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ORIGINAL ARTICLE

Do prior neurological comorbidities predict COVID-19 severity and death? A 25-month cross-sectional multicenter study on 7370 patients

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Abstract

Background The prognosis of COVID-19 cases that suffer from particular comorbidities is worse. The impact of chronic neurological disorders (CNDs) on the outcome of COVID-19 patients is not clear yet. This study aimed to assess whether CNDs can predict in-hospital mortality or severity in COVID-19 patients.

Methods Following a cross-sectional design, all consecutive hospitalized patients with PCR-confirmed COVID-19 who were hospitalized at three centers from February 20th, 2020 to March 20th, 2022, were studied. CND was defined as neurological conditions resulting in permanent disability. Data on demographic and clinical characteristics, COVID-19 severity, treatment, and laboratory findings were evaluated. A multivariate Cox-regression log-rank test was used to assess the primary outcome, which was in-hospital all-cause mortality. The relationship among CND, COVID-19 severity and abnormal laboratory findings was analyzed as a secondary endpoint.

Results We studied 7370 cases, 43.6% female, with a mean age of 58.7 years. 1654 (22.4%) patients had one or more CNDs. Patients with CNDs had higher age, were more disabled at baseline, and had more vascular risk factors and comorbidities. The ICU admission rate in CND patients with 59.7% was more frequent than the figure among non-CND patients with 20.3% ($p=0.044$). Mortality of those with CND was 43.4%, in comparison with 12.8% in other participants ($p=0.005$). Based on the Cox regression analysis, CND could independently predict death (HR 1.198, 95% CI 1.023–3.298, $p=0.003$).

Conclusion CNDs could independently predict the death and severity of COVID-19. Therefore, early diagnosis of COVID-19 should be considered in CND patients.

Highlights

- COVID-19 is a widespread infection all over the world with a high case fatality rate (CFR).
- The prognosis of COVID-19 cases that suffer from particular comorbidities might be worse.
- The implication of chronic neurological disorders (CNDs) in COVID-19 patients is largely unexplored.
- Find the clinical predictors of severity and mortality of COVID-19 patients to prioritize limited resources and decrease mortality among vulnerable COVID-19 patients.

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Keywords SARS-CoV · Neurological complications · Death rate · Prognostic factors

Introduction

As of March 12, 2022, coronavirus disease 2019 (COVID-19) has caused 452,201,564 infections and 6,029,852 deaths, resulting in a case fatality rate (CFR) of approximately 1.4%, which is higher than the 1% CFR reported for influenza [1, 2]. In Iran, first confirmed COVID-19 patients were reported on February 19, 2020. By March 12, 2022, 7,113,591 COVID-19 patients had been reported by Iran's surveillance system, 138,572 of whom lost their lives, yielding a CFR of 2% [2].

According to the literature, hypertension, diabetes, cardiovascular disease (CVD), pulmonary disease, and cancer are associated with higher severity of COVID-19 and higher death rate [3–8]. However, the implication of chronic neurological disorders (CNDs) in COVID-19 patients is largely unexplored [9].

Access to evidence about the differential impact of the outbreak has progressively spread out and experts emphasized the need for sufficient focus on the effect of the COVID-19 outbreak on the marginalized groups such as individuals suffering from major mental problems, learning problems, and neurodevelopmental problems [10].

Suffering from CNDs is accompanied by some problems, including declined awareness of risk and inadequate adherence to personal protection recommendations, medical comorbidities, delayed referral to receive healthcare services due to problems related to recognizing or reporting physical presentations because of cognitive or motivational disorders, socioeconomic deprivations, and barriers related to receiving health services, which in turn result in enhanced risk COVID-19 and its severity [11, 12].

We currently know a little about whether prior neurological comorbidities implicate outcomes in patients with COVID-19. A new review reported a frequency of 1.4–40%, with a pooled percentage of having a pre-existing neurological disorder of 8.0% in hospitalized COVID-19 cases [13]. A study that analyzed the implication of CNDs presence among 576 hospitalized COVID-19 patients noted that CNDs could independently predict in-hospital mortality. This study also noted that those with CND died sooner than others [9]. A study that analyzed 4 studies reported a ~2.5-fold enhance in odds of severe COVID-19 with a history of cerebrovascular disease [14]. Based on a recent finding, a history of cerebrovascular disease was higher among COVID-19 cases who were hospitalized in the intensive care unit (ICU) [5]; however, some studies classified cerebrovascular disease and cardiovascular disorders in one group [15], which may be misleading.

By the end of February 2022, Iran had left behind five crises of COVID-19 with relatively high CFR [16]. Also, based on some valid anticipations Iranian population will experience the sixth peak in the upcoming summer [17]. This situation is an immense challenge for the Iranian National Health Service [16, 17]. Therefore, finding clinical predictors of severity and mortality associated with COVID-19 infection is crucially practical to judicious use of limited resources and make an effort to decrease mortality among vulnerable COVID-19 patients [14].

This 25-month cross-sectional study aimed to evaluate if the pre-existing neurological disorders are associated with a worse prognosis in COVID-19 cases.

Methods

Participants and data source

This cross-sectional study included adult cases aged 18 years or higher with severe COVID-19 infection who were hospitalized in three free-of-charge hospitals of Taemin Ejtemai organizations, Markazi province, Iran. This 25-month study period consisted of all consecutive patients from February 20th, 2020 to March 20th, 2022. Demographic and clinical characteristics of patients were collected using the admission report, emergency department (ED) history and Hospital Information System (HIS). In fact, we prepared a checklist for each enrolled patient so that extracted data from the resources could be transmitted to the checklist. The completion and confirmation of the checklists were assigned to physicians who were involved in the project.

Treatment was performed based on the national COVID-19 protocol standard of care (SOC) [18].

COVID-19 diagnosis

Real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay (LightMIx Modular SARS-CoV (COVID-19) E-gene and LightMIx Modular SARS-CoV (COVID-19) RdRP, Roche Diagnostics S.L.) of nasopharyngeal, oropharyngeal, and sputum samples were used to diagnose COVID-19. Positive cases were defined as positive if any test result was positive for SARS-CoV-2 RNA or negative if all test results were negative [9, 19]. Cases with no PCR-confirmed diagnosis were excluded. Participants were

recruited following a probabilistic approach, and all consecutive cases were recruited. Only hospitalized cases were recruited.

Data collection and variables

Demographic variables included age and sex. Concerning comorbidities, the following variables were considered: the presence of hypertension (systemic blood pressure higher than 140/90 mmHg in two prior determinations), diabetes (fasting blood glucose >126 mg/dl on two separate tests, HbA1c > 6,5%, blood glucose level >200 mg after oral glucose overload or blood glucose level >200 mg/dl with diabetes symptoms), smoking habit (current or in the preceding 6 months), cardiovascular diseases (coronary artery disease, congenital heart disorders, cardiomyopathies, arrhythmia, valvular heart disorder, aortic aneurysms, and peripheral artery disease), chronic respiratory diseases (chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases, interstitial lung disorders, and pulmonary hypertension), cancer, and immunocompromised state (congenital or acquired).

Information on previous comorbidities were self-reported, gathered from previous clinical documentation provided by the patient, or reported by the referring physician, and were identified from structured electronic health record diagnostic fields (HIS) that is a well-established software infrastructure in Tamin Ejtemai organizations.

According to the World Health Organization, CNDs are defined as neurological diseases that (a) resulted in persistent disability, (b) decreased functioning, and (c) interfered with the ability to participate in activities [20].

In this study, at first we assessed the following neurological disorders that could fulfill criteria (a) (b) and (c). Then, we included those ones that fulfilled all three criteria.

Investigated neurological disorders included *dementia, movement disorders, prior stroke with long-term sequelae, neuromuscular disorders, spinal disorders, symptomatic central nervous system cancer, chronic encephalopathies, or neuroinflammatory diseases*. (Full definition in Supplementary Material Table 1).

The modified Ranking Scale (mRS) was used to investigate the baseline performance. The mRS ranged from lack of symptoms (score of zero) to death (score of six), which 3 was considered as the presence of moderate disability and the need for assistance [21]. Using the codes defined as the neurological diagnosis, data on neurological disorders were extracted from HIS using billing/encounter diagnoses, external claim diagnoses, and problems occurred during hospitalization prior to their testing encounter.

Concerning the clinical presentation, laboratory findings, and imaging, we assessed whether the source of contagion was suspected or not, general symptoms including fever (defined as axillary temperature ≥37.5%), asthenia, cough, cutaneous rash, dyspnea, diarrhea, chest pain, expectoration, headache, myalgia, nausea, odynophagia, rhinorrhea, and vomiting [22]. The frequency of abnormal chest imaging, either by X-ray or Computerized Tomography (CT) was also analyzed.

The abnormal laboratory findings on admission and during the hospitalization period were assessed. The following parameters were considered: leukocytes [cell count × 109/L, reference value (RV):4–10], lymphocytes (count × 109/L, RV: 0.9–5.2), platelets (count × 109/L, RV: 150–400), hemoglobin (g/dL, RV: 12–16), lactate dehydrogenase (U/L, RV: 135–250), international normalized ratio (INR, RV: 0.8–1.3), D-dimer (ng/dL, RV: < 500), glomerular filtration rate corrected by body area (mL/min/1.73 m^2, RV > 90), C-reactive protein (mg/L, RV: 1–5), and ferritin (ng/mL, RV: 15–150).

The received treatment was analyzed, which based on the local SOC, was the possible drug dose regimes hydroxychloroquine 400 mg bid for 5 days, lopinavir/ritonavir 400/100 mg bid, remdesivir 200/100 mg daily, methylprednisolone 250 mg three consecutive days [18]. The need for oxygen therapy, receiving mechanical ventilation, the need for ICU admission, and the all-cause mortality were also considered. Care transition time was assessed in terms of days from initiation of presentations to: (1) hospitalization; (2) ICU admission; and (3) death. COVID-19 severity was considered based on the American Thoracic Society guidelines for community-acquired pneumonia [23] (Supplementary Material Table 2). Severe COVID-19 was defined as the presence of either severe pneumonia or acute respiratory distress syndrome (ARDS) [24].

Study outcomes

The primary outcome was death during hospitalization due to COVID-19 in cases suffering from CNDs. It was calculated using multivariate regression and survival probability by Cox regression, adjusted by the possible confounders and effect modifiers. Death related to the COVID-19 infection was considered as a death in cases who were RT-PCR positive for SARS-CoV-2, independently from pre-existing disorders that may result in death. As secondary endpoints, this study also intended to investigate the COVID-19 severity in patients with CND and abnormal COVID-19-related laboratory results.

Data analysis

Qualitative and ordinal variables are provided as frequency and percentage. On the other hand, continuous variables

are described using medians, interquartile range (IQR), and minimum–maximum value or mean and standard deviation (SD). Missing data was managed by complete case analysis.

The χ^2 was administered for comparing categorical variables. The p value was adjusted using Bonferroni for multiple comparisons correction. In addition, student t test was employed to compare categorical and continuous variables. Statistical significance was considered when p value < 0.05, after adequate adjustment.

There was no need to determine the sample size, as the study is exploratory in nature.

A univariate single regression analysis of all baseline variables was used for the primary outcome, and all variables that were significantly associated with higher odds of death (i.e., p value ≤ 0.1) were included in a univariate multiple regression analysis.

All CNDs were analyzed together. The results are provided as odd ratios (OR) and 95% confidence interval (CI).

We did a model for proportional hazards assumptions (using Schoenfeld residuals) and nonlinearity in relationship between the log hazard and the covariates (using Martingale-residual plots) to evaluate if CND is a time-dependent variable or not. As a result, we found out that CND is not a time-dependent variable. Hence, Cox-regression analysis with a hazard ratio (HR) was used to evaluate survival probability, adjusted by all the significant covariates in the univariate single regression analysis. Differences in Kaplan–Meier curves were analyzed by the log-rank test.

A similar analysis was used for severe-COVID-19 infection, which was the secondary endpoint. A regression analysis, which was adjusted for age, mRS, and gender, was used to assess whether laboratory parameters are more often abnormal in cases with CND.

Also, after adjusting for age, mRS, gender, VRFs and comorbidities, a linear regression analysis was used to calculate the impact of CND situation (CND or non-CND) on the interval between symptom onset and ED visit, ICU admission, and death. This impact is known as B coefficient or Standardized Coefficient. Data analysis was administered using SPSS version 26 by DGA.

Ethical considerations

The institutional review board of Taemin Ejtemai organizations, Markazi province, Iran, approved the study (code: 1400-133-2). All participants signed the written informed consent, which was designed based on local IRB recommendations.

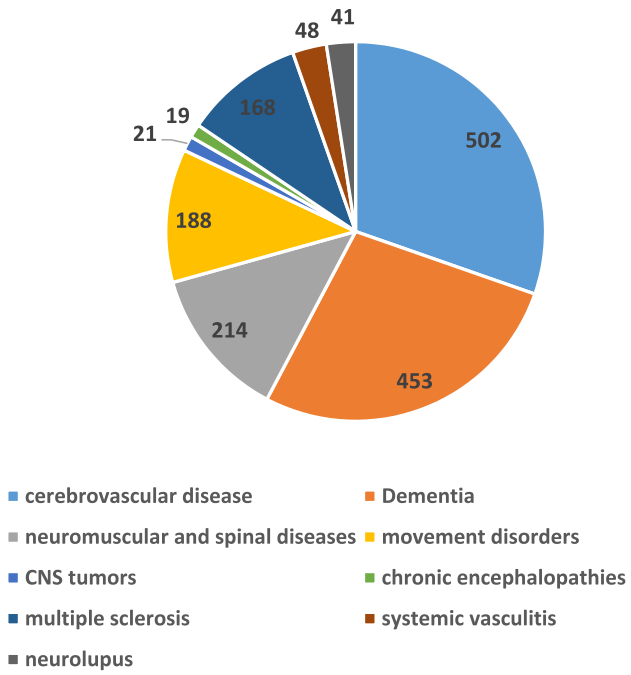

Fig. 1 The number of specific chronic neurological disorders among 1654 patients with COVID-19 plus CNDs

Results

A total of 7546 consecutive adult patients were hospitalized at three target hospitals during the study period, being excluded 176 patients. Flow diagram of participants is provided in Graphical abstract. Forty-three percent ($n = 3218$) of participants were female, with a mean age of 58.7 (SD: 8.4). The youngest and oldest participants were 19 and 87 years, respectively. In addition, 1654 (22.4%) cases had at least one CND.

The most frequent CNDs ($n = 502$; 30.3%) belonged to patients with cerebrovascular disease. After that, the frequency of Dementia and neuromuscular/spinal diseases were 453 (27.3%) and 214 (12.9%) cases, respectively. Figure 1 illustrates the number of CNDs separately.

Most patients with CND were females. In addition, they were older, had a higher rate of disability at baseline, and the prevalence of hypertension, diabetes, and cardiac disease was higher among them. Demographic characteristics, frequency of vascular risk factors (VRFs), and prevalence of comorbidities, separated by CND status, are provided in Table 1.

The source of the contagion was suspected in 5011 (67,9%) of all participants; and there was no difference between those suffering from a CND (n = 909; 54.9%) and others ($n = 2806$; 49.09%).

Among COVD 19 patients with CNDs, fever was the most common manifestations. Cough, weakness, diarrhea,

Table 1 Demographic variables, vascular risk factors frequency and comorbidities

	All patients ($n=7370$)	Chronic neurological disorders ($n=1654$)	No-neurological comorbidity ($n=5716$)	Adjusted p value
Mean age	58.7 (8.4)	65.1 (7.3)	52.3 (9.4)	<0.001[a]
Female sex	3218 (43.6%)	984 (59.4%)	2234 (39%)	0.002[b]
Hypertension	3887 (52.7%)	1320 (79.8%)	2567 (44.9%)	<0.001[b]
Diabetes	1652 (22.4%)	680 (41.1%)	972 (17%)	0.001[b]
Smoking habit	1531 (20.7%)	330 (19.9%)	1201 (21%)	0.988[b]
Cardiac disease	1886 (25.5%)	678 (40.9%)	1208 (21.1%)	0.003[b]
Respiratory disease	1702 (23%)	413 (24.9%)	1289 (22.5%)	0.239[b]
Cancer	921 (12.4%)	248 (14.9%)	673 (11.7%)	0.177[b]
Immunodepression	250 (3.3%)	49 (2.9%)	201 (3.5%)	0.095[b]
Mean mRS	0.59 (1.2)	1.89 (1.21)	0.27 (0.56)	<0.001[a]

mRS modified Rankin scale

[a]Student *t* test

[b]Two-sided Fisher's exact test

Table 2 Frequency and type of general presenting symptoms in the whole sample and the two groups

Symptoms	All patients ($n=7370$)	Chronic neurological disorders ($n=1654$)	No-neurological comorbidity ($n=5716$)	Adjusted p value
Fever	5878 (79.7%)	1306 (78.9%)	4572 (79.9%)	0.918
Cough	5008 (67.9%)	893 (53.9%)	4115 (71.9%)	0.002
Dyspnea	3758 (50.99%)	843 (50.9%)	2915 (50.99%)	0.699
Weakness	3312 (44.9%)	512 (30.9%)	2800 (48.9%)	0.001
Diarrhea	2723 (36.9%)	380 (22.9%)	2343 (40.9%)	0.033
Headache	1774 (24%)	165 (9.97%)	1609 (28.1%)	0.002
Myalgia	1958 (26.5%)	244 (14.7%)	1714 (29.9%)	0.038
Chest pain	719 (9.7%)	148 (8.9%)	571 (9.9%)	0.441
Weakness	1162 (15.7%)	248 (14.9%)	914 (15.9%)	0.814
Expectoration	1309 (17.7%)	281 (16.9%)	1028 (17.9%)	0.556
Odynophagia	534 (7.2%)	132 (7.9%)	402 (7%)	0.612
Lightheadedness	312 (4.2%)	31 (1.8%)	680 (11.8%)	0.001
Vomiting	850 (11.5%)	264 (15.9%)	228 (3.9%)	0.360
Arthralgia	327 (4.4%)	99 (5.9%)	228 (3.9%)	0.787
Rhinorrhea	222 (3%)	58 (3.5%)	164 (2.8%)	1.000
Rash	174 (2.3%)	89 (5.3%)	85 (1.4)	0.025

p value adjusted for multiple comparisons

myalgia, headache and lightheadedness were less prevalent among those with CNDs than non-CNDs. However, the frequency of rash and vomiting were significantly greater than non-CND patients. Table 2 contains the frequency and type of general presentations.

Time (in days) from symptoms' onset to ED, ICU, and death

For cases suffering from CND, the mean time between initiation of presentations and ED visit was 6.12 (SD: 3.12) days, in comparison with 4.88 (SD: 2.67) days in those with no CND. After adjusting for age, mRS, gender, VRFs and comorbidities, linear regression analysis (LRA) was significant (B coefficient − 1.346, 95% CI − 2.756 to − 0.34, $p=0.036$). Based on the B coefficient, CND situation has a negative impact on the time interval. It means that patients with CND went to the ED later than patients without CND.

Regarding ICU admission, the mean time between symptom onset and ICU admission in cases suffering from CND was 7.34 (SD: 4.88) days, versus 9.18 (SD: 2.13) days in patients without CND. After adjusting, LRA was significant

Table 3 Treatment received per group and severity of COVID-19 disease

	All patients ($n=7370$)	Chronic neurological disorders ($n=1654$)	No-neurological comorbidity ($n=5716$)	Adjusted p value
Remdesivir	6034 (81.8%)	1405 (84.9%)	4629 (80.9%)	0.455
Hydroxychloroquine	6594 (89.4%)	1452 (87.7%)	5142 (89.9%)	0.873
Methylprednisolone	3690 (50%)	778 (47%)	2912 (50.9%)	0.661
Anticoagulant	5648 (76.6%)	1190 (71.9%)	4458 (77.9%)	0.318
Oxygen therapy	4998 (67.8%)	1455 (87.9%)	3543 (61.9%)	0.009
Any ventilatory support	1363 (18.4%)	562 (33.9%)	801 (14%)	0.001
Invasive ventilation	1117 (15.1%)	432 (26.1%)	685 (11.9%)	0.003
ICU admission	2152 (29.1%)	988 (59.7%)	1164 (20.3%)	0.044
Mild disease	485 (6.5%)	82 (4.9%)	403 (7%)	0.723
Pneumonia	2064 (28%)	178 (10.7%)	1886 (32.9%)	0.001
Severe pneumonia	2738 (37.1%)	909 (54.9%)	1829 (31.9%)	0.044
ADRS	1343 (18.2%)	529 (31.9%)	814 (14.2%)	0.027
Death	1451 (19.6%)	718 (43.4%)	733 (12.8%)	0.005

p value adjusted for multiple comparisons

ICU intensive care unit, *ADRS* acute distress respiratory syndrome

(B coefficient − 2.233, 95% CI − 2.545 to − 0.18, $p=0.003$). Based on the B coefficient, CND situation has a negative impact on the time interval between symptom onset and ICU admission. It means that patients with CND went to the ICU earlier than patients without CND.

Concerning the interval between symptom onset and death, the mean time in patients with CND with 8.14 (SD: 3.12) days was less than the figure in patients without CND with 12.17 (SD: 2.12) days. After adjusting, LRA was significant (B coefficient − 1.514, 95% CI − 2.674 to − 0.29, $p=0.004$). Based on the B coefficient, CND situation has a negative impact on the time interval between symptom onset and death. It means that patients with CND died earlier than patients without CND.

Diagnosis and management of patients

Chest imaging was abnormal in 6854 patients (92.9%). Frequency of remdesivir (84.9 vs. 80.9%, $p=0.455$), hydroxychloroquine (87.7 vs. 89.9%, $p=0.873$), and methylprednisolone use (47 vs. 50.9%, $p=0.661$) was similar between patients with and without CNDs. Furthermore, frequency of anticoagulant therapy (71.9 vs. 77.9%, $p=0.318$) was similar. Need of oxygen therapy (87.9 vs. 61.9%, $p=0.009$) and frequency of ventilator support (26.1 vs. 11.9%, $p=0.003$) were more common in CND cases. Likewise, ICU admission rate in CND patients with 59.7% was more frequent than the figure among non-CND patients with 20.3%. ($p=0.044$).

The course of the disease

Regarding the clinical course, 4081 (55.3%) cases suffered from severe pneumonia or ADRS, and 1451 (19.6%) died. The frequency of non-severe pneumonia was lower in cases suffering from a CND (10.7 vs. 32.9%, $p=0.001$), and severe pneumonia (54.9 vs. 31.9%, $p=0.044$) and ADRS (31.9 vs. 14.2%, $p=0.027$) were more frequent. Mortality of CND patients was 43.4%, compared to 12.8% in the rest of the sample ($p=0.005$). Information on treatment and severity of COVID-19 infection are provided in Table 3.

Primary endpoint: predictors of mortality

According to the univariate single regression analysis, baseline disability, age, diabetes, pulmonary disease, cardiac diseases, cancer, and chronic neurological disease were associated with higher odds of mortality.

Based on the univariate multiple regression analysis, which was performed on variables that were significant in the univariate single regression analysis, baseline disability (mRS3) and chronic neurological disorders presented a significant association (Table 4).

Based on the Cox regression, survival over time of those suffering from a CND was lower than others (HR 1.198, 95% CI 1.023–3.298, $p=0.003$), following adjustment for all variables included in the univariate multiple regression analysis (i.e., age, mRS, gender, presence of hypertension, diabetes, smoking habit, history of cardiac disease, pulmonary disorders, and history of cancer; Table 5). Figure 2 shows cumulative survival curves.

Table 4 Predictors of mortality: univariate single and univariate multiple regression analysis

	Type of analysis	OR	95% CI	*p* value	*B* coefficient[a]
mRS3	Single	9.413	5.562–18.423	0.004	–
	Multiple	3.133	1.065–5.147	0.032	2.877
Age	single	1.766	1.056–1.988	< 0.001	–
	Multiple	1.056	1.030–1.091	0.788	0.889
Female sex	Single	0.784	0.344–1.067	0.067	–
	Multiple	0.689	0.241–1.093	0.054	0.766
Hypertension	Single	2.532	2.026–4.891	0.088	–
	Multiple	1.451	0.709–2.014	0.119	1.075
Diabetes	Single	1.053	0.322–2.671	0.002	–
	Multiple	1.362	0.844–2.018	0.981	1.656
Smoking	Single	1.311	1.056–2.112	0.511	–
	Multiple	1.198	0.788–2.099	0.432	1.551
Cardiological disorders	Single	2.332	1.065–3.891	< 0.001	–
	Multiple	1.209	0.513–1.889	0.533	1.114
Pulmonary disorders	Single	1.122	0.896–2.223	0.008	–
	Multiple	0.819	0.342–1.856	0.981	1.779
Cancer	Single	1.017	1.002–2.433	0.003	–
	Multiple	1.891	0.565–2.717	0.323	1.898
Immunosuppression	Single	1.012	0.509–3.129	0.565	–
	Multiple	1.418	0.304–3.012	0.232	2.664
CND	Single	2.819	1.342–4.422	0.044	–
	Multiple	1.643	1.018–2.099	0.001	1.442

mRS modified Rankin Scale, *OR* odds ratio, *CI* confidence interval, *CND* chronic neurological disorders

[a]*B* coefficients are presented for multiple linear regression analysis

Table 5 Predictors of mortality. Cox-regression multivariate analysis

	HR	95% CI	*p* value
mRS3	2.819	1.513–3.117	0.771
Age	1.076	1.022–2.096	0.542
Female sex	1.032	0.543–1.218	0.670
Hypertension	1.241	0.619–1.877	0.054
Diabetes	1.253	0.418–1.573	0.371
Smoking	0.419	0.225–2.188	0.285
Cardiological disorders	1.819	0.815–2.159	0.065
Pulmonary disorders	1.127	0.318–1.168	0.349
Cancer	1.516	0.819–1.743	0.843
CND	2.187	1.018–3.566	0.005

Predictors of severe COVID-19 infection

Based on the univariate single regression analysis, baseline disability, age, diabetes, smoking, and CND were associated with higher odds of severe COVID-19 infection. However, in the univariate multiple regression analysis, only mRs ($p = 0.043$) and CND ($p = 0.004$) were still significant (Table 6).

Laboratory findings

Except for GFR ($p = 0.061$), the frequency of abnormal results for other laboratory factors was higher during hospitalization in comparison with the admission (Table 7).

The odds of having enhanced INR during hospitalization were higher for those suffering from a CND (OR 1.715, 95% CI 1.122–3.189, $p = 0.031$). Also, those with a CND had higher odds of enhanced CRP on admission (OR 1.714, 95% CI 0.309–3.189, $p = 0.041$) and also during hospitalization (OR 5.972, 95% CI 0.809–28.144, $p = 0.001$), after adjusting for age, mRS, gender, and history of hypertension, diabetes, smoking habit, and other comorbidities (Table 8).

Discussion

The majority of protocols developed for COVID-19 management emphasized close monitoring of those with comorbidities [25]. Nevertheless, there are few recommendations for neurological comorbidities. The majority of previous studies did not investigate the frequency of CND comorbidities in cases suffering from COVID-19 infection [7, 9]. Based on our study, CND could independently predict in-hospital mortality and severity of COVID-19.

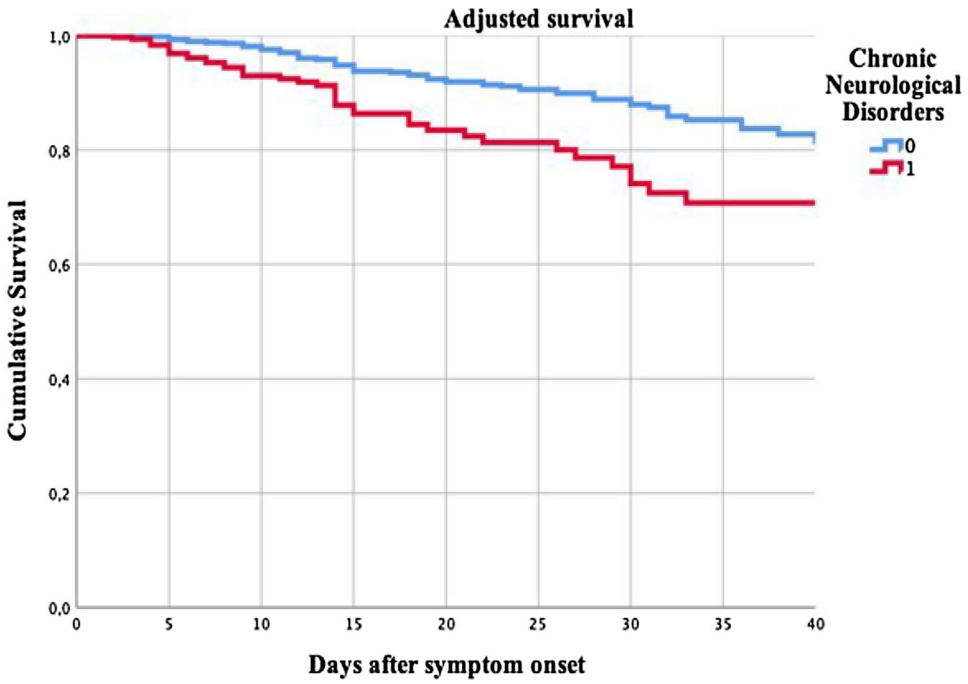

Fig. 2 Cumulative survival of patients with and without chronic neurological disorders. Kaplan–Meier curves. *Y* axis: cumulative survival. *X* axis: days after the symptoms onset

Those suffering from a CND were older, disability was higher among them, and had a higher prevalence of VRFs and other comorbidities, which all were associated with increased risk of mortality in most COVID-19 series [1–3].

COVID-19 clinical presentations in CND patients were not as common as we expected from COVID-19 disease. Indeed, the frequency of some typical symptoms, such as cough and weakness, was lower. Moreover, the most frequently reported neurological symptoms, myalgia, and headache [26, 27], were less common. By contrast, the frequency of uncommon COVID-19 symptoms such as rash and vomiting [9] was significantly more than the figures in non-CND patients.

The frequency of ADRS and severe pneumonia was higher among those suffering from CND. In addition, they had higher rates of mortality and ICU admissions. So, why did CND patients have worse outcomes compared with non-CND ones?

The reasons might be the worst baseline performance, being older, the uncommon clinical expression, and the higher frequency of VRFs and other comorbidities. Moreover, it can be attributed to the delayed ED presentation. In this regard, in the present study, cases with CND came later to the ED compared with non-CND patients. However, a retrospective cohort study included 576 COVID-19 hospitalized patients has shown that the mean time between initiation of presentations and ED visit in cases suffering from CND with 5.27 (SD: 7.72) was significantly less than the figure in non-CND patients with 7.81 (SD: 5.66) days ($p = 0.046$) [9]. Furthermore, a cohort performed on 201 cases with a confirmed diagnosis of COVID-19 pneumonia did not mention any considerable connection between the latency time and COVID-19 prognosis [8]. Hence, the observed worse prognosis cannot be attributed to delayed treatment.

This study also intended to evaluate whether those suffering from a CND received standard medication and intensive care intervention less often. More than 70% of CND patients received pharmacological treatment according to the local SOC. Although the clinical advantage of such drugs is still not identified [28], the observed worse prognosis cannot be attributed to limitations regarding the provided treatment.

Due to the collapse of the health system, ICU guidelines deemed to prioritize the resource allocation to those patients with a confirmed higher potential benefit [29]. However, in this study, those suffering from a CND benefited from ICU admission (59.7%) more than non-CND ones (20.3%). Hence, the lack of standard intensive care intervention could not be the reason for the worse prognosis.

The need of oxygen therapy and invasive ventilation was more frequent in those suffering from a CND. Also, ICU admission occurred faster in CND patients. Therefore, a probable reason for the higher mortality is higher severity of COVID-19 in CND patients compared with non-CND ones.

This study also intended to investigate whether abnormal laboratory values is more common in those suffering a CND compared to others after adjusting for all variables that were potentially confounder. Nevertheless, only enhanced INR and CRP showed a significant association.

Higher frequency of INR in those suffering a CND is difficult to find and can be attributed to hepatic failure due

Table 6 Predictors of severe COVID-19 disease: univariate single and univariate multiple regression analysis

	Type of analysis	OR	95% CI	*p* value	*B* coefficient[a]
mRS3	Single	2.817	1.012–3.616	0.002	–
	Multiple	1.998	1.032–2.718	0.043	2.433
Age	Single	2.754	1.086–2.217	< 0.001	–
	Multiple	1.005	0.588–1.798	0.418	1.889
Female sex	Single	0.655	0.214–1.719	0.079	–
	Multiple	1.719	0.836–1.719	0.554	1.554
Hypertension	Single	1.627	1.526–2.719	0.091	–
	Multiple	1.532	0.809–2.012	0.315	1.655
Diabetes	Single	2.056	1.156–3.677	0.002	–
	Multiple	1.719	0.977–2.566	0.716	1.321
Smoking	Single	2.544	1.068–2.578	0.001	–
	Multiple	1.053	0.819–1.982	0.715	0.979
Cardiological disorders	Single	1.899	1.054–1.997	0.421	–
	Multiple	1.617	0.467–1.891	0.815	1.544
Pulmonary disorders	Single	0.819	0.446–1.032	0.079	–
	Multiple	1.546	0.992–1.878	0.072	1.434
Cancer	Single	1.013	0.544–1.817	0.895	–
	Multiple	1.023	0.676–1.529	0.082	1.243
Immunosuppression	Single	1.017	0.728–1.552	0.882	–
	Multiple	1.045	0.824–1.628	0.091	1.798
CND	Single	2.518	1.023–4.057	0.044	–
	Multiple	2.716	1.052–3.083	0.004	2.654

mRS modified Rankin Scale, *OR* odds ratio, *CI* confidence interval, *CND* chronic neurological disorders

[a]*B* coefficients are presented for multiple linear regression analysis

Table 7 Frequency of abnormal values on admission and during the hospitalization period among 7370 patients with COVID-19

	% abnormal on admission	% abnormal during hospitalization	Adjusted *p* value
Leukocytes (RV 4–10)[a]	1842 (24.9%)	5011/7370 (67.9%)	0.003
Lymphocytes (RV 0.9–5.2)[a]	3095/7370 (41.9%)	5306/7370 (71.9%)	0.001
Hemoglobin (RV 12–16)[a]	1105/7370 (14.9%)	3758/7370 (50.9%)	< 0.001
Platelets (RV 150–400)[a]	1842/7370 (24.9%)	3611/7370 (48.9%)	0.032
LDH (RV 135–250)[b]	2505/7370 (33.9%)	5745/7370 (77.9%)	0.001
Corrected GFR (RV > 90)[c]	5085 (68.9%)	5232 (70.9%)	0.061
INR (RV 0.8–1.3)	1695 (22.9%)	4274 (57.9%)	0.001
D-dimer (RV: < 500)[d]	3537 (47.9%)	6264 (84.9%)	0.023
C-reactive protein (RV: 1–5)[e]	3537 (47.9%)	7075 (95.9%)	0.001
Ferritin (RV: 15–150)[f]	4643 (62.9%)	7001 (94.9%)	0.005

p value adjusted for multiple comparisons

RV reference value, *LDH* lactate dehydrogenase, *GFR* glomerular filtration rate, *INR* international normalized ratio

[a]Units: count × 109/L

[b]Units: U/L

[c]Units: mL/min/1.73 m^3

[d]Units: ng/dL

[e]Units: mg/L

[f]Units: ng/mL

Table 8 Results of the regression analysis in the association between CND and abnormal laboratory parameters

	Situation	OR	95% CI	Adjusted *p* value
Abnormal leukocyte count (RV 4–10 × 109/L)	On admission	1.815	0.812–2.996	0.067
	During hospitalization	1.312	0.740–1.615	0.112
Lymphopenia (< 900 lymphocytes × 109/L)	On admission	1.457	0.801–2.133	0.614
	During hospitalization	1.766	1.412–2.129	0.418
Anemia (< 129 units/L)	On admission	1.668	0.771–2.918	0.412
	During hospitalization	1.132	0.719–2.329	0.082
Abnormal platelet count (RV 150–400)	On admission	0.817	0.412–1.018	0.441
	During hospitalization	1.719	0.993–2.516	0.912
Increased LDH (> 250 Units/L)	On admission	1.688	0.711–2.712	0.058
	During hospitalization	1.836	1.012–2.995	0.077
Abnormal GFR (< 90 mL/min/1.73 m^3)	On admission	1.014	0.614–1.813	0.521
	During hospitalization	0.712	0.311–1.552	0.605
Increased INR (> 1.3)	On admission	1.301	0.504–2.981	0.097
	During hospitalization	1.715	1.122–3.189	0.031
Abnormal D-dimer (> 500 ng/dL)	On admission	1.722	0.904–2.602	0.179
	During hospitalization	1.144	0.703–2.122	0.899
Increased CRP (> 5 mg/L)	On admission	1.714	0.309–3.189	0.041
	During hospitalization	5.972	0.809–28.144	0.001
Increased ferritin (> 150 ng/mL)	On admission	0.817	0.302–2.981	0.516
	During hospitalization	0.711	0.435–2.189	0.467

OR odds ratio, *CI* confidence interval, *GFR* glomerular filtration rate, *INR* international normalized ratio

p value by age, modified Rankin scale and sex

to sepsis, declined levels of vitamin K, or acute liver failure [30]. Therefore, another plausible explanation for worse prognosis of those suffering a CND is the higher fragility and lower reserve of them [31].

The role of CND as an independent predictor of in-hospital mortality is well-established [32, 33]. There are evidence indicating the connection between history of stroke and a higher odds of severe COVID-19 infection [14]. This issue can be attributed to various reasons, such as frequency of delirium [18, 34], malnutrition [35], impaired respiratory function [36], and worse self-management [37], many of which can be exacerbated by COVID-19 and the use of personal protective equipment adds to difficulty of its management [38].

Limitations

This study has some limitations., including using an operative definition of CND, according to the persistent effect on functionality; nevertheless, this definition is not perfect. In addition, the relevance of all neurological disorders is not similar. The authors suggest focusing on the particular impact of various neurological comorbidities and their separate analysis in future studies.

Also, since the pandemic, we have faced SARS-CoV-2 variants. We should have considered these variants in the analysis. Unfortunately, we did not have any access to specific PCR tests. The clarification of COVID-19 subtypes in at-risk patients might improve our prospects in the future.

We tried to coordinate and observe health members' performance who involved in caring of COVID-19 patients in our three hospitals. Although different management of patients, especially at the nursing care level in different hospitals, are an acknowledged fact, we should have involved the impact of the type of inpatient care and differences in administered protocols, when analyzing the data.

Even though our study was carried out in three medical centers, we suggest following a multinational design, mainly due to differences observed in adjusted mortality rates reported in various nations. One cannot conclude whether it is due to genetic-related factors for severe COVID-19 or differences among healthcare systems.

Also, this research did not include a long-term follow-up, and a number of participants were still hospitalized at the end of the study, which probably has resulted in an underestimation of mortality. Also, the sample does not represent the whole population, as we only recruited hospitalized cases, which probably affected the results.

In this study, we included only hospitalized patients. This recruitment is a potential bias. However, we wanted to have strong access to patients to evaluate the primary and secondary outcomes closely and without losing the

participants. In this regard, we recommend future studies consider both groups of hospitalized and outpatients to achieve stronger results.

We had a significant problem with the vaccination status. we did not enroll patients who had a history of COVID-19 vaccination in the study. We made this decision because of a significant lack of reporting systems. Actually, based on a report system that was dedicated to COVID-19 vaccination status in our region, we could just inform if a patient got a vaccine or not, but the specific details, such as the type of vaccine and in which round the patients were, were unclear. Consequently, it was confusing if we enrolled vaccination status in the study without knowing about the name and other specific features of the vaccines. So, we just enrolled unvaccinated patients. However, we strongly recommend that future studies enroll vaccination status to obtain more reliable results.

We did not assess genetic causes that could link COVID-19 severity and neurological diseases. Based on a review article, the early- and late-onset Alzheimer's disease genes play a role in the susceptibility of patients who currently suffer or have recovered from COVID-19 to Alzheimer's disease [39]. To draw a better picture of the relationship between COVD 19 and neurological disorders, we suggest that future studies consider genetic links between COVD 19 and CNDs.

Conclusion

CNDs could independently predict the death and severity of COVID-19. Therefore, early diagnosis of COVID-19 should be considered in CND patients. In these at-risk COVID-19 patients, continuous monitoring can be used for preventing complications and improving outcomes. The reasons why CND patients with COVID-19 had worse outcomes might be the worst baseline performance, the uncommon clinical presentations, delayed emergency department (ED) presentation, and more severe COVID-19 disease. However, these reasons are widely controversial.

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Data Availability The data for this article is available.

Declarations

Conflict of interest All authors declared that they had no conflict of interest.

Ethical approval The study protocol was approved by the Institutional Review Board of Arak University of Medical Sciences. All participants signed the written informed consents (designed based on local review board recommendations) before entering the study. This study was designed and conducted according to the Declaration of Helsinki and its subsequent revisions.

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