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What is the impact of previous cerebrovascular disease on critical COVID-19 patients' mortality? A prospective cohort study

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ABSTRACT

Objectives: We aimed to evaluate the effect of previous cerebrovascular disease (CVD) on mortality rates of critically ill COVID-19 patients.
Materials & methods: A prospective cohort study was performed between May/2020 and May/2021, at a tertiary-care-center. We consecutively included adult patients admitted to intensive care units (ICU) having as primary diagnosis Acute Respiratory Distress Syndrome due to SARS-CoV-2, requiring invasive mechanical ventilation for >48 h. We considered as exposure the diagnosis of previous CVD and as main outcome the in-ICU mortality.
Results: The study sample included 178 patients: 74.2% were males, with a mean age of 63 ± 12.4 years-old(yo). Previous CVD was documented in 17 patients (9.6%). During the study period, the mortality rate at ICU was of 33.1% ($n = 59$). The proportion of mortality at ICU was higher in patients with prior CVD (58.8% vs 30.4%; $p = 0.02$). Also, older patients (66 ± 11.4 yo vs. 62 ± 12.7 yo, $p = 0.04$) and those with higher score at SAPSII at ICU admission (47.8 ± 15.4 vs. 40.7 ± 15.9; $p = 0.01$) had a higher ICU deathrate. Patients with previous CVD had a 2.70 (95%CI = 1.36–5.39) higher likelihood of dying compared to those who had no previous CVD. After adjustment (for gender, age, SAPSII and total length of stay), multivariate Cox analysis revealed that previous CVD remained a strong predictor for in-ICU death in critically ill COVID-19 patients (*HR = 2.51; 95%CI = 1.15–5.51*).
Conclusions: Previous CVD was significantly associated to higher mortality in critical COVID-19 patients. We suggest that, in patients with previous CVD, prioritization of vaccination strategies should be implemented alongst with higher surveillance when infected with SARS-CoV-2.

1. Introduction

COVID-19 firstly emerged in December 2019, with a report of severe flu-like-illness in China [1]. After the disease spread to over 110 countries, a global pandemic was declared on March 2020 and as of that date the number of cases has been increasing daily, posing a severe health threat at a global scale [2]. After almost two years, this novel disease has provoked over 5 million deaths [3].

Most infected patients are asymptomatic or paucisymptomatic. Nevertheless, up to 15% have severe disease and around 5% became critically ill requiring ventilatory support [4].

Part of the biomedical research has focused on identifying risk factors associated with greater severity or higher mortality in COVID-19 patients, in order to improve preventive and therapeutic strategies. Demographic factors, such as age and gender, as well as comorbidities, such as diabetes, obesity, and cardiovascular diseases, were repeatedly associated with higher mortality [5]. Regarding the association between previous cerebrovascular disease (CVD) and mortality due to COVID-19, most studies have found a positive association [6–8]. Nevertheless, prior studies included both ambulatory and hospitalized patients, and thus were not directed to critically ill COVID-19 patients.

As so, we aimed to access the impact of previous CVD on the

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mortality rates of critically ill COVID-19 patients.

2. Materials and methods

2.1. Study design and definitions

Prospective cohort study including patients admitted to Intensive Care Units (ICU) of an Intensive Care Medicine Department of a tertiary-care center in Portugal, from May 2020 to May 2021. The sample recruitment methodology was systematic, with consecutive inclusion of all eligible patients.

Inclusion criteria encompassed the diagnosis of Acute Respiratory Distress Syndrome (ARDS) due to SARS-CoV-2 requiring ICU admission and invasive mechanical ventilation for >48 h, and age > 18 years-old (yo).

The study was approved by our institutional review board and performed in accordance with Helsinki declaration.

A COVID-19 case was assumed when a positive result on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens was depicted before ICU admission.

ARDS was defined as an acute syndrome of lung inflammation and increased alveolar-capillary permeability associated with severe hypoxia and bilateral infiltrates on chest radiographs, with no evidence of left heart failure, in line with the Berlin definition [9].

Invasive mechanical ventilation (IMV) was defined as a form of artificial ventilation that included an endotracheal tube (ETT) and a mechanical ventilator [10].

We included under the label "previous CVD" any past cerebral infarction (ischemic strokes and silent infarctions), transient ischemic attacks and intracerebral hemorrhages (stroke and silent intracerebral hemorrhages), in accordance with the American Heart Association/American Stroke Association definitions [11,12].

The cause of death was determined using a pre-specified set of syndromes defined a priori, based on the review of the existing literature [13]. COVID-19 related multiple organ dysfunction syndrome (MODS) was defined as the dysfunction of two or more systems/organs, including pulmonary, hematologic, cardiac, neurological, renal, hepatic, and gastrointestinal, that were not existent before SARS-CoV-2 infection [14]. ICU-acquired infections were defined according to confirmed microbiological assessment or strong clinical suspicion without microbiological assessment. Indeed, we have considered secondary infection as a cause of death according to (1) the existence of a secondary infection, and (2) a compatible clinical course with clinical deterioration occurring after a transient improvement following admission [13]. Refractory hypoxemia was identified in case of a PaO2 < 60 mmHg for >1 h while receiving a FiO2 of 1.0 that led to intractable hypoxemia and/or hypercapnia [15]. Fatal mesenteric or limb ischemia, fatal myocardial infarction, pulmonary embolism leading to cardiac arrest and major strokes accounted for fatal thromboembolic events [13].

2.2. Data collection methods

The main investigator was responsible for the assessment of electronic clinical records (ECR) of included patients. Previous CVD was considered in the presence of confirmed clinical and/or neuroimagiological (including computed tomography and magnetic resonance imaging, reported by senior neuroradiologists of our center) findings. Data from selected patients were gathered on an anonymized electronic database and each patient received a unique code number to secure their anonymity.

2.3. Predictive variables and outcomes

Mortality at ICU was the main outcome. Data regarding the severity of the disease (including number of days at ICU and total length of stay; number of days under IMV, extracorporeal membrane oxygenation (ECMO), renal replacement therapy and vasopressor support) were also evaluated. The predictive variables were the following: age, gender, previous functional status assessed through the modified Ranking scale (mRS), comorbidities (including hypertension, diabetes *mellitus,* hyperlipidemia, obesity, smoking habits, atrial fibrillation, ischemic heart disease, heart failure, peripheral vascular disease, chronic pulmonary obstructive disease (CPOD), asthma, sleep apnea, chronic kidney disease, psychiatric pathology, oncologic pathology and immunosuppression [6,16]), previous cerebrovascular disease (type) and a severity score at ICU admission (the *Simplified Acute Physiology Score* (SAPS) II).

2.4. Sample size calculation and Statistical analysis

Due to lack of data on the effect of previous CVD on mortality in critical COVID-19 patients, we used data from a population-based cohort [6]. Considering an expected prevalence on the unexposed patients of 0.10, a relative risk of 3, a power of 80% and a level of significance of 0.05, we estimated that a total sample size of 118 patients would be required.

Statistical analysis was performed using SPSS program version 27 (IBM® Corporation, Armonk, NY). Categorical variables are summarized as frequencies and percentages, and continuous variables as mean and standard deviation (variables with normal distributions). Normal distribution was checked using histogram visual inspection. Chi-square test or Fisher's exact test were used, as appropriate, to compare categorical variables. Continuous variables were compared between groups using independent samples *t*-test. For the time-to-event analyses regarding the main outcome (mortality), cumulative incidence of event curves was estimated for each group (previous CVD versus no previous CVD). They were considered separately by using the Kaplan-Meier method and were compared statistically by using the log-rank test. We fitted a multivariable Cox proportional regression model, with the time unit being the number of ICU days until death. The model was adjusted for all covariates with a significant association with the dependent variable using the Backward-Wald methodology (cut-off for entry = 0.05; cut-off for exclusion = 0.10). All reported *p*-values are two-tailed, with a p-value <0.05 indicating statistical significance.

3. Results

The study sample consisted of 178 eligible patients admitted to the ICU during the study period, with a mean age of 63 ± 12.4 years-old (yo), 74.2% were men. Cases with previous CVD were 17 (9.6%), mostly ischemic strokes (47.1%), followed by transient ischemic attacks (23.5%), silent (17.6) and hemorrhagic (11.8%) strokes. Sociodemographic data, comorbidities and characteristics regarding critical respiratory illness, with a comparative analysis between cases with and without previous CVD, are summarized in Table 1.

Patients with previous CVD were more frequently dyslipidemic and had more often a history of ischemic heart disease. Patients with previous CVD had higher SAPS II at ICU admission; nevertheless, no significant differences were found regarding other parameters used as metrics of the severity of critical illness, as the number of days at the ICU and the total length of stay, number of days under IMV, ECMO, renal replacement therapy and vasopressor support.

During the study period, the mortality rate at the ICU was of 33% ($n = 59$). ICU deathrates at 30 and 90 days were 64.4% ($n = 38$), and 84.7% ($n = 50$), respectively. After ICU discharge, there were 2 additional deaths (one on the first 90 days, and another on the first 180 days).

A total of 58.8% ($n = 10$) of cases with previous CVD died during ICU stay, compared to 30.4% ($n = 49$) of the patients without previous CVD (p-value = 0.018). The median time to death was 25 days for patients with previous CVD and 116 days for patients without this comorbidity.

Causes of in-ICU death of the sample were the following: COVID-19 MODS ($n = 26$, 44.1%), ICU acquired infections ($n = 20$, 33.9%),

Table 1
Sociodemographic, comorbidities and characteristics regarding the critical illness of the sample.

Characteristic	Total cohort (n = 178)	No previous CVD (n = 161)	Previous CVD (n = 17)	p-value
Sociodemographic characteristics				
Male gender, n(%)	132 (74.2)	117 (72.7)	15 (88.2)	0.25
Age, mean (SD)	63.1 (12.4)	62.7 (12.5)	67.8 (10.6)	0.11
mRS, n(%)				0.18
0	176 (98.9)	160 (99.4)	16 (94.1)	
1	0 (0)	0 (0)	0 (0)	
2	2 (1.1)	1 (0.6)	1 (5.9)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	
Comorbidities				
Hypertension, n(%)	108 (60.7)	96 (59.6)	12 (70.6)	0.38
Diabetes *Mellitus*, n(%)	69 (38.8)	59 (36.6)	10 (58.8)	0.07
Hyperlipidemia, n(%)	89 (50.0)	76 (47.2)	13 (76.5)	0.02
Obesity, n(%)	78 (43.8)	73 (45.3)	5 (29.4)	0.21
Smoking habits, n(%)	6 (3.4)	6 (3.7)	0 (0.0)	1.00
Atrial fibrillation, n(%)	13 (7.3)	13 (8.1)	0 (0.0)	0.62
Ischemic heart disease, n(%)	12 (6.7)	8 (5.0)	4 (23.5)	<0.01
Heart failure, n(%)	10 (5.6)	8 (5.0)	2 (11.8)	0.25
Peripheral vascular disease, n(%)	19 (10.7)	17 (10.6)	2 (11.8)	1.00
CPOD, n(%)	7 (3.9)	7 (4.3)	0 (0.0)	1.00
Asthma, n(%)	10 (5.6)	9 (5.6)	1 (5.9)	1.00
Sleep apnea, n(%)	20 (11.2)	18 (11.2)	2 (11.8)	1.00
Chronic kidney disease, n (%)	12 (6.7)	9 (5.6)	3 (17.6)	0.09
Psychiatric pathology, n(%)	28 (15.7)	27 (16.8)	1 (5.9)	0.48
Oncologic pathology, n(%)	20 (11.2)	18 (11.2)	2 (11.8)	1.00
Immunosuppression, n(%)	13 (7.3)	12 (7.5)	1 (5.9)	1.00
>3 comorbidities[a], n (%)	104 (58.4)	12 (70.6)	92 (57.1)	0.29
Characteristics regarding critical respiratory illness				
SAPS II, mean (SD)	43.0 (16.0)	41.4 (14.7)	58.6 (20.7)	<0.01
ICU length of stay (days), median (IQR)	28.5 (199)	30 (199)	19 (100)	0.17
Hospital length of stay (days), median (IQR)	42 (309)	43 (260)	33 (306)	0.23
Number of days under IMV, median (IQR)	20 (197)	20 (197)	19 (101)	0.21
Number of days under vasopressors, median (IQR)	5 (130)	5 (130)	3 (38)	0.56
Number of days under ECMO support, median (IQR)	51 (193)	53 (193)	22 (81)	0.79
Number of days under renal replacement therapy, median (IQR)	21 (71)	22 (71)	13 (31)	0.87

Legend: CVD = Cerebrovascular disease; CPOD = Chronic pulmonary obstructive disease; ECMO = extracorporeal membrane oxygenation; mRS = modified Rankin scale; n = number of patients; SD = Standard deviation.
[a] Including all aforementioned comorbidities.

refractory hypoxemia ($n = 11$, 18.6%) and fatal thrombotic events (n = 2, 3.4%). No significative differences were found regarding the causes of death between patients with and without previous CVD. COVID-19 MODS was the cause of death in 23 patients without previous CVD (46.9%) and in 3 patients with previous CVD (30%; p-value = 0.08). A total of 16 patients without previous CVD (32.7%) and 4 patients with previous CVD (40%) died from ICU acquired infections (p-value = 0.27). Refractory hypoxemia was responsible for 9 deaths (18.4%) in the group of patients without previous CVD and for 2 deaths (20%) in the group with previous CVD (p-value = 0.60). The remaining cases (2 patients without previous CVD and 1 patient with previous CVD) died from fatal thrombotic events (p-value = 0.31).

Regarding the two patients that died after ICU discharge, none had previous CVD; in one patient, the cause of death was a fatal thrombotic event whereas in the other patient cause was death was not captured (out-hospital death).

Having a previous CVD was associated with an increased likelihood of dying in the ICU of 2.70 (95% Confidence interval (95%CI) 1.36–5.39) – Fig. 1A, compared to critically ill COVID-19 patients without this comorbidity.

We also found that older age (66 ± 11.4 yo vs. 62 ± 12.7 yo, p-value = 0.04) and higher Simplified Acute Physiology Score (SAPS) II at admission (47.8 ± 15.4 vs. 40.7 ± 15.9; p-value = 0.007) were associated with higher mortality (Table 2). Additionally, patients that survived ICU had a significantly higher ICU (34 (199) vs 18 (194); p-value = 0.02) and total length of stay (49 (309) vs. 23 (201); $p < 0.01$) (Table 2).

Using multivariate survival Cox analysis to adjust for the effect of gender (male gender; HR = 2.59; 95%CI = 1.12–5.97; p-value = 0.026), age (HR = 1.02; 95%CI = 0.93–1.04; p-value = 0.165), SAPS II at admission (HR = 0.99; 95%CI 0.98–1.01; p-value = 0.568) and total length of stay (HR = 0.95; 95%CI = 0.93–0.96; p-value<0.01), previous CVD remained independently associated with an increased risk of death in critically ill COVID-19 patients (HR = 2.51; 95%CI = 1.15–5.51; p-value = 0.021) – Fig. 1B.

In order to address specifically the impact of CVD on in-ICU mortality, we have also performed a subanalysis to access if patients without previous CVD that presented a similar level of ischemic disease (previous ischemic heart disease) also had higher mortality rates. Indeed, in our sample, the presence of ischemic heart disease was not significantly associated with a higher ICU deathrate (41.7% vs 32.5% p-value = 0.54).

4. Discussion

Our study revealed that, amongst critically ill COVID-19 patients, having previous CVD more than doubled the risk of death during ICU stay, irrespective of age, gender, severity of disease at ICU admission (SAPS II score) and total length of stay. The positive association of CVD with COVID-19 mortality has been previously described in some studies [6–8], but not unanimously [17]. Indeed, patients with previous CVD, possibly due to weaker immune functions (namely post stroke immunosuppression) and poorer organ functions, are thought to have higher risk of severe infections and mortality, according to Zhang L et al[8]. Also, and according to Lazcano U et al population-based study, individuals with previous CVD might carry a higher risk of mortality due to a previous impaired functional status or to their higher risk of cardiovascular events that can be precipitated by the setting of infection and hypercoagulability related to COVID-19 [6]. Nevertheless, data specifically regarding critically ill COVID-19 patients still lacks in the hitherto literature.

Our investigation differs from previous studies, as most of these were retrospective cohorts including ambulatory and hospitalized patients, and none was an exclusively ICU patients' prospective analysis. Additionally, previous studies have shown lack of standardization regarding CVD definition using broader and less well-specified definitions [18,19]. Indeed, our study used the international definitions, endorsed by institutions of reference of this area of knowledge [11,12]. Moreover, our study included data regarding the cause of death in the ICU patients, which was also not captured in previous analysis [6,20].

Several mechanisms have been proposed to explain the increased risk of mortality amongst critical respiratory patients with previous CVD. The presence of brain medullary cardiorespiratory or autonomic nervous system dysfunction may potentially cause circulatory and respiratory dysfunction, which can increase the risk of contracting

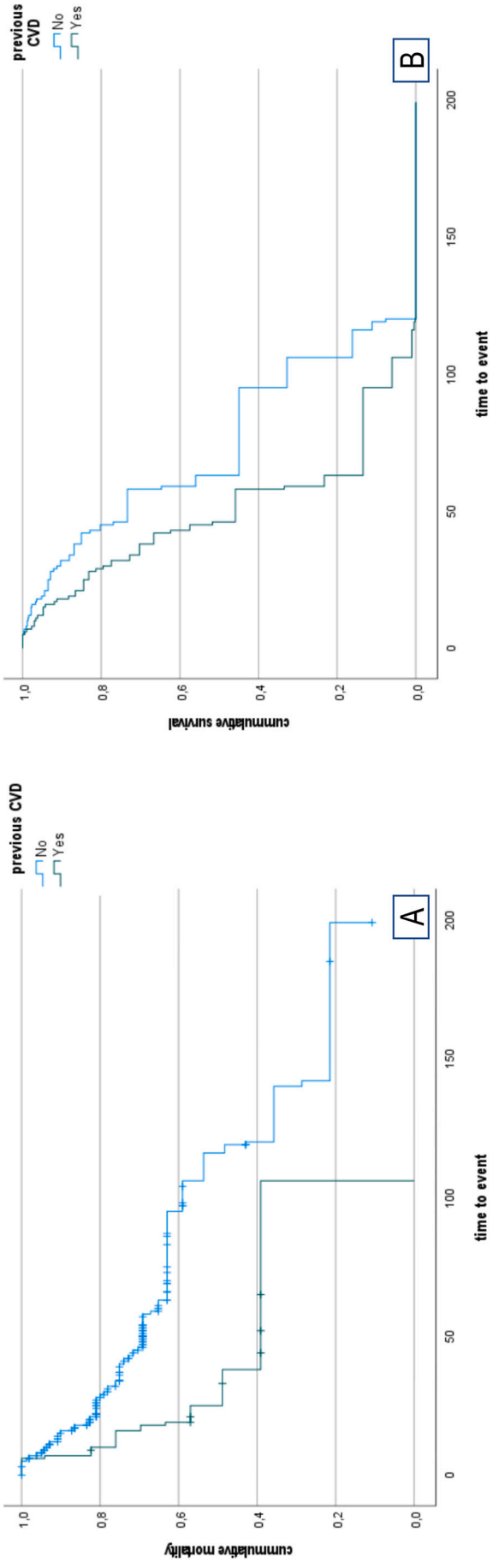

Fig. 1. Survival curve performed through Kaplan-Meyer method (unadjusted; A) and through Cox regression (adjusted; B).

Table 2
Bivariate analysis of characteristics associated with mortality in the ICU.

Characteristic	Total cohort (n = 178)	Survivor (n = 119)	Non survivor (n = 59)	p-value
Sociodemographic characteristics				
Male gender, n(%)	132 (74.2)	87 (73.1)	45 (76.3)	0.65
Age, mean (SD)	63.1 (12.4)	61.7 (12.7)	65.8 (11.4)	0.04
mRS, n(%)				1.00
0	176 (98.9)	118 (99.2)	58 (98.3)	
1	0 (0)	0 (0)	0 (0)	
2	2 (1.1)	1 (0.8)	1 (1.7)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	
Comorbidities				
Hypertension, n(%)	108 (60.7)	74 (62.2)	34 (57.6)	0.56
Diabetes *Mellitus*, n(%)	69 (38.8)	47 (39.5)	22 (37.3)	0.78
Hyperlipidemia, n(%)	89 (50.0)	61 (51.3)	28 (47.5)	0.63
Obesity, n(%)	78 (43.8)	57 (47.9)	21 (35.6)	0.12
Smoking habits, n(%)	6 (3.4)	5 (4.2)	1 (1.7)	0.67
Atrial fibrillation, n(%)	13 (7.3)	9 (7.6)	4 (6.8)	1.00
Ischemic heart disease, n(%)	12 (6.7)	7 (5.9)	5 (8.5)	0.54
Heart failure, n(%)	10 (5.6)	6 (5.0)	4 (6.8)	0.73
Peripheral vascular disease, n (%)	19 (10.7)	13 (10.9)	6 (10.2)	0.88
CPOD, n(%)	7 (3.9)	4 (3.4)	3 (5.1)	0.69
Asthma, n(%)	10 (5.6)	9 (7.6)	1 (1.7)	0.17
Sleep apnea, n(%)	20 (11.2)	14 (11.8)	6 (10.2)	0.75
Chronic kidney disease, n(%)	12 (6.8)	7 (5.9)	5 (8.5)	0.53
Psychiatric pathology, n(%)	28 (15.7)	21 (17.6)	7 (11.9)	0.32
Oncologic pathology, n(%)	20 (11.2)	13 (10.9)	7 (11.9)	0.85
Immunosuppression, n(%)	13 (7.3)	6 (5.0)	7 (11.9)	0.75
Previous CVD, n(%)	17 (9.6)	7 (5.9)	10 (16.9)	0.02
Characteristics regarding critical respiratory illness				
SAPS II, mean (SD)	43.0 (16.0)	40.7 (15.9)	47.8 (15.4)	<0.01
ICU length of stay (days), median (IQR)	28.5 (199)	34 (199)	18 (194)	0.02
Hospital length of stay (days), median (IQR)	42 (309)	49 (309)	23 (201)	<0.01
Number of days under IMV, median (IQR)	20 (197)	21 (159)	18.5 (197)	0.80
Number of days under vasopressors, median (IQR)	5 (130)	5 (130)	5 (123)	0.73
Number of days under ECMO support, median (IQR)	49 (193)	46 (155)	74 (192)	0.08
Number of days under renal replacement therapy, median (IQR)	21 (71)	18.5 (50)	22.5 (71)	0.83

Legend: CPOD = Chronic pulmonary obstructive disease; CVD = Cerebrovascular disease; mRS = modified Rankin scale; n = number of patients; SD = Standard deviation.

opportunistic infections (viral and bacterial) [21]. Another possible hypothesis is the relative immobility of post-stroke patients, which increases the risk for hypercoagulable state that culminates in thrombus formation [22]. Additionally, emerging evidence demonstrates that extrapulmonary viral invasion, including of the central nervous system, causes substantial neuronal damage [23]. Indeed, it seems extremely plausible that, in patients with lower neurological reserve, an infectious pathogen with neurotropism can lead to higher damage, in comparison with patients with absence of previous neurological dysfunction. Moreover, acute stroke patients with COVID-19 seem to have higher mortality rates than stroke patients without this infection, in accordance with Harrison SL *et al* study [24].

Patients with previous CVD were similar to patients without previous

CVD in most characteristics, with the exception of having significantly higher rates of hyperlipidemia and ischemic heart disease, in line with previous studies [6,20]. Moreover, we analyzed which factors were associated with higher mortality rates: asides from CVD, older age and higher scores on SAPS II were also significantly associated with higher mortality. These data are also in line with previous studies outside the ICU setting [8,17,19].We found a higher mortality rate in patients with previous CVD compared to other studies, which probably stems from restricting the study sample to critically ill COVID-19 patients who have, a priori, a higher risk of death than those admitted to other hospital medical wards. Indeed, our data also suggests that previous CVD is an independent risk factor for ICU mortality on COVID-19 patients, which is in line with Lazcano U et al population-based study [6]. Also, not only previous CVD critical COVID-19 patients had higher mortality rates, but also had a lower median number of days until this adverse event, also in accordance with the literature [6].

Our study presents some limitations. Sample size was calculated based on rates in the general population, given the absence of studies in ICU patients. This study data was abstracted from ECR, and as blinding of data collectors to previous DVC status of patients was not possible, an ascertainment bias could not be excluded. Nonetheless, all information was collected following a prespecified standardized form. We are aware of the fact that ethnicity information was not incorporated, and non-White ethnicity has been found to be a risk factor for COVID-19 mortality in population-based studies [7]. Also, and due to the fact that not all patients have performed neuro-imaging studies, additional cases of silent CVD could be overlooked, with an underestimation of the real prevalence of this entity. Likewise, cases of transient ischemic attacks could also have been underestimated due to underreporting. Furthermore, and given the pandemic effect on the ICU rates of admission, this earlier and higher rate of mortality of the CVD population can also be an overestimation since in critical COVID-19 patients with severe comorbidities (as previous CVD patients), the therapeutic roof could not be the same to patients without any prior comorbidities. Nonetheless, our sample had mostly often previous functional independence on all daily-life activities, in line with the ICU setting of the study.

5. Conclusions

We believe that our study provides valuable information with implications on clinical practice. As we report a higher rate of mortality amongst critical COVID-19 patients with previous CVD, even after adjusting for diseases' severity at admission and length of stay, we conclude that prioritizing vaccination and heightened surveillance in this subgroup of COVID-19 patients should be implemented. Additionally, we encourage prognostic research to include CVD as a component of prognostic models. Further studies, ideally multicentric, are warranted to access the possible differential impact of previous CVD between critical and non-critical COVID-19 patients.

Statements

I confirm that our Institution Ethics Review Board (Comissão de Ética para a Saúde – Centro Hospitalar Universitário de São João, Faculdade de Medicina da Universidade do Porto), approved this study (n° 169/20). Also, on behalf of all authors I deny any potential conflicts of interests and sources of funding. Regarding data sharing, the data that support the findings of this study are available from the corresponding author upon reasonable request.

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