 10% (95%CI 7.4–13) and 12% (95%CI 7.9–16) after 10, 20 and 30 days, respectively (Table 4). A total of 70 patients died (8.1%) after a median of 8 days on the ward (IQR 3.8–14).

3.4. Thrombotic complications and survival in ICU admitted COVID-19 patients in the second wave

Of the 358 ICU patients, 48 patients (13%) were diagnosed with 49 thrombotic complications; 42 patients were diagnosed with VTE, of whom 39 had a PE, and 5 patients with an ATE, while 1 patient was diagnosed with both VTE and ATE (a combination of PE and stroke; Table 3). Three of the 6 ATE events were ischemic strokes, 2 patients had a myocardial infarction, and 1 patient had a peripheral arterial embolism. Thrombotic complications were diagnosed after a median of 8 days on the ICU (IQR 3–13). The cumulative incidence of any thrombotic complication, adjusted for competing risk of death, was 13% (95%CI 8.8–17) after 10 days, 21% (95%CI 15–28) after 20 days, and 26% (95%

Table 2
Baseline characteristics of hospitalized COVID-19 patients in the second and first wave.

	Total second wave (*N*=947)[a]	Total first wave (*N*=579)[a]	Ward second wave (*N*=860)	Ward first wave (*n*=485)	ICU second wave (*N*=358)	ICU first wave (*n*=178)
Age (mean, SD)	66 (13)	67 (13)	66 (14)	67 (14)	64 (12)	64 (11)
Male sex (n, %)	603 (64%)	380 (66%)	536 (62%)	305 (63%)	263 (74%)	131 (74%)
Body weight in kg (median, IQR)	83 (74–95)	84 (73–95)	83 (73–95)	83 (73–95)	85 (77–96)	85 (75–95)
BMI (median, IQR)	28 (25–31)	N/A	28 (25–32)	N/A	28 (26–31)	N/A
Active cancer (n, %)[b]	60 (6.3%)	24 (4.1%)	57 (6.6%)	24 (4.9%)	15 (4.2%)	4 (2.2%)
Prior history VTE (n, %)	51 (5.4%)	23 (4.0%)	47 (5.5%)	22 (4.5%)	19 (5.3%)	5 (2.8%)
Therapeutic anticoagulation at admission (n, %)	127 (13%)	77 (13%)	120 (14%)	67 (14)	38 (11%)	22 (12%)
Days of COVID-19 symptoms before admission (median, IQR)	7 (4–10)	N/A	7 (4–10)	N/A	7 (4–10)	N/A
Days of hospital admission (median, IQR)[c]	9 (4–18)	7 (4–11)	6 (3–11)	5 (3–8)	11 (4–19)	11 (6–19)
Start of high-dose dexamethasone at admission (n, %)	845 (89%)	N/A	767 (89%)	N/A	344 (96%)	N/A

Note: SD: standard deviation; IQR: interquartile range; VTE: venous thromboembolism; n: number; ICU: Intensive Care Unit; N/A: not available.

[a] 271 patients had been admitted to both ward and ICU in the second wave; 84 patients had been admitted to both ward and ICU in the first wave.

[b] Defined as a diagnosis of cancer within 6 months before the study inclusion, or receiving treatment for cancer at the time of inclusion or any treatment for cancer during 6 months prior to inclusion, or recurrent locally advanced or metastatic cancer.

[c] For all patients: admission until discharge, transfer to a different hospital, death or end of data collection (30 November 2020), whichever came first. For ICU: admission to ICU until ICU discharge, transfer from ICU, death on ICU or 30 Nov, whichever came first.

Table 3
Thrombotic complications in COVID-19 ward and ICU patients in the second wave.

Type of event	Ward		ICU	
	Number of cases	Relevant details	Number of cases	Relevant details
Pulmonary embolism	58	– 10 in central pulmonary arteries – 29 in segmental arteries – 18 limited to subsegmental arteries – 1 unknown	39	– 5 in central pulmonary arteries – 16 in segmental arteries – 18 limited to subsegmental arteries
Other venous thrombotic complications	3	– 1 deep-vein thrombosis of the leg – 1 upper extremity deep-vein thrombosis (not catheter related) – 1 portal vein thrombosis	4	– 1 deep-vein thrombosis of the leg (catheter related) – 3 upper extremity deep-vein thromboses (of which 1 catheter related)
Arterial thrombotic complications	14	– 9 ischemic strokes – 3 myocardial infarctions – 1 peripheral embolism upper extremity – 1 thrombosis in endovascular aneurysm repair	6	– 3 ischemic strokes – 2 myocardial infarctions – 1 peripheral embolism upper extremity

Table 4
Adjusted[a] cumulative incidences of thrombotic complications in COVID-19 ward and ICU patients in the second wave.

	Total (N=947) n% (95% CI)	Ward (N=860) n% (95% CI)	ICU (N=358) n% (95% CI)
All thromboses			
10 days	12% (9.8–15)	8.6% (6.6–11)	13% (8.8–17)
20 days	16% (13–19)	11% (8.6–15)	21% (15–28)
30 days	21% (17–25)	13% (9.1–18)	26% (19–34)
VTE			
10 days	12% (8.5–13)	7.4% (5.6–9.7)	12% (7.9–16)
20 days	15% (12–18)	10% (7.4–13)	19% (14–26)
30 days	19% (15–23)	12% (7.9–16)	23 (17–30)
ATE			
10 days	2.3% (1.4–3.5)	1.6% (0.87–2.8)	1.6% (0.15–3.7)
20 days	2.5% (1.5–3.9)	1.6% (0.87–2.8)	2.2% (0.80–4.8)
30 days	2.9% (1.7–4.6)	1.6% (0.87–2.8)	3.1% (1.2–6.6)

Note: All thrombotic complications: VTE and ATE combined; VTE: venous thrombotic complications; ATE: arterial thrombotic complications; n: number; CI: confidence interval.
[a] Adjusted: cumulative incidence adjusted for competing risk of death.

Table 5
Adjusted[a] cumulative incidences of thrombotic complications in COVID-19 ward and ICU patients in the first wave[b].

	Total (N=579) n% (95% CI)	Ward (N=485) n% (95% CI)	ICU (N=178) n% (95% CI)
All thromboses			
10 days	12% (8.9–15)	4.6% (2.6–7.6)	23% (17–30)
20 days	24% (18–30)	6.0% (3.0–10)	37% (28–46)
30 days	25% (18–32)	6.0% (3.0–10)	38% (29–47)
VTE			
10 days	11% (7.7–14)	3.1% (1.5–5.8)	22% (16–29)
20 days	21% (16–28)	4.5% (1.9–8.7)	33% (25–42)
30 days	23% (16–29)	4.5% (1.9–8.7)	35% (26–44)
ATE			
10 days	2.2% (1.1–4.1)	1.5% (0.53–3.5)	2.7% (0.87–6.2)
20 days	3.2% (1.4–6.4)	1.5% (0.53–3.5)	3.8% (1.4–8.4)
30 days	4.4% (1.9–8.8)	1.5% (0.53–3.5)	5.6% (2.0–12)

Note: All thrombotic complications: VTE and ATE combined; VTE: venous thrombotic complications; ATE: arterial thrombotic complications; n: number; CI: confidence interval.
[a] Adjusted: cumulative incidence adjusted for competing risk of death.
[b] Numbers of the separate analysis of ward and ICU patients slightly differ from the data published [20], as different separation criteria were applied.

CI 19–34) after 30 days, respectively. The CTPA and/or ultrasonography confirmed VTE adjusted cumulative incidences were 12% (95%CI 7.9–16), 19% (95%CI 14–26) and 23% (95%CI 17–30), respectively (Table 4). A total of 74 patients died (21%) after a median of 16 days on the ICU (IQR 10–23).

Table 6
Cox regression analyses in the second versus the first wave of COVID-19 patients.

		Hazard ratio (95% CI)[a]	
		Crude	Adjusted[b]
Mortality	Total cohort	0.54 (0.42–0.69)	0.53 (0.41–0.70)
	ICU	0.76 (0.52–1.1)	0.80 (0.54–1.2)
	Ward	0.36 (0.25–0.51)	0.41 (0.29–0.59)
All thrombotic complications	Total cohort	0.94 (0.69–1.3)	0.89 (0.65–1.2)
	ICU	0.47 (0.31–0.70)	0.46 (0.30–0.70)
	Ward	2.0 (1.2–3.4)	1.8 (1.1–3.2)
VTE	Total cohort	0.89 (0.64–1.2)	0.86 (0.61–1.2)
	ICU	0.44 (0.29–0.67)	0.44 (0.28–0.68)
	Ward	2.3 (1.3–4.4)	2.2 (1.1–4.1)
ATE	Total cohort	0.98 (0.47–2.1)	0.85 (0.41–1.8)
	ICU	0.52 (0.17–1.7)	0.45 (0.14–1.4)
	Ward	1.3 (0.45–3.6)	1.2 (0.44–3.6)

Note: All thrombotic complications: VTE and ATE combined; VTE: venous thrombotic complications; ATE: arterial thrombotic complications; ICU: intensive Care Unit; n: number; CI: confidence interval.
[a] Second wave relative to first wave.
[b] Adjusted for baseline characteristics: sex, age, weight.

3.5. Comparison of thrombotic complications and survival in the first versus the second wave

The local protocols for thrombosis prophylaxis are shown in Supplementary Table 1. The baseline characteristic of patients in the first and second wave were mostly comparable (Table 2). The incidences of thrombotic complications in the first wave are shown in Table 5, with details about the thrombotic complications in Supplementary Tables 2 and 3. Compared to patients observed in the first wave, the adjusted hazard ratio (HR) for overall mortality in all patients (ward and ICU combined) in the second wave was 0.53 (95%CI 0.41–0.70; Table 6). The adjusted HRs for overall mortality in the ICU and ward patients separately were 0.80 (95%CI 0.54–1.2) and 0.41 (95%CI 0.29–0.59), respectively. Compared to patients in the first wave, the adjusted HR for any thrombotic complications in the second wave was 0.89 (95%CI 0.65–1.2; Table 6). These HRs for any thrombotic complications in the ICU and ward patients separately were 0.46 (95%CI 0.30–0.70) and 1.8 (95%CI 1.1–3.2), respectively. A similar trend in hazard ratios was seen when VTEs and ATEs were analyzed separately, although the difference between ATEs diagnosed on the ward and ICU was less pronounced than in VTEs. In the second wave, VTEs were diagnosed after a median of 4 days (IQR 1–9) after hospital admission in the second wave, versus after a median of 6 days (IQR 3–11) in the first wave (p=0.057).

In the two hospitals that participated in both the first and second wave study (LUMC and Amphia hospital), Cox regression subgroup analysis yielded a HR of 0.62 (95%CI 0.45–0.86) for overall mortality, and a HR of 1.4 (0.90–2.1) for all thrombotic complications in the total cohort. In these two hospitals, 186/473 patients (39%) were subjected to at least 1 CTPA in the second wave, whereas this was 21% (95/460 patients) in the first wave, for a relative risk of 1.9 (95%CI 1.5–2.4). When assessing the PE location, 36 out of 96 (38%) PEs diagnosed in the second wave were limited to subsegmental arteries which was 12/51 (24%) in the first wave, leading to an absolute increase of 14% (95%CI −2.1 to 28).

4. Discussion

In this study, we made important observations. Compared to COVID-19 patients in the first wave, the risk of overall mortality was 47% lower among all patients in the second wave. Second, patients in the second wave had cumulative incidences of thrombotic complications, that were still considerably high and comparable to patients in the first wave, even though patients in the second wave received more advanced COVID-19 therapy as well as higher doses of LMWH as thromboprophylaxis. Of note, the risk of thrombotic complications among all patients was comparable between the first and second wave, while an increased risk of thrombotic complications in ward patients was observed and a decreased risk in ICU patients. The latter is likely due to a lower threshold of early diagnostic testing for thrombotic complications. For instance, PE were diagnosed a median of two days earlier in the second wave, and mostly before patients were transferred to the ICU, rather than upon or after ICU admission, the latter which was the case in the first wave. We have also other explanations for our findings. First, compared to the first wave, the number of diagnostic tests performed was doubled in the second wave. The lack of a lower incidence in the second wave may therefore be partly explained by detection bias. The fact that we observed a 14% increase in the prevalence of pulmonary emboli limited to the subsegmental pulmonary arteries, might even point to overdiagnosis in the second wave, i.e. very small clots of uncertain relevance [23]. An alternative, technical explanation for this increase could be that the CTPA image quality was better in the second wave, with better visualization of subsegmental arteries, because more patients were diagnosed while they were admitted in the ward and not intubated, allowing for scanning during breath-hold [24]. On the other hand, detection and treatment of PEs, even small ones, may also have contributed to the better overall prognosis in the second wave, which is an argument against overdiagnosis. We previously demonstrated that in general, the thrombus load of PE in COVID-19 patients is lower than in non-COVID-19 patients, and the distribution of the PEs is more peripheral [25,26]. Third, most thrombotic events were diagnosed after admittance and not at presentation to the hospital. It is therefore possible that either the doses of LMWH prophylaxis were insufficient to prevent thrombosis, or that the state-of-the-art COVID-19 treatment regimens and in particular high doses of dexamethasone, could have contributed to an increase in thrombotic complications. The latter is well known to occur in patients with Cushing's disease and exogenous cortisol excess [27,28]. Of note, the occurrence of thrombotic complications was not mentioned in the dexamethasone trials published to date [29,30]. Ongoing randomized controlled trials will determine whether higher intensity than standard pharmacotherapeutic thromboprophylaxis regimes will ultimately improve the prognosis of COVID-19 patients by preventing more thrombotic complications without giving too much bleeding. A final explanation could involve a direct SARS-CoV-2-specific procoagulant effect also involving recruitment of the contact system, that is not mitigated by the current COVID-19 targeted treatment regimens, including LMWH that had little impact on contact coagulation activation markers, contributing to local thrombosis in the affected lung segments [11].

Implications of our findings include a continuing need for careful attention to provision of adequate thromboprophylaxis and a low threshold for diagnostic imaging upon clinical suspicion of thrombotic complications. Also, in order to prevent overdiagnosis of PE, we propose to adhere to current recommended diagnostic algorithms applying an assessment of pre-test probability and D-dimer testing and especially algorithms that apply a pre-test probability dependent D-dimer threshold [31]. In this respect, it is interesting that, although D-dimer levels are often increased in COVID-19, a reported 18–56% of the patients had D-dimer values below 1000 ng/mL [31–34]. This stepwise diagnostic approach has been shown to reduce the diagnosis of subsegmental PE without affecting the prognosis of patients with suspected acute PE [35], although admittedly not studied in COVID-19 yet. Importantly, we do not recommend starting therapeutic anticoagulation solely based on high D-dimer levels, as this will lead to considerable overtreatment.

Our study has limitations and strengths. We performed an observational study with participating hospitals having different diagnostic algorithms, thromboprophylactic strategies and patient case mixes. The fact that 17% of patients in the second wave was either transferred to another hospital or still admitted to the hospital at the end of data collection could have introduced bias, as these patients were still at risk for thrombotic complications and death. However, also 23% of the patients in first wave were still admitted to the hospital at the end of data collection, thus making the comparison of mortality and thromboses valid. Finally, as we did not have information about the total number of performed CTPAs in the first wave, we could not calculate the ratio between positive and performed tests and compare this between the two waves, which could have further supported our reasoning. Importantly, the baseline characteristics of the first and second wave were comparable, the study design was identical and data collection was performed in the same way. Further strengths of our study include the large number of patients, the detailed scrutinization of patient charts using a standardized protocol and eCRF, and independent adjudication of endpoints.

In conclusion, we observed a reduced risk for overall mortality, coupled with an unchanged high incidence of thrombotic complications in patients admitted because of COVID-19 in the second wave, compared to the first wave. Careful attention to provision of adequate thromboprophylaxis remains invariably warranted. It remains to be demonstrated by randomized trials whether full dose anticoagulation will lead to lower incidences of thrombotic complications and associated lower mortality, without inducing too much bleeding.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix B. Supplementary data

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