ORIGINAL ARTICLE

Development of post-COVID-19 cardiovascular events: an analysis of clinical features and risk factors from a single hospital retrospective study

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SUMMARY

Cardiovascular complications after a SARS-CoV-2 infection are a phenomenon of relevant scientific interest. The aim of this study was to analyze the onset of post-COVID-19 cardiovascular events in patients hospitalized in a tertiary care center.

This is a retrospective study conducted on patients hospitalized over a period of three months. The patients were older than 18 years of age and had a diagnosis of COVID-19 infection confirmed from a nasopharyngeal swab sample. Anamnestic and clinical-laboratory data were collected. Cardiovascular events at 30 days were defined as follows: arrhythmias, myocardial infarction, myocarditis, and pulmonary embolism. Univariate analysis (Student's t-test or Mann-Whitney U test, as appropriate) and multivariate analysis (multinomial logistic regression) were applied to the data.

A total of 394 patients were included; they were mostly males and had a median age of 65.5 years. Previous cardiovascular disease was present in 14.7% of patients. Oxygen therapy was required for 77.9%, and 53% received

anticoagulant therapy. The overall 30-day mortality was 20.3%. A cardiovascular event developed in 15.7% of the subjects. These were mainly pulmonary embolism (9.4%), followed by arrhythmias (3.3%), myocardial infarction (2.3%), and myocarditis (0.8%). Patients who developed cardiovascular events upon univariate analysis were significantly older, with major comorbidities, a more compromised respiratory situation, and a higher mortality rate. Multivariate analysis revealed independent factors that were significantly associated with the development of cardiovascular events: hypertension, endotracheal intubation, and age older than 75 years.

In patients with COVID-19, the development of a cardiovascular event occurs quite frequently and is mainly seen in elderly subjects with comorbidities (especially hypertension) in the presence of a severe respiratory picture.

Keywords: COVID-19, cardiovascular diseases, SARS-CoV-2.

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■ INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the virus responsible for a specific disease defined as coronavirus disease 2019 (COVID-19), which over the

course of 2020 became a global pandemic. The key pathophysiological element of severe cases of the disease is a pattern of acute respiratory distress syndrome (ARDS) with alveolar lung damage, including alveolar hyaline membranes. Although in most cases COVID-19 symptoms are predominantly pulmonary, there are reports of signs of acute heart failure, arrhythmias, hypotension, tachycardia, and a high number of concomitant events, especially in patients admitted to intensive care unit [1]. The Italian and European Society of Cardiology has recommended caution, as physicians may place less emphasis on cardiological symptoms masked by more obvious respiratory symptoms [2, 3].

To date, the studies performed on the association between cardiovascular diseases and COVID-19 have been retrospective observational analyses, often from single centers. A meta-analysis of six studies including 1,527 patients with COVID-19 reported the rates of hypertension, cardiovascular and cerebrovascular disease, and diabetes to be 17.1%, 16.4%, and 9.7%, respectively [4]. Moreover, patients affected by these comorbidities required admission more frequently to intensive care units. In addition, in an extensive analysis by Wu et al., higher mortality rates were observed in patients with COVID-19 affected by cardiovascular disease (10.5%), diabetes (7.3%), and high blood pressure (6.0%) than in those without these comorbidities (2.3%) [5]. Some initial data on the Italian population seem to confirm the increased risk of mortality in subjects with these co-morbidities [6]. According to studies published to date, it appears that subjects with previous cardiovascular disease and cardiovascular risk factors may have a higher risk of COVID-19 as well as a poorer prognosis [7, 8]. Concerning acute cardiac consequences of COVID-19, one of the first studies conducted in China on 41 patients with COVID-19 showed an increase of cardiac troponin at high sensitivity (>28 pg/ml) in five patients [9]. In another study conducted on 138 patients, 36 had severe symptoms and were treated in intensive care, and an increase in the concentration of cardiac markers of myocyte necrosis was reported (median creatine kinase concentration of 18 U/I compared to 14 U/I) [10]. These data suggest that patients with severe pulmonary symptoms often have complications affecting myocardial tissue [11].

High levels of serum troponin have been described in many patients affected by COVID-19, with significant differences in serum levels between deceased patients and survivors [12]. In a meta-analysis of four studies that included a total of 341 patients, the average cardiac troponin I levels were significantly higher in patients with severe COVID-19 disease than in patients with milder disease [13].

Recent studies have revealed that 19-27% of hospitalized patients with moderate and severe forms of COVID-19 develop acute myocardial damage, represented by an increase in troponin above the 99th percentile of the upper limit of reference (ultra-sensitive troponin I or troponin T) [14, 15]. Among patients with acute myocardial damage, 50-60% died, and in the group of patients with acute myocardial damage, mortality was significantly increased (compared to patients without acute myocardial damage), even among those who did not have a known history of cardiovascular disease [16]. In addition, several cases of acute myocarditis related to COVID-19 have been described [17, 18]. Arrhythmias have been described in numerous cases of patients with COVID-19. For example, the symptom "palpitations" was present as a presenting symptom in 7.3% of a cohort of 137 patients admitted to hospital with a diagnosis of COVID-19 [19]. In another cohort of patients hospitalized in China, cardiac arrhythmias were reported in 16.7% of cases and were much more frequent in patients admitted to intensive care [20]. Venous thromboembolism is another comorbidity to be considered. In fact, since these patients are hospitalized for a long time with the infection, and often in critical conditions, they are at high risk of developing venous thromboembolism [21].

The aim of this study was to analyze the incidence of cardiovascular events in patients hospitalized for SARS-CoV-2 infection.

■ PATIENTS AND METHODS

This was a retrospective, observational cohort study of prospectively collected data conducted in five hospital wards (Infectious Diseases, Pneumology, Intensive Care Unit, Internal Medicine, and Critical Area) of Modena University Hospital (Italy). The study population was adults (≥18 years) with COVID-19 confirmed by polymerase chain reaction (PCR) from a nasopharyngeal swab sample who were admitted to the centers

between February 21, 2020 and May 31, 2020. All consecutive patients hospitalized for COVID-19 pneumonia documented on chest X-ray during the study period were considered eligible. The criterion for hospitalization was the presence of respiratory failure requiring any oxygen support. All subjects who survived had a 30-day follow-up after hospital discharge. Data on baseline signs, symptoms, comorbidities, treatments, outcomes, blood count, and biochemical and cardiac markers were collected. All data, including electrocardiograms (ECGs), were electronically recorded. All patients received standard of care treatment at the time of hospital admission according to the regional COVID-19 guidelines of Emilia Romagna [22]. Azithromycin 500 mg per day, hydroxychloroquine (400 mg × 2 on days 1 and 2 and then 200 mg × 2 from day 3 to day 6), and oxygen support to target an SaO2 reaching at least 90% were part of the standard treatment. Prophylaxis with low-molecular-weight heparin consisted of 4000 U once a day for weight under 100 kg and 6000 U once a day for weight over 100 kg. Based on scientific evidence published during the study period, no patients received darunavir/cobicistat after March 18 [23]. Cardiovascular events were defined as follows:

1) acute myocardial infarction, defined by typical electrocardiographic alterations not previously known and troponin alteration above the 99th percentile of the reference values;
2) new onset of ECG documented arrhythmia, specifically atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia;
3) myocarditis, whose diagnosis was based on clinical and radiological criteria (echocardiogram and/or cardiac MRI) in accordance with European guidelines [24];
4) pulmonary thromboembolism, diagnosed on

the clinical suspicion of the treating physician and always confirmed by computed tomography angiography.

Statistical analyses

Continuous variables were summarized as median and 95% confidence interval. Categorical variables were summarized as absolute and relative frequencies. For descriptive analysis, continuous variables were compared using Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. P-values less than 0.05 were considered statistically significant. Multinomial logistic regression was performed for the analysis of independent risk factors. All the factors that were significant to the descriptive analysis were included. The numerical variables that were significant were categorized on the basis of the median value. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). All procedures performed in the study were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and were approved by the institutional ethical committee.

■ RESULTS

During the observation period, 394 patients were enrolled. Table 1 presents the demographic, anamnestic, and clinical characteristics of the study population. Males accounted for 69.8% of the patients, and the median age was 65.5 years. Comorbidities were present in 35.7% of the patients, with the most represented condition being hypertension (29.4%). A positive clinical history

Table 1 - General characteristics of the study population.

Total Patients: 394												
Anamnestic data		*N/ Median*	*95% CI/%*	*Signs & symptoms*	*N/ Median*	*95% CI/%*	*Chemical parameters*	*Median*	*95% CI*	*Clinical diary*	*N/ Median*	*95% CI/%*
Sex	M	275	69.8	Mean blood pressure	95 mmHg	95-100	Lactates mg/dL	8	7-10	P/F < 250	227	57.6
	F	119	30.2	Temperature	37	37-38	GPT_ALT UI/L	31	28-35	P/F < 150	170	43.1
Age		65.5	63-69	Breathing rate	22	18-23	Creatinine mg/dL	0.81	0.79-0.86	P/F	263	250-270

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Total Patients: 394										
Anamnestic data	*N/ Median*	*95% CI/ %*	*Signs & symptoms*	*N/ Median*	*95% CI/%*	*Chemical parameters*	*Median*	*95% CI*	*Clinical diary*	*N/ Median*	*95% CI/%*
BMI	26.7	26.12-27.78	Dyspnea	209	53	Hemoglobin g/dL	12.30	12.20-12.7	Darunavir	174	44.2
Comorbidity	148	37.6	Cough	113	28.7	White blood cells n/mmc	6190	5880-6920	Immunological therapy	180	45.7
COPD	22	5.6	Conjunctivitis	8	2.0	Platelets 103/mmc	207	193-224	Anakinra	8	2.0
Diabetes	45	11.4	Rhinorrhea	4	1.0	LDH UI/L	50	47-53	Tocilizumab	172	43.7
Hypertension	116	29.4	Pharyngo-dynia	11	2.8	Sodium mEq/L	137	137-138	Anticoagulant therapy (prophylaxis at entry/ already in Tp)	209	53
Previous cardiovascular disease • Ischemic cardiopathy • Atrial fibrillation • Valvular disease • Hearth failure • PE • Other	58 21 17 4 2 2 12	14.7 5.3 4.3 0.5 0.5 0.5 3	Headache	25	6.3	Potassium mEq/L	3.8	3.8-3.9	Oxygen therapy	307	77.9
Chronic renal failure	21	5.3	Purulent sputum	7	1.8	Glycemia mg/dL	92	86-101	NIV	109	27.7
Cancer	14	3.6	Not purulent sputum	15	3.8	PCR mg/dL	6.20	6.10-6.7	Intubation	72	18.3
Other (HIV, hepatitis, rheumatologic diseases, transplantation, psychiatric diseases)	87	22.1	Fatigue	61	15.5	PCT ng/mL	4.35	0.20-8.5	Death Respiratory Cardiovascular Over-infection Other	80 77 1 1 1	20.3 19.5 0.2 0.2 0.2
Hematologic diseases	9	2.3	Hemoptysis	5	1.3	Ferritin ng/mL	543	392-642			
Obesity	41	10.4	Diarrhea	39	9.9	Troponin ng/dL	543	392-641			
Charlson score	1	1-2	Myalgia	17	4.3	BNP ng/dL	69	62-273			
			Chills	17	4.3	SOFA score	2	2–3			
			Tonsillar edema	1	0.3						
			Lympha-denomegaly	1	0.3						
			State of consciousness (altered)	10	2.5						

for cardiovascular events was noted in 14.7% of the patients. The median Charlson score was 1. In terms of signs and symptoms, 53% of the patients had dyspnea, and 28.7% had a cough. The median respiratory rate was 22 respirations per minute (other details in Table 1). Biohumoral results are presented in Table 1. The median SOFA score was 2 (more details in Table 1). Regarding COVID-19 therapies, 44.2% of the patients had therapy with darunavir/cobicistat. One-hundred and eighty (45.7%) patients underwent immuno-

logical therapy; 172 (43.7%) received tocilizumab and eight (2%) received anakinra. Two-hundred and nine (53%) of the patients received prophylactic anticoagulant therapy; there were patients who were already being treated for previous diseases. Oxygen support was required for 77.9% of the patients; 27.7% underwent non-invasive ventilation (NIV), and 18.3% underwent endotracheal intubation. Overall mortality at 30 days was 20.3% (80 patients, 77 of whom died of respiratory causes).

During the follow-up after COVID-19, 62 patients (15.7%) developed a cardiovascular event: 13 patients (3.3%) had an arrhythmia, three patients (0.8%) had myocarditis, nine patients (2.3%) had an acute myocardial infarction, and 37 patients (9.4%) had a pulmonary thromboembolism (Table 2).

The 62 patients with cardiovascular events (Table 3) were older (72.5 years vs 63, P<0.001) and more frequently had chronic obstructive pulmonary disease (COPD) (P=0.006), diabetes (P=0.034), hyper-

Table 2 - Development of cardiovascular events

	No.	%
Total cardiovascular events	62	15.7
Arrhythmias	13	3.3
Myocardial infarction	9	2.3
Myocarditis	3	0.8
Pulmonary embolism	37	9.4

Table 3 - Univariate analysis between patients who developed cardiovascular events and patients who did not.

Value	*Patients with cardiovascular event development (N=62)*		*Patients with no cardiovascular event development (N=332)*		*P-Value*
	Median/N	*IQR/%*	*Median/N*	*IQR/%*	
Anamnestic data					
Sex	42	67.7	233	70.2	0.701
Age	72.5	67-75	63	61-67	**<0.001**
BMI	26.12	25.47-31.14	26.99	26.23-27.78	0.346
Comorbidities	31	50	117	35.2	0.08
COPD	8	12.9	14	4.2	**0.006**
Diabetes	11	17.7	34	10.2	**0.034**
Hypertension	33	53.2	83	25	**<0.001**
Previous cardiovascular disease • Ischemic cardiopathy • Atrial fibrillation • Valvular disease • Hearth failure • PE • Other	19 8 7 1 1 1 1	30.6	39 13 10 3 1 1 11	11.7	**<0.001**
Chronic renal injury	8	12.9	13	3.9	**0.004**
Neoplastic disease	4	6.3	10	3.0	**0.017**
Others	16	25.8	71	21.4	0.441
Hematological disease	1	1.6	8	2.4	64
Obesity	10	16.1	31	9.3	0.071
Charlson score	2	1-3	1	1-2	0.299

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Value	Patients with cardiovascular event development (N=62)		Patients with no cardiovascular event development (N=332)		P-Value
	Median/N	IQR/%	Median/N	IQR/%	
Signs & symptoms					
Mean blood pressure	95	90-105	95	95-100	0.432
Temperature	37	37-38	37	37-38	0.110
Breathing rate	23	20-26	22	22-25	0.394
Dyspnea	40	64.5	169	50.9	**0.049**
Cough	17	27.4	96	28.9	0.268
Conjunctivitis	1	1.6	7	2.1	0.254
Rhinorrhea	0	0.0	4	1.2	0.173
Pharyngodynia	2	3.2	9	2.7	0.235
Headache	2	3.2	23	6.9	0.103
Purulent sputum	1	11.6	6	1.8	0.229
Not purulent sputum	4	6.5	11	3.3	0.163
Fatigue	12	19.4	49	14.8	0.164
Hemoptysis	0	0.0	5	1.5	0.142
Diarrhea	5	8.1	34	10.2	0.179
Myalgia	3	4.8	14	4.2	0.235
Chills	1	1.6	16	4.8	0.095
Tonsillar edema	0	0.0	1	0.3	0.165
Lymphadenomegaly	0	0.0	1	0.3	0.165
State of consciousness (altered)	5	8.1	5	1.5	**0.003**
Clinical diary					
P/F <250 mmHg	42	67.7	185	55.7	0.079
P/F <150 mmHg	36	58.1	133	40.1	**0.009**
P/F Value	176	97-263	266	256-275	**<0.001**
Darunavir	19	30.6	155	46.7	**0.020**
Immunological therapy	33	53.2	147	44.3	0.194
Anakinra	2	3.2	6	1.8	
Tocilizumab	31	50.0	141	42.5	
Anticoagulant therapy (prophylaxis at entry/already on Tp)	36	58.1	173	52.1	0.388
Oxygen therapy	49	79.0	258	77.7	0.818
NIV	28	45.2	81	24.4	**<0.001**
Intubation	22	35.5	50	15.1	**<0.001**
Death • Respiratory • Cardiovascular • Over-infection • Other	28 27 1 0 0	45.2 96.4 3.6 0.0 0.0	52 50 0 1 1	15.7 96.2 0.0 1.9 1.9	*<0.001*

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Value	Patients with cardiovascular event development (N=62)		Patients with no cardiovascular event development (N=332)		P-Value
	Median/N	IQR/%	Median/N	IQR/%	
Chemical parameters					
Lactates mg/dL	12	11-18	7	6-9	**0.015**
GPT_ALT UI/L	36	26-42	30	26-34	0.695
Creatinine mg/dL	0.87	0.77-0.83	0.8	0.77-0.83	0.124
Hemoglobin g/dL	11.5	10.7-12.7	12.3	12.2-12.7	**0.027**
White blood cells n/mmc	7250	5600-8130	6155	5800-6910	0.819
Platelets 10^3/mmc	214	179-287	203	189-224	0.126
LDH UI/L	42	38-64	51	49-54	0.533
Sodium mEq/L	138	137-140	137	137-138	0.288
Potassium mEq/L	3.9	3.7-4.1	3.8	3.8-3.9	0.215
Glycemia mg/dL	100	86-108	91	86-101	0.870
PCR mg/dL	6.60	6.1-7.6	6.10	5.8-6.5	**0.033**
Ferritin ng/mL	142.5	69-207	579	434-848	0.130
Troponin ng/dL	31	12-35	12	12-30	**0.042**
BNP ng/dL	273	259-508	36	29-92	**0.003**
SOFA score	5	4-7	2	2-3	**<0.001**

Table 4 - Multivariate analysis (logistic regression): independent factors associated with cardiovascular event development.

Factor	OR	95% CI	P–value
Sex	0.684	0.334-1.401	0.299
COPD	1.072	1.072-3.045	0.907
Hypertension	2.228	1.005-4.940	**0.048**
Diabetes	0.603	0.231-1.574	0.301
Previous cardiovascular disease	1.852	0.697-4.923	0.217
Renal chronic failure	1.334	0.391-4.545	0.645
Neoplastic disease	1.075	0.242-4.774	0.924
Dyspnea	1.143	0.516-2.529	0.742
State of consciousness	0.308	0.067-1.421	0.131
P/F <150 mmHg	0.826	0.349-1.958	0.665
Darunavir	0.501	0.249-1.008	0.053
NIV	1.238	0.569-2.693	0.591
Intubation	4.936	2.178-11.190	**<0.001**
Age >75y	2.032	1.014-4.075	**0.046**
SOFA score >2	1.638	0.805-3.333	0.173
Lactate >12 mg/dl	1.310	0.565-3.039	0.530
Hemoglobin >12 gr/dl	1.042	0.545-1.991	0.901
PCR >5 mg/dl	1.223	0.588-2.542	0.173

tension (P<0.001), chronic renal disease (P=0.004), and cancer (P=0.017). In terms of symptoms, patients who developed a cardiovascular event had significantly more dyspnea (64.5% vs 50.9%, P=0.049) and more often had an altered state of consciousness (8.1% vs 1.5%, P=0.003). Concerning treatments for patients with a cardiovascular event, fewer received darunavir/cobicistat therapy (30.6% vs 46.7%, P=0.020), and more underwent NIV (45.2% vs 24.4%, P<0.001) and endotracheal intubation (35.5% vs 15.1%, P=0.001). Mortality was higher in the group of patients who developed a cardiovascular event (45.2% vs 15.7%, P<0.001), but there were no significant differences in the cause of death. Concerning laboratory parameters, the two groups showed significant differences in the values of lactates (P=0.015), haemoglobin (P=0.027), PCR (P=0.033), troponin (P=0.042), and brain natriuretic peptide (BNP) (P=0.003). The median SOFA score was significantly worse in the group with cardiovascular events (5 vs 2, P<0.001). Multivariate analysis factors independently associated with the onset of cardiovascular events were hypertension (OR 2.228, P=0.048), endotracheal intubation (OR 4.936, P<0.001), and age over 75 years (OR 2.032, P=0.046).

◼ DISCUSSION

In this work, we observed an incidence of a cardiovascular event occurring 30 days after hospitalization of 15.7%. They were especially common in elderly patients with comorbidities and a more compromised clinical respiratory condition. The demographic and clinical presentations of the patients are comparable to those reported in other studies [25]. More than half of the patients had a very compromised respiratory situation, defined by a P/F ratio <250. This is probably due to the fact that the patients had a high median age and that the study population included patients who were hospitalized in intensive care wards. Interestingly, 44% of the patients were treated with darunavir/cobicistat. These were the first patients with COVID-19 treated in our hospital when data on the lack of efficacy of protease inhibitors had not yet been published [26]. Almost half of the patients underwent immunological therapy with tocilizumab. This is because our hospital, and in particular the Infectious Diseases Center, led the tocilizumab in patients with Severe CO-

VID-19 Pneumonia Study (TESEO) on the use of tocilizumab in the treatment of COVID-19, which showed good results in terms of survival, especially in patients with a compromised respiratory situation [27]. The observed mortality rate at 30 days was 20%. This result is substantially in line with what reported in the literature, considering a recent analysis of in-hospital mortality rates that varied in relation to several factors, such as comorbidity, severity of the clinical setting, and need for endotracheal intubation [28].

With regard to the rationale behind the relationship between viral infection and cardiovascular complications, the American College of Cardiology referred to what is known about influenza. Experts agree that influenza increases risks in people with past cardiovascular disease (coronary heart disease or heart failure) and those at risk of cardiovascular events (diabetics, obese, and hypertensive individuals) [29]. This is mainly for three reasons: the severe inflammatory response that occurs following infection, with a consequent increase in acute coronary syndromes; myocardial depression/myocarditis, resulting in heart failure; and the risk of arrhythmia, which is probably associated with acute inflammation.

In this study, the development of cardiovascular events 30 days after hospitalization occurred in approximately 15% of the patients. It should be noted that this prevalence is lower than what is reported in the literature. For example, a recent meta-analysis observed an incidence of acute cardiac damage of 25%, while myocardial infarction occurred in 2.5% of the patients in the present study [30]. Different countries have adopted different strategies, both in terms of hospitalization criteria and in testing for COVID-19. These factors may be responsible for selection bias and may have influenced the estimates of the impact of the virus on populations, both in terms of lethality and in the characteristics of the examined populations. It is therefore likely that the incidence of cardiac manifestations may be high in patients with COVID-19. This may be understood to be not only about the risk of plaque instability linked to inflammation but also in terms of hypoxemia, potentially leading to a mismatch between supply and demand with the development of type II myocardial infarction, especially in the context of severe infection and ARDS. Furthermore, the severe inflammatory response and hemodynamic

changes occurring during severe forms of COVID-19 could contribute to the instability of atherosclerotic plaques in predisposed individuals and thus to the development of acute coronary syndromes (type I myocardial infarction) [31].

Arrhythmias occurred in 3.3% of the patients in this study, which is once again a lower percentage than what is reported in the literature, where the percentages vary between 7.5% and 16.7% [32, 33]. In all the studies mentioned, there does not seem to be a direct correlation between COVID-19 and cardiac arrhythmias; it seems to occur mainly due to systemic illness. However, it is relevant in the interpretation of the arrhythmia data that almost all of the patients in this study were treated with a combination of azithromycin plus hydroxychloroquine. These drugs are known to expose the patient to a risk of potentially fatal ventricular arrhythmias due to QT elongation [34]. With regard to the onset of myocarditis as a complication or as a clinical manifestation of infection with SARS-CoV-2, the literature is mainly based on case reports, and the data present many biases in relation to the difficult diagnosis and symptomatology, which is not easily distinguishable from the others typical of COVID-19 [35]. The onset of pulmonary thromboembolism or arterial and venous embolism in general has been widely reported in the literature, with data ranging from 7.7% to 14.7% to 23.4%; this phenomenon is in relation to the admission department and the intensity of care [36-38]. The higher incidence of pulmonary embolism in the most critical patients is a fact already highlighted in the literature that has been confirmed by this study. Pulmonary embolism in COVID-19 patients is probably related to higher procoagulant activity linked to the increased state of inflammation [39, 40].

Overall, the development of cardiovascular events observed in this study is generally lower than what is reported in the literature. This is probably related to the high percentage of patients in this study (more than half) undergoing anticoagulant prophylaxis immediately after hospitalization. At the present time, scientific evidence suggests prophylaxis against thromboembolism with anticoagulants for all patients hospitalized with COVID-19 [41].

Patients who developed a cardiovascular event had a history of major comorbidities, in particular COPD, diabetes, renal failure, previous cardiovascular events, and neoplastic diseases. These data seem to be consistent with what we already know about the general population in which the cardiovascular risk is higher in people with co-morbidities [42-44]. The onset of an additional stressful element such as COVID-19, with its cytokine storm and state of hypercoagulability, may have favored the development of a cardiovascular event in those subjects with a favorable substrate, which is represented by the known risk factors. To support this argument in our work, the patients who developed a cardiovascular event had a poorer basal respiratory situation, represented by a low P/F ratio, increased use of NIV, and orotracheal intubation. Significantly more patients who developed a cardiovascular event died. The causes of death did not vary between the two groups, so the higher mortality in the cardiovascular group is probably due to the higher number of comorbidities and severity of COVID-19. It is known from the literature that underlying diseases are a risk factor for a severe trend of COVID-19 [45].

Apparently, fewer patients who developed a cardiovascular event received darunavir. This data is affected by a possible bias; in fact, as highlighted in the methods section, patients did not receive darunavir after March 18 due to a change in the therapeutic protocol. It is known that darunavir/cobicistat has many pharmacological interactions, some of which can have a positive or negative impact on the development of cardiovascular events, especially arrhythmias [46]. Independently associated risk factors in the cardiovascular group were hypertension, advanced age, and endotracheal intubation. Age and hypertension have been extensively studied in the literature as cardiovascular risk factors [47, 48]. Intubation is also an independent risk factor. We know that in the general population, cardiovascular risk is increased in elderly patients with hypertension who are intubated for surgery and that this risk is increased especially in the first days after intubation [49]. In our opinion, orotracheal intubation is a proxy for the severity of SARS-CoV-2 disease, and, as already widely demonstrated, the most critical COVID-19 patients are at greater risk of mortality and severe events, including the development of cardiovascular events [50]. Thus, patients who developed a cardiovascular event were those who had greater respiratory and functional involvement.

One important limitation of this study is that it is a retrospective study. Also, the analysis of the development of cardiovascular events was limited to 30 days due to lack of follow-up data. Another limitation is that cardiogenic shock, heart failure, and newly diagnosed valvulopathy were not considered among cardiovascular events.

In conclusion, we observed that post-COVID-19 cardiovascular complications are more frequent in elderly patients with hypertension and with more severe courses of COVID-19, as represented by the need for orotracheal intubation. The state of hyperinflammation and increased coagulation seems to favor the development of cardiovascular events in subjects already predisposed due to age and co-morbidity.

Ethics approval and consent to participate
The study was reviewed and approved by the University of Modena e Reggio Emilia local institutional Ethical Committee (Comitato Etico Provinciale di Modena). The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All involved persons gave their informed verbal witnessed consent. Data were collected anonymously.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Cuomo G participated in data collection, performed the statistical analysis, and wrote the manuscript. Puzzolante C and Iadisernia V participated in the design of the study and the database application and helped draft the manuscript. Santoro A, Menozzi M, Carli F, Digaetano M, Orlando G, Franceschini E, Bedini A, Meschiari M, Manzini L, Corradi L, Milic J, Borghi V, Brugioni L, Pietrangelo A, Clini E, and Girardis M participated in data collection and patient recruitment. Guaraldi G and Mussini C were substantial contributors to the conception and design of the study, interpretation of data, critical revision of the manuscript, and final approval of the version to be published. All authors read and approved the final manuscript.

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