Neurological comorbidities and COVID-19-related case fatality: A cohort study

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ABSTRACT

Background: Neurological involvement in Coronavirus disease-2019 (COVID-19) is widely recognized. However, the role of pre-existing neurological comorbidities in modulating COVID-19-related mortality still remains unclear. This cohort study evaluates the COVID-19-related case fatality rate (CFR) of patients with pre-existing neurological diseases.
Methods: We retrospectively evaluated all patients consecutively admitted to our hospital with a diagnosis of COVID-19 between March and April 2020. We used a multivariate regression analysis to estimate the association between pre-existing neurological diseases and COVID-19-related mortality. Then, we compared the CFR and survival curves of two cohorts (patients suffering vs. those not suffering from pre-existing neurological disease), matched trough the propensity score (PS). Age and other comorbidities were considered for PS calculation. We applied a 1:1 matching for the entire neurological cohort and, separately, for cerebrovascular, neurodegenerative, and other neurological diseases.
Results: Among 332 patients, 75 (22.6%) were affected by pre-existing neurological disease ($n = 29$ cerebrovascular, $n = 26$ neurodegenerative, $n = 20$ others). From the multivariate regression analysis, they resulted with a significant increase of COVID-19-related mortality (OR:2.559; 95%CI 1.181–5.545; $p < 0.017$). From the cohort analysis, CFR resulted 2-fold higher in patients with neurological disease (48.0% vs. 24.0%; $p = 0.002$). CFR was significantly higher in patients with neurodegenerative diseases compared to matched individuals (73.9% vs. 39.1%; $p = 0.017$), while CFR increase in patients with cerebrovascular diseases did not reach statistical significance (48.3% vs. 41.4%; $p = 0.597$).
Conclusions: Pre-existing neurological comorbidities, in particular neurodegenerative diseases, increase significantly COVID-19-related case fatality, indicating a clear priority for viral screening, access to care facilities and vaccination in these populations.

1. Introduction

Since its first discovery in December 2019, Coronavirus disease-2019 (COVID-19) has affected more than 190 million people and caused over 4 million deaths worldwide, as of July 21, 2021 [1]. Although the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection mostly presents with mild or no symptoms, elderly individuals and patients suffering from chronic diseases such as hypertension, diabetes, malignancy, lung disease, and renal failure, show significantly higher risk for severe infection, hospitalization, admittance to intensive care units (ICUs), and death [2–4]. Neurological symptoms have been reported in 35–50% of COVID-19 cases and found to be associated with a

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more severe disease [5,6] and higher mortality [7]. Conversely, the role of pre-existing neurological conditions in modulating the severity and mortality of COVID-19 remains to be clarified. A recent study from our group [8] reported neurological comorbidities, in particular dementia and cerebrovascular diseases, as independent risk factors for a more severe course of SARS-CoV-2 infection, while another study from Spain [9] reported an association between a pre-existing neurological condition and COVID-19 mortality. In addition, some studies investigating specific neurological diseases, reported that dementia [4,6,10], stroke [4,11–13], and Parkinson's disease (PD) [14,15] may be associated with higher mortality. Other studies, applying a generic definition of "neurological disorders", reported higher mortality in patients affected by neurological diseases [4,16–18], while a recent systematic review and meta-analysis on the impact of comorbidities on COVID-19 severity, hospitalization, and mortality did not include any neurological disease in the analysis due to the lack of data available [19]. Against this background, no previous studies have comprehensively analyzed the impact of different types of neurological diseases on the outcome of COVID-19 using a cohort design with matched patients.

We conducted a retrospective cohort study with the aim of comparing the 30-day COVID-19-related case fatality rate (CFR) of patients with and without pre-existing neurological comorbidities by enrolling a large sample of COVID-19 patients who were consecutively admitted to the Emergency Room (ER), and matching them with a propensity score (PS) approach.

2. Methods

2.1. Patients selection

We retrospectively analyzed the clinical notes of all patients consecutively admitted to the ER of "Città della Salute e della Scienza di Torino" University Hospital between 3rd March 2020 and 14th April 2020, and diagnosed as suffering from COVID-19 by means of a positive Reverse Transcription Polymerase Chain Reaction nasopharyngeal swab. The medical history collected in the ER and ongoing therapies were used to determine the presence of neurological and non-neurological comorbidities; in uncertain cases, previous clinical notes available in our hospital electronic archives were revised. A medical condition was attributed to the patients in the following cases: a) a defined diagnosis, and/or b) unequivocal diagnostic test results, and/or c) specific medical/surgical treatment, and/or d) active specialistic follow-up were reported in patients' medical notes. The severity of COVID-19 at the time of admission to ER was evaluated by means of the 2007 Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia [20]. Severe disease was identified in patients presenting with one major criterion or three or more minor criteria (Supplementary Table 1). To define the COVID-19 onset, we considered the first appearance of symptom(s) suggestive for infection (e.g., fever, cough, dyspnea, sore throat, anosmia/dysgeusia, myalgia/arthralgia/asthenia, thoracic pain, abdominal pain, diarrhea, nausea, vomiting, confusion, headache, dizziness, conjunctivitis, and others). We recorded the type of patients' discharge from the ER (i.e., home, ward without mechanical respiratory support, ward with non-invasive mechanical respiratory support, ICU) and their 30-day CFR. We considered only deaths directly related to COVID-19 (disease-specific CFR). Moreover, in order to include only deaths caused by COVID-19 and to avoid the counting of deaths related to non-specific long-term complications, we chose the 30-day CFR as primary outcome measure. In case of non-hospitalized patients, mortality/survival data were searched in our electronic archives, which are constantly updated by the regional registry office. When follow-up data could not be retrieved, patients or caregivers were directly contacted by telephone call.

2.2. Study aims and design

The primary aim of the current study was to compare the 30-day COVID-19-related CFR between COVID-19 patients suffering from neurological diseases and those with no neurological comorbidities. To take into account the coexistence of other relevant clinical and demographic characteristics that might have affected the COVID-19-related mortality, we designed a retrospective cohort study by means of the PS [21], matching patients affected by neurological diseases with non-affected patients with similar age, comorbidities, and hospitalization regimen. The PS approach allows to account for systematic differences in patients' characteristics in observational cohort studies, reducing potential biases due to confounding variables [22].

The secondary study aim was to evaluate the impact of different neurological diseases on the 30-day CFR.

2.3. Statistical analysis

In the descriptive statistics, mean, standard deviation and range were used for continuous variables, while frequencies were used for categorical data. The Mann-Whitney and Pearson χ^2 tests were used for comparisons between groups when appropriate. A univariate binary logistic regression was used to estimate the odd ratio (OR) of death (dependent variable) entering the following demographic and clinical features as independent variables: gender, age, severe COVID-19 at onset, hospitalization regimen (i.e. no mechanical respiratory support/non-invasive mechanical support/invasive mechanical support in ICU vs. discharge at home), the presence of neurological diseases, arterial hypertension, diabetes, renal failure, COPD, neoplastic disease. This was followed by a second multivariate binary logistic regression analysis that included as independent variables every feature resulting significantly associated with death. Then, we performed a 1:1 matching between patients with and without neurological diseases, calculating the PS with a multivariable logistic regression model, which considered exclusively the variables that resulted statistically significant at the first univariate logistic regression analysis. The samples were matched via a nearest neighbor approach (individuals matched according to a similar PS); caliper matching without replacement was used, with a caliper width set at 0.15 times the standard deviation of the PS. After creation of the PS-matched samples, we assessed the covariate balance between them, considering it satisfactory when the means of the covariates across the two groups presented with an absolute difference of <10%; continuous and categorical variables were compared using the Mann-Whitney or Pearson χ^2 tests, as appropriate.

The CFR between the matched groups was compared using the Pearson χ^2 test; Kaplan-Meier survival curves and Cox regression analysis were used to evaluate differences in the survival distributions.

We applied the same approach with PS for both the entire sample of neurological patients and the different types of neurological diseases. In order to minimize the loss of statistical power, we arbitrarily considered individuals suffering from a specific neurological disease as a separate group if their number was ≥20.

Patients with any missing data on their medical history or COVID-19 course were excluded from the analyses.

Samuels and colleagues [17] reported a general mortality rate of 16% in patients evaluated in the Florida Memorial Healthcare System facilities, with neurological diseases associated with a 4-fold higher mortality rate; based on these observations, we estimated that a sample of 54 neurological patients would have been sufficiently large to detect an increased CFR of at least 2.5-fold in patients with neurological compared to those without a neurological diseases, with 80% power at the 5% level of significance.

All reported *p*-values are referred to two-tailed tests, with $p < 0.05$ considered as cut-off for statistical significance. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 26 for Mac, Chicago, IL); PS was calculated with the PS matching SPSS R-extension

utility.

2.4. Ethics

This study received approval from the ethical standards committee on human experimentation (*Comitato Etico Interaziendale AOU Città della Salute e della Scienza di Torino, AO Ordine Mauriziano di Torino, ASL Città di Torino*; Protocol number 00172/2020, approved on 5th May 2020), and patients gave their written informed consent.

3. Results

Clinical notes of 344 consecutive patients were revised. Twelve patients (3.5%) were excluded from the analyses, all of them for missing follow-up data. The main demographic and clinical features of the remaining 332 patients who entered the final analyses, as well as the differences between patients with or without preexisting neurological diseases, are summarized in Table 1.

Seventy-five patients (22.6%) were suffering from pre-existing neurological diseases. They were older and presented with a higher burden of comorbidity than those without pre-existing neurological conditions (Table 1); in particular, they had a significant higher rate of arterial hypertension, renal failure, and malignancy, while the rates of diabetes and chronic obstructive pulmonary diseases (COPD) were higher, but not statistically different between the two groups (Table 1). The CFR rate in patients with neurological disease was more than 4-fold higher than that observed in patients with no neurological comorbidity.

3.1. Risk factors for mortality

The univariate binary logistic regression analysis (Table 2) revealed that the 30-day COVID-19-related mortality was significantly associated with the presence of neurological disease (OR: 7.549; $p < 0.001$), together with an older age, the presence of arterial hypertension, diabetes, renal failure, COPD, or neoplastic disease. Severe COVID-19 at

Table 1
Demographic and clinical features of the sample.

Demographic and Clinical features	Total ($N = 332$)	Neurological disease ($N = 75$)	No neurological disease ($N = 257$)
Gender (males/females)	199/133 (59.9%/ 40.1%)	37/38 (49.3%/ 50.7%)	162/95 (63.0%/ 37.0%)*
Age (years)	61.9 ± 17.6 (15–98)	74.2 ± 16.1 (30–97)	58.3 ± 16.5 (15–98)**
Arterial Hypertension	155 (46.7%)	55 (73.3%)	100 (38.9%)**
Neoplastic Diseases	45 (13.6%)	21 (28.0%)	24 (9.3%)**
Diabetes	40 (12.0%)	12 (16.0%)	28 (10.9%)
Chronic Obstructive Pulmonary Disease	41 (12.3%)	13 (17.3%)	28 (10.9%)
Moderate-to-Severe Renal Failure	18 (5.4%)	10 (13.3%)	8 (3.1%)*
Severe infection	115 (34.6%)	50 (66.7%)	65 (25.3%)**
Hospitalization regimen			
- Home	121 (36.4%)	12 (16.0%)	109 (42.4%)**
- Ward without mechanical respiratory support	169 (50.9%)	45 (60.0%)	124 (48.2%)*
- Ward with mechanical respiratory support	24 (7.2%)	12 (16.0%)	12 (4.7%)**
- Intensive Care Unit	18 (5.4%)	6 (8.0%)	12 (4.7%)
Deaths (30-day CFR)	64 (19.3%)	36 (48.0%)	28 (10.9%)**

Results are reported as average ± standard deviation (range) or absolute values (percentage), as appropriate. CFR: case fatality rate.

* Significant difference between patients with and without neurological diseases ($p < 0.05$).

** Significant difference between patients with and without neurological diseases ($p < 0.01$).

Table 2
Univariate and multivariate logistic regression analysis of association between patients' characteristics and 30-day case fatality.

Demographic and Clinical features	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Male Gender	1.143 (0.652–2.004)	0.642	–	–
Age	1.129 (1.095–1.164)	< 0.001	1.108 (1.071–1.146)	< 0.001
Neurological Disease	7.549 (4.146–13.747)	< 0.001	2.559 (1.181–5.545)	0.017
Arterial Hypertension	5.544 (2.919–10.529)	< 0.001	1.661 (0.729–3.786)	0.227
Neoplastic Disease	3.930 (2.008–7.693)	< 0.001	1.759 (0.725–4.267)	0.212
Diabetes	2.606 (1.272–5.341)	0.009	1.098 (0.575–2.468)	0.935
Chronic Obstructive Pulmonary Disease	5.346 (2.678–10.673)	< 0.001	3.506 (1.410–8.721)	0.007
Moderate-to-Severe Renal Failure	6.019 (2.271–15.953)	< 0.001	1.420 (0.320–6.294)	0.645

Results are reported as Odds Ratio (OR); 95% Confidence Interval (CI) is reported in brackets. P-value: statistical significance. All variables resulting associated with the 30-day mortality at the univariate analysis were included in the multivariate analysis.

onset represented the main risk factor for a fatal outcome (OR: 58.091; $p < 0.001$), alongside the need for hospitalization (OR: 10.942 for hospitalization without mechanical respiratory support; OR: 36.056 for non-invasive mechanical support; OR: 62.267 for ICU admission; $p < 0.001$). On the multivariate analysis (Table 2), the presence of neurological diseases remained independently associated with mortality (OR: 2.559; $p = 0.017$), as well as COPD (OR: 3.506; $p = 0.007$), older age (OR: 1.108; $p < 0.001$), and severity of SARS-CoV-2 infection (OR: 24.134; $p < 0.001$).

3.2. Cohort analysis

3.2.1. Neurological disease and COVID-19 case fatality

Age, COVID-19 severity at onset, hospitalization regimen, and all comorbidities that resulted significantly associated with COVID-19 case fatality at the univariate regression analysis were considered as covariates for the PS calculation.

The 75 patients with neurological diseases were matched with 75 patients without neurological diseases. All covariates resulted well balanced between the two groups (Table 3), with no significant differences and no variables showing an absolute difference > 10%.

Patients affected by neurological diseases showed a significant 2-fold higher CFR than those without neurological comorbidity (48.0% vs. 24.0%; $p = 0.002$); the Cox regression analysis confirmed this significant difference between the two groups (OR: 2.532, 95%CI 1.438–4.466; $p = 0.001$) (Fig. 1).

3.2.2. Different neurological comorbidities and COVID-19 case fatality

Cerebrovascular diseases were the most common neurological comorbidity, affecting 38.7% of patients ($n = 29/75$, including 7 patients with hemorrhagic and 22 with ischemic stroke), followed by cognitive impairment (33.3%, including 4 patients with Mild Cognitive Impairment (MCI), 10 with Alzheimer's Disease or Alzheimer's Disease-like dementia, and 11 with vascular dementia), migraine or chronic tension-type headache or trigeminal neuralgia (14.7%; $n = 11$), epilepsy (6.7%; $n = 5$), peripheral neuropathy (5.3%; $n = 4$), and PD (1.3%; $n = 1$).

To maintain an adequate number of patients in each group for the cohort analyses, we divided the sample in: a) Cerebrovascular diseases ($n = 29$ patients); b) Neurodegenerative diseases ($n = 26$, with $n = 25$ affected by cognitive impairment and $n = 1$ by PD); and c) Other

Table 3

Demographic and clinical features after propensity score matching – All neurological diseases.

Demographic and Clinical features	Neurological disease (N = 75)	No neurological disease (N = 75)	P value
Age (years)	74.2 ± 16.1 (30–97)	73.1 ± 15.6 (31–95)	0.576
Arterial Hypertension	55 (73.3%)	53 (70.7%)	0.716
Neoplastic Diseases	21 (28.0%)	19 (25.3%)	0.712
Diabetes	12 (16.0%)	13 (17.3%)	0.827
Chronic Obstructive Pulmonary Disease	13 (17.3%)	13 (17.3%)	0.999
Moderate-to-Severe Renal Failure	10 (13.3%)	7 (9.3%)	0.440
Severe infection	50 (66.7%)	49 (65.3%)	0.863
Hospitalization regimen			0.770
- Home	12 (16.0%)	14 (18.7%)	
- Ward without mechanical respiratory support	45 (60.0%)	47 (62.7%)	
- Ward with mechanical respiratory support	12 (16.0%)	7 (9.3%)	
- Intensive Care Unit	6 (8.0%)	7 (9.3%)	

Results are reported as average ± standard deviation (range) or absolute values (percentage), as appropriate. *P*-value: statistical significance.

neurological diseases (n = 20; migraine/chronic tension-type headache/trigeminal neuralgia, n = 11; epilepsy, n = 5; and peripheral neuropathy, n = 4).

After applying the PS method, all 29 patients with cerebrovascular diseases, 23 out of 26 patients with neurodegenerative diseases (n = 22 patients with cognitive impairment and n = 1 with PD), and all 20 patients with other neurological diseases were matched with patients without neurological diseases.

In all the three cohort analyses, the covariates resulted well balanced between groups after the PS matching (Table 4-6), with no significant differences and no variables showing an absolute difference > 10%.

Compared to matched controls, patients with cerebrovascular diseases showed a higher CFR, albeit not reaching the statistical threshold (48.3% vs. 41.4%; *p* = 0.597), consistent with the Cox regression analysis (OR: 1.277, 95%CI 0.591–2.761; *p* = 0.534) (Fig. 2A), while

patients with neurodegenerative diseases showed a significantly higher CFR (73.9% vs. 39.1%; *p* = 0.017), confirmed through Cox regression analysis (OR: 3.026, 95%CI 1.337–6.847; *p* = 0.008) (Fig. 2B). Patients with other neurological diseases showed a CFR similar to that of patients without neurological diseases (15.0% vs. 20.0%; *p* = 0.677), as confirmed by Cox regression analysis (OR: 0.744, 95%CI 0.167–3.326; *p* = 0.699) (Fig. 2C). Among the three patients who died, two were affected by epilepsy and one by peripheral neuropathy.

4. Discussion

In this cohort study we evaluated the COVID-19-related CFR of patients with pre-existing neurological diseases, compared with patients without neurological comorbidities. We performed a multivariate

Table 4

Demographic and clinical features after propensity score matching – Cerebrovascular diseases.

Demographic and Clinical features	Cerebrovascular disease (N = 29)	No cerebrovascular disease (N = 29)	P value
Age (years)	75.3 ± 13.1 (49–97)	73.0 ± 13.8 (45–93)	0.559
Arterial Hypertension	26 (89.7)	25 (86.2)	0.687
Neoplastic Diseases	12 (41.4)	11 (37.9)	0.788
Diabetes	6 (20.7)	5 (17.2)	0.738
Chronic Obstructive Pulmonary Disease	6 (20.7)	7 (24.1)	0.753
Moderate-to-Severe Renal Failure	2 (6.9)	3 (10.3)	0.640
Severe infection	19 (65.5)	19 (65.5)	0.999
Hospitalization regimen			0.851
- Home	3 (10.3)	2 (6.9)	
- Ward without mechanical respiratory support	16 (55.2)	18 (62.1)	
- Ward with mechanical respiratory support	7 (24.1)	5 (17.2)	
- Intensive Care Unit	3 (10.3)	4 (13.8)	

Results are reported as average ± standard deviation (range) or absolute values (percentage), as appropriate. P-value: statistical significance.
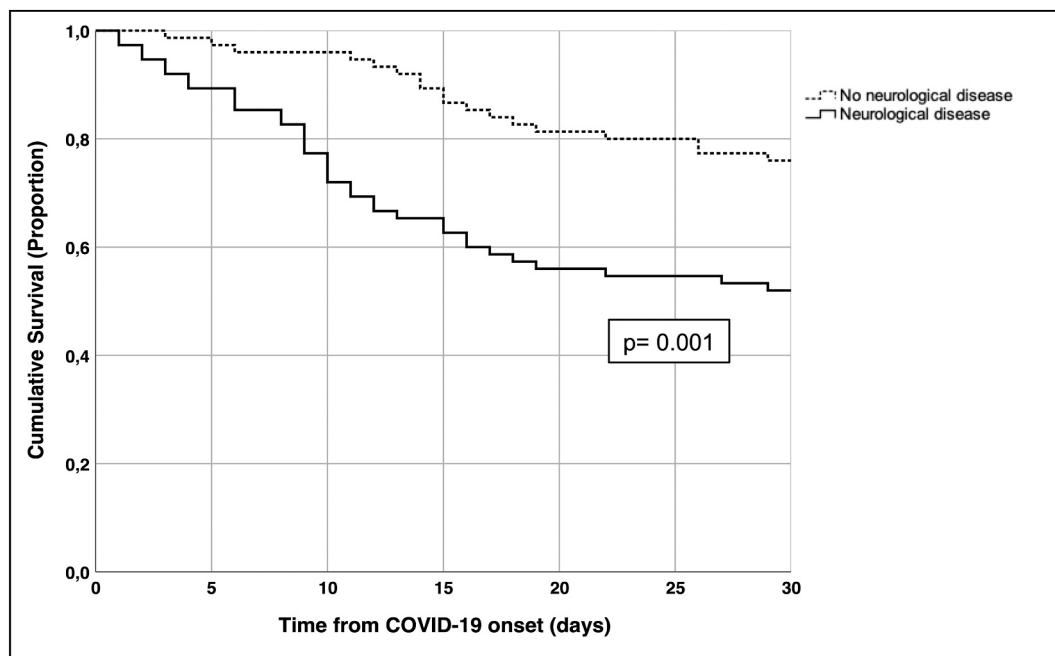
Fig. 1. Survival curves of patients with and without neurological diseases. Kaplan-Meier survival curves showing a significant lower 30-day survival rate of patients affected by neurological diseases (*n* = 75) compared to matched patients without neurological comorbidity (*n* = 75). The *p* value refers to Cox regression analysis

Table 5

Demographic and clinical features after propensity score matching – Neurodegenerative diseases.

Demographic and Clinical features	Neurodegenerative disease (N = 23)	No neurodegenerative disease (N = 23)	P value
Age (years)	83.4 ± 6.6 (64–94)	81.3 ± 10.7 (60–93)	0.886
Arterial Hypertension	18 (78.3)	17 (73.9)	0.730
Neoplastic Diseases	2 (8.7)	3 (13.0)	0.636
Diabetes	4 (17.4)	3 (13.0)	0.681
Chronic Obstructive Pulmonary Disease	4 (17.4)	3 (13.0)	0.681
Moderate-to-Severe Renal Failure	3 (13.0)	3 (13.0)	0.999
Severe infection	21 (91.3)	20 (86.9)	0.636
Hospitalization regimen			0.886
- Home	1 (4.3)	1 (4.3)	
- Ward without mechanical respiratory support	17 (73.9)	19 (82.6)	
- Ward with mechanical respiratory support	3 (13.0)	2 (8.7)	
- Intensive Care Unit	2 (8.7)	1 (4.3)	

Results are reported as average ± standard deviation *(*range) or absolute values (percentage), as appropriate. P-value: statistical significance.

Table 6

Demographic and clinical features after propensity score matching – Other neurological diseases.

Demographic and Clinical features	Other neurological disease (N = 20)	No neurological disease (N = 20)	P value
Age (years)	59.6 ± 18.5 (30–87)	61.0 ± 13.7 (34–85)	0.925
Arterial Hypertension	9 (45.0)	10 (50.0)	0.752
Neoplastic Diseases	6 (30.0)	5 (25.0)	0.723
Diabetes	1 (5.0)	2 (10.0)	0.548
Chronic Obstructive Pulmonary Disease	2 (10.0)	3 (15.0)	0.633
Moderate-to-Severe Renal Failure	2 (10.0)	2 (10.0)	0.999
Severe infection	8 (40.0)	8 (40.0)	0.999
Hospitalization regimen			0.880
- Home	8 (40.0)	6 (30.0)	
- Ward without mechanical respiratory support	9 (45.0)	10 (50.0)	
- Ward with mechanical respiratory support	2 (10.0)	2 (10.0)	
- Intensive Care Unit	1 (5.0)	2 (10.0)	

Results are reported as average ± standard deviation (range) or absolute values (percentage), as appropriate. P-value: statistical significance.

analysis by means of the PS method, matching patients with and without neurological diseases, and considering a wide range of covariates known to affect the clinical outcome of COVID-19, including age, infection severity, hospitalization regimen, and the presence of other comorbidities. We considered the entire cohort of patients with neurological diseases as well as different types of neurological conditions (i.e., cerebrovascular diseases, neurodegenerative diseases, and others). Patients with neurological comorbidity showed a lower 30-day survival rate and, after dividing them into different neurological diseases, neurodegenerative disorders remained significantly associated with a higher CFR.

To date, neurological diseases have been considered, along with a broad spectrum of comorbidities, in the context of studies aiming at evaluating different risk factors for COVID-19 severity and mortality. However, the precise estimate of the role of neurological diseases, and the comparison between neurological vs. non-neurological patients, are mainly limited by the fact that patients with neurological diseases are frequently older and more affected by other comorbidities. A retrospective analysis of 2820 patients reported increased adjusted odds of having severe COVID-19 and fatal outcome in patients with neurological disease [16]. Two observational studies reported a 4.6-fold [17] and a 2.9-fold [18] higher COVID-19-related mortality in neurological patients, evaluated by a multivariate approach, while other studies reported, in univariate analyses only, a significant association between mortality and neurological diseases [23] or cerebrovascular and neurodegenerative disorders [11,12]. Using a large health electronic analytic platform (OpenSAFELY) that includes 40% of all patients in England, Williamson and colleagues [4] evaluated the cause of nearly 11,000 COVID-19-related deaths, identifying a 2.1-fold and a 2.5-fold increased mortality risk in patients affected by stroke or dementia, and other neurological diseases, respectively.

Consistently, our current findings show that neurological comorbidities are strongly correlated with higher case fatality risk in both the univariate (OR: 7.5) and multivariate (OR: 2.5) analyses. Moreover, the cohort analysis based on the PS approach confirmed a 2-fold higher CFR in patients suffering from neurological disease. Notably, we included in the PS matching as covariates also patients' infection severity at onset and patient's hospitalization regimen, which are two important factors affecting the outcome of COVID-19.

Importantly, after dividing the entire sample of patients with neurological comorbidity into different subgroups of neurological diseases, we found variable degrees of association with case fatality in the cohort analysis. Patients with cerebrovascular diseases showed higher CFR with no significant differences in comparison to matched patients without neurological comorbidity. This result is consistent with previous findings [7,18], though other Authors reported significantly higher mortality in cerebrovascular patients [6,11,12], in particular in ICU populations [13]. Moreover, a recent meta-analysis demonstrated the role of cerebrovascular diseases in determining poor outcomes in COVID-19 hospitalized patients [24]. The lack of significant difference in the CFR between patients with and without cerebrovascular diseases in our study is likely due to the coexistence, in both groups, of additional risk factors for COVID-19-related mortality, such as hypertension, diabetes, and COPD [4]. Nevertheless, 48% CFR in patients with cerebrovascular disorders is well above the 12% CFR reported in the general population from Piedmont, our Italian region, during the February–May 2020 period [25]. This implicates that cerebrovascular diseases, along with older age, may represent a relevant predictor of COVID-19-related mortality.

In our sample, over 70% of patients with neurodegenerative disorders died, with a significantly higher CFR in comparison to matched patients with no neurological comorbidity. Again, our results confirm previous data on both institutionalized patients [10] and general population [4,10], and highlight the importance of the association between cognitive impairment and a more severe form of COVID-19 [6,8]. Some Authors postulated a higher COVID-19-related mortality in demented patients as due to a reduced access to care facilities [26], in particular ICUs [17], in favor of younger and less debilitated people. However, in our current study, the rate of patients with neurodegenerative diseases who were admitted to ICU or treated with mechanical respiratory support was similar to that of matched patients not suffering from neurodegenerative diseases. Though, this observation is partially tempered by the presence, among these patients, of 4 subjects affected by MCI, whose neurological impairment is not completely superimposable to that of demented patients. The strong, independent, association observed between neurodegenerative diseases and COVID-19 case fatality is likely related to the intrinsic frailty of these patients [27]. In population-based studies, patients with dementia showed a higher rate of complications due to hospitalization, and a poorer outcome compared with elderly non-demented patients [28]. Moreover, dementia has previously been associated with a 2-fold risk of mortality in community-acquired pneumonia [29].
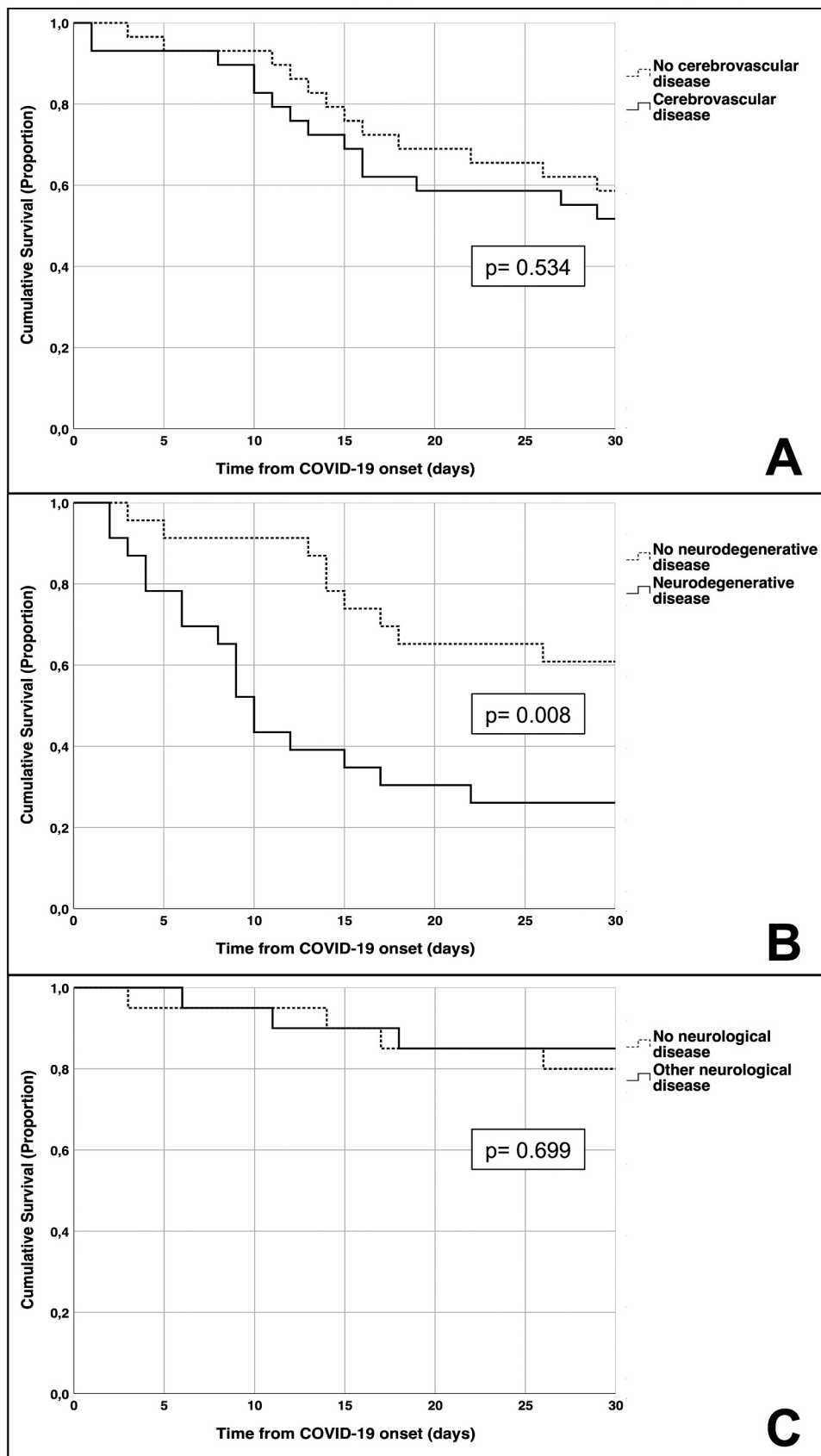
Fig. 2. Survival curves of patients with and without cerebrovascular diseases, neurodegenerative diseases, or other neurological diseases. Kaplan-Meier survival curves comparing the 30-day survival rate of patients affected by cerebrovascular (*n* = 29 patients) (A), neurodegenerative (*n* = 23 patients) (B), or other neurological diseases (*n* = 20 patients) (C), and 1:1 matched patients without neurological comorbidity. The *p* values refer to Cox regression analysis.

The higher vulnerability of patients affected by chronic neurological diseases, and in particular by neurodegenerative diseases, could be explained by a reduced functional reserve and a lower resilience to acute events, which strongly increase the detrimental effect of SARS-CoV-2 infection on already debilitated patients. Moreover, even thought our results were adjusted for age and other comorbidities, it should be taken into account that an older age and a higher comorbidity burden associate frequently with neurological diseases. Finally, the interaction between an already damaged nervous system and a virus with proven neurotropism [30] might promote a more severe form of infection and poorer outcomes, as previously observed in the SARS-CoV epidemic in 2003 [31]. Our robust result needs to be further investigated in tailored studies to assess biological and social causes of this increased risk of mortality, whose importance goes well beyond our understanding of the effects of COVID-19 pandemic.

In our sample, other neurological comorbidities were not associated with an increased risk of COVID-19-related mortality. This latter subgroup of patients had indeed a similar CFR (15%) in comparison to patients without neurological comorbidity, when considering both the entire non-neurological sample (10.9%) and matched patients in the cohort analysis (20%). In particular, no patients with chronic headache/ neuralgia died, while the CFR of epileptic patients was similar to that reported in previous studies [32,33].

The main limitations of our study are represented by the relatively small sample size, in particular when considering specific types of neurological diseases, and the single-center retrospective design, which partially restricts the generalizability of our findings. Nonetheless, our statistical design has controlled for major potential biases that may affect this kind of studies and result in uncertain conclusions. Moreover, some important comorbidities, such as cardiac diseases, were not included in the analyses. However, this limitation is partially tempered by the inclusion in the multivariate analysis of several comorbidities frequently associated with cardiac diseases. Finally, though the choice of using the 30-day CFR was made to focus only on deaths directly related to COVID-19, we acknowledge that some long-term deaths related to COVID-19 complications may have been missed.

In conclusion, our cohort study reports a significant association between pre-existing neurological diseases and COVID-19 case fatality, strengthening previous observations and endorsing the role of specific neurological comorbidities as predictors of worse COVID-19 outcome. Indeed, patients affected by neurological disorders showed a significant higher CFR compared to those without neurological conditions; this observation is even more important when considering that our results were adjusted for age, other comorbidities, COVID-19 severity, and hospitalization regimen. In particular, we observed that neurodegenerative and cerebrovascular diseases were independently and frequently associated with a fatal outcome, suggesting the need for greater attention for proactive viral screening, access to care facilities, and vaccination planning in these frail populations.

Supplementary data to this article can be found online at https://doi. org/10.1016/j.jns.2021.117610.

Authorship statement

Alberto Romagnolo: conception and design of the study; analysis and interpretation of data; writing the first draft.

Gabriele Imbalzano: acquisition and interpretation of data; critical revision for important intellectual content.

Carlo Alberto Artusi: acquisition and interpretation of data; critical revision for important intellectual content.

Roberta Balestrino: acquisition and interpretation of data; critical revision for important intellectual content.

Claudia Ledda: interpretation of data; critical revision for important intellectual content.

Francesco Giuseppe De Rosa: interpretation of data; critical revision for important intellectual content.

Franco Riccardini: interpretation of data; critical revision for important intellectual content.

Elisa Montanaro: interpretation of data; critical revision for important intellectual content.

Marco Bozzali: interpretation of data; critical revision for important intellectual content.

Mario Giorgio Rizzone: interpretation of data; critical revision for important intellectual content.

Maurizio Zibetti: interpretation of data; critical revision for important intellectual content.

Leonardo Lopiano: conception and design of the study; interpretation of data; critical revision for important intellectual content.

All the co-authors listed above gave their final approval of this manuscript version and agreed to be accountable for all aspects of the work.

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Data access and responsibility statement

A. Romagnolo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Financial disclusures and conflicts of interest

Dr. Romagnolo has received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco, Chiesi Farmaceutici, Medtronic, and UCB Pharma.

Dr. Imbalzano has no financial conflicts to disclose.

Dr. Artusi has received travel grants from Zambon and Abbvie.

Dr. Balestrino has no financial conflicts to disclose.

Dr. Ledda has no financial conflicts to disclose.

Prof De Rosa has no financial conflicts to disclose.

Dr. Riccardini has no financial conflicts to disclose.

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Prof Bozzali is member of the Advisory board of Roche Pharmaceuticals and has received honoraria for lecturing from Biogen Pharma.

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