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Original article

The effects of Alzheimer's and Parkinson's disease on 28-day mortality of COVID-19



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INFO ARTICLE

Article history:

Received 12 July 2021

Received in revised form

18 August 2021

Accepted 27 August 2021

Available online 13 September 2021

Keywords:

Alzheimer

Parkinson

COVID-19

Neurodegenerative

Mortality

Survival

ABSTRACT

We compared the prognosis of inpatients with a known diagnosis of Alzheimer's or Parkinson's disease who have COVID-19 infection with other hospitalized patients with COVID-19. Our cohort study started in October 2020 and ended in May 2021 and included inpatients with COVID-19 infection who were admitted to hospitals. From a total of 67,871 patients with a confirmed diagnosis of COVID-19, a sample of 3732 individuals were selected of which 363 had Alzheimer's, and 259 had Parkinson's disease. All patients had both positive RT-PCR test and positive chest CT for COVID-19. The outcome was dead within 28 days of admission and the predictors were a large number of demographic and clinical features, and comorbidities recorded at patients' bedside. Mortality were 37.5%, 35.1%, and 29.5% in patients with Alzheimer's disease, Parkinson's disease; and in other patients, respectively. The hazard ratio for Alzheimer's disease was 1.27 (95% CI, 1.06–1.53, $p = 0.010$) and for Parkinson's disease was 1.17 (95% CI, 0.94–1.46, $p = 0.171$). Age was a predictor of mortality, hazard ratio = 1.04 (95% CI, 1.03–1.05, $p < 0.001$). Patients with Alzheimer's disease and COVID-19 infection were older and more likely to have a loss of consciousness on admission (both $p \leq 0.001$). We concluded that inpatients with Alzheimer's disease have an increased risk for 28-day mortality from COVID-19 and healthcare settings should be ready to provide critical care for them such as early intubation and immediate O₂ therapy. However, Parkinson's disease does not significantly predict higher mortality of COVID-19.

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<https://doi.org/10.1016/j.neurol.2021.08.002>

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1. Introduction

Reducing mortality of COVID-19 requires the development of risk-based strategies [1]. Risk stratification allows to identify patients with a higher likelihood for mortality and to prioritize the allocation of health resources [2]. Overall, inpatient mortality from COVID-19 is 15–20%, and 40% of hospitalized patients require intensive care [3]. However, reports from different populations show variability in mortality rates of COVID-19 [1]. Hospital mortality is estimated to be less than 5% for individuals younger than 40 years, 35% for patients aged 70 to 79 years, and more than 60% for people 80 to 89 years of age [4]. Individuals undergoing kidney transplant or dialysis; and patients with cancer, diabetes, neurologic or cardiovascular diseases are suggested to be at increased risk for mortality [5–9].

Research studies suggested that SARS-CoV-2 can invade the central nervous system and initiate neurological manifestations [10,11]. Dementia has been reported as common comorbidity in patients with COVID-19 [12,13]. Also, Alzheimer's disease (AD) is suspected of increasing the mortality rate of COVID-19 among inpatients and people living in care homes [14–16]. The restrictions imposed due to the COVID-19 pandemic are capable of worsening motor and non-motor symptoms in Parkinson's disease (PD) [17]. Studies suggested that case fatality is higher in patients having COVID-19 and Parkinson's disease [18]. However, some researchers suggested that PD does not increase mortality from COVID-19 [19].

Overall, the study design, populations, sample size, and the diagnostic criteria of COVID-19 varied between studies on the mortality risk of COVID-19 in patients with neurodegenerative diseases (NDD) [20]. These inconsistencies lead to inconclusive mortality data and necessitate further epidemiological studies [21,22]. Particularly, a longitudinal follow-up of patients is required to reveal the impact of NDD on mortality of COVID-19 [23].

Early at the onset of COVID-19, findings on chest computerized tomography (CT) include ground-glass opacity with bilateral peripheral involvement in multiple lobes and consolidation [24]. The disease is commonly diagnosed using a reverse transcription-polymerase chain reaction (RT-PCR) test with 20% to 67% false-negative based on time since exposure [25]. In patients with clinical suspicion of COVID-19, the negative test result should be interpreted together with other clinical and paraclinical evidence [25].

The aim of conducting this longitudinal study was to compare the prognosis of inpatients with a known diagnosis of AD or PD who have COVID-19 infection with other hospitalized people with COVID-19. We researched the risk of mortality within 28 days of admission using a large number of clinical indicators. The diagnosis of COVID-19 infection was confirmed by both RT-PCR and chest CT for all patients. We hypothesized that the three groups would differ in mortality risk of COVID-19.

2. Patients and methods

2.1. Design and settings

We assessed the risk for mortality of COVID-19 among patients with and without NDD. Our multicenter cohort study

of hospitalized patients started in October 25, 2020 and ended in May 27, 2021. The target population was people with COVID-19 infection who were admitted to university healthcare centers. This research was conducted by the Critical Care Quality Improvement Research Center, affiliated with Shahid Beheshti University of Medical Sciences. We gathered data with the help of 63 medical universities in their 816 affiliated healthcare centers. Ethics approval was obtained from the Institutional Review Boards of Shahid Beheshti University of Medical Sciences with the ethics code of IR.SBMU.RETECH.REC.1399.499. At the admission time, written consent was taken from all participants or their companions. No personally identifiable information including the patient's name and social security number was entered into the analytical data.

2.2. Eligibility

We included all people who were hospitalized with a confirmed diagnosis of COVID-19 infection. All patients were monitored for progressive signs of respiratory failure and shock. Acute respiratory distress syndrome was diagnosed based on the Berlin definition [26]. We used pharmacological prophylaxis to prevent thromboembolism when not contraindicated. The complications associated with critical care, such as ventilator-associated pneumonia and catheter-related bloodstream infection, were prevented according to the standard practice [27,28]. The registration process was online using a single electronic form. Patients were considered as having the new coronavirus infection if they had a positive RT-PCR test plus a positive chest CT finding for COVID-19. The RT-PCR result was reported based on testing collected specimens from the upper respiratory tract. Radiologists or pulmonologists read CT images using the guidelines reported in the literature [29]. Both RT-PCR test results and CT findings were recorded as binary values. People with AD or PD were identified with their past medical history and records. At each healthcare center a general practitioner was responsible for data collection. At the end of the process of patient pooling, we had three groups of COVID-19 (COV), COV + AD, and COV + PD.

2.3. Outcome and predictors

The outcome was dead within 28 days of admission. Because there is still no definitive cure for COVID-19 infection we considered that the predictive effect of the interventions is small compared with the other predictors. Most of the data were collected early in admission and later in reviewing patients' medical records. All predictors were clinical features and were recorded easily at patients' bedside to achieve high practicality. Collected data were saved as a Microsoft Excel® spreadsheet. For resolving the imbalance in NDD we carried out random sampling of the COV group. Predictors with a less than 5% frequency for at least one of its levels were considered as highly imbalanced and were excluded from further analysis. There were no missing data for the outcome variable and duration of hospital stay. We did not recognize any possibility for lacking randomness for missing data in predictors and imputed them.

2.4. Statistical analyses and modeling

Results are presented as mean (SD) for continuous variables and as absolute numbers (percentage) for categorical data. The means of the continuous variables were compared using t-test or Analysis of Variance (ANOVA) tests where appropriate. Either a χ^2 or Fisher exact test was used for testing differences among the groups for categorical variables. For statistical analyses, p-values less than 0.05 were considered significant. Median hospital stay (day) was compared among three groups with the Kruskal-Wallis test, and between two groups with the Wilcoxon rank sum test. The survival curves for the three groups of patients were constructed with the Kaplan-Meier method and were compared with the log-rank test. The Cox proportional-hazards model was used to investigate the association between survival time and predictors. We used R software version 4.0.2 for data analysis and visualization. R is a free software environment, well known for its statistical and machine learning libraries and graphics. We used a variety of R packages for the analysis. All the packages were downloaded from the Comprehensive R Archive Network (<https://cran.r-project.org/>), the official R package repository, or the GitHub (<https://github.com/>) website.

3. Results

3.1. Sample

We had 67,871 patients with a confirmed diagnosis of COVID-19 of which 622 (0.9%) had NDD. Of the patients with NDD, 363 (58.4%) had AD, and 259 (41.6%) had PD. Because of severe imbalance in the number of patients with NDD, we randomly under-sampled the COV group to provide 1:5 ratios of COV+NDD: COV patients in the final sample. Each COV patient was randomly selected as an individually age- and sex-matched to NDD patients. At the end of the process, the analytic sample included 3732 patients (3110 COV, 363 COV + AD, and 259 COV + PD) and 320 (0.3%) missing data. The missing data included 247 (6.6%) for the respiratory rate, 64 (1.7%) for O₂ therapy, 3 (0.08%) for PaO₂, 3 (0.08%) for the temperature at admission, and 3 (0.08%) for the day of beginning the symptoms before admission. The missing data were imputed using predictive mean matching. We excluded highly imbalanced predictors from the analysis including seizure, paresis or plegia, dermatologic and hematologic problems, liver diseases, HIV/AIDS, cancer, chemotherapy or immune deficiency, loss of smell or taste, abdominal or chest pain, vomiting, diarrhea, vertigo, urological disease or dialysis, smoking or drug abuse, and asthma. Fig. 1 shows the flow of data in this study.

Based on the remaining features, Table 1 shows the characteristics of the two groups of patients. Mortality rates were 29.5%, 37.5%, and 35.1% in COV, COV + AD, and COV + PD, respectively. The percentages of intubation, O₂ therapy on admission, loss of consciousness, respiratory distress, systolic hypertension, diabetes, cardiovascular disease, and AD were significantly higher and the percentages of myalgia and headache were significantly lower in dead patients. Also, there was a significant difference in respiratory rate categories

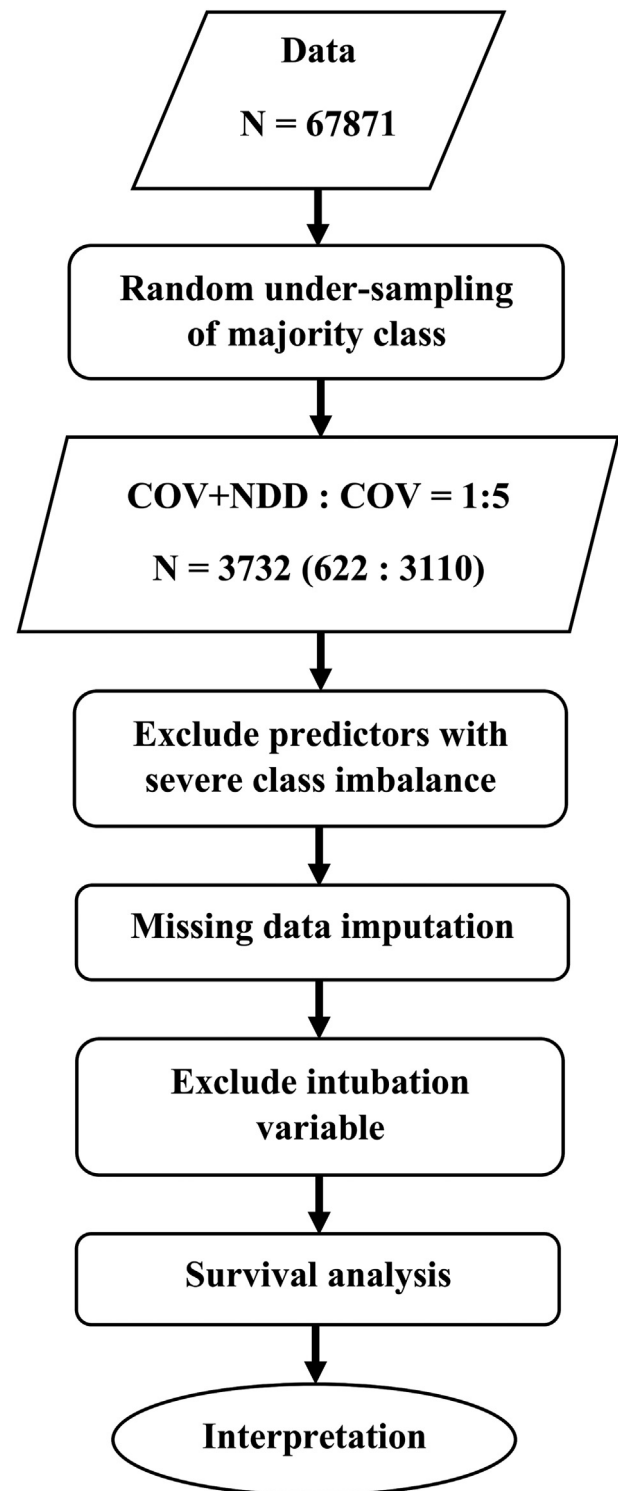


Fig. 1 – Data flow chart of the study. COV: patient with a confirmed diagnosis of COVID-19 infection; NDD: neurodegenerative diseases.

between alive and dead patients. In addition, dead people were older and presented with a lower PaO₂ on admission. It seems that the symptoms progressed more quickly in the dead group before admission. Also, comparisons of the three groups indicated that patients with COV + AD were the oldest and

Table 1 – Patients’ characteristics in alive and dead groups.

Feature	Group		p	Group			p
	Alive (n = 2586)	Dead (n = 1146)		COV (n = 3110)	COV + AD (n = 363)	COV + PD (n = 259)	
Intubation (%)	75 (2.9)	514 (44.9)	< 0.001*	476 (15.3)	67 (18.5)	46 (17.8)	0.197
Mean (SD) age (year)	76.1 (10.1)	79.7 (8.3)	< 0.001*	77.2 (9.7)	80.2 (7.9)	73 (10.5)	0.001*
Woman (%)	978 (37.8)	420 (36.6)	0.519	1165 (37.5)	153 (42.1)	80 (30.9)	0.017*
Mean (SD) PaO ₂ (mmHg)	88.4 (7.9)	81.9 (13.1)	< 0.001*	86.5 (10.2)	85.5 (10.7)	86.3 (9.7)	0.271
O ₂ therapy early at admission (%)	1293 (50.0)	687 (59.9)	< 0.001*	1635 (52.6)	215 (59.2)	130 (50.2)	0.035*
Respiratory Rate (%)							
< 14	4 (0.2)	13 (1.1)	< 0.001*	14 (0.5)	2 (0.6)	1 (0.4)	0.921
14–18	669 (25.9)	246 (21.5)		770 (24.8)	83 (22.9)	62 (23.9)	
18–22	1417 (54.8)	560 (48.9)		1656 (53.2)	188 (51.8)	133 (51.4)	
22–28	431 (16.7)	263 (22.9)		564 (18.1)	76 (20.9)	54 (20.8)	
> 28	65 (2.5)	64 (5.6)		106 (3.4)	14 (3.9)	9 (3.5)	
Mean (SD) Temperature (°C)	37.2 (1.6)	37.2 (0.7)	0.785	37.2 (1.5)	37.2 (0.7)	37.3 (0.7)	0.989
Fever (%)	837 (32.4)	382 (33.3)	0.587	1004 (32.3)	121 (33.3)	94 (36.3)	0.4
Loss of Consciousness (%)	153 (5.9)	210 (18.3)	< 0.001*	238 (7.7)	81 (22.3)	44 (17)	< 0.001*
Respiratory Distress (%)	1451 (56.1)	813 (70.9)	< 0.001*	1911 (61.4)	202 (55.6)	151 (58.3)	0.073
Myalgia (%)	803 (31.1)	305 (26.6)	0.007*	997 (32.1)	59 (16.3)	52 (20.1)	< 0.001*
Cough (%)	1105 (42.7)	486 (42.4)	0.883	1383 (44.5)	125 (34.4)	83 (32.0)	< 0.001*
Systolic Hypertension (%)	821 (31.7)	410 (35.8)	0.017*	1019 (32.8)	117 (32.2)	95 (36.7)	0.415
Nausea (%)	219 (8.5)	75 (6.5)	0.052†	268 (8.6)	13 (3.6)	13 (5.0)	< 0.001*
Anorexia (%)	397 (15.4)	150 (13.1)	0.08	459 (14.8)	53 (14.6)	35 (13.5)	0.862
Headache (%)	218 (8.4)	57 (5.0)	< 0.001*	252 (8.1)	10 (2.8)	13 (5.0)	< 0.001*
Diabetes (%)	529 (20.5)	268 (23.4)	0.049*	672 (21.6)	80 (22)	45 (17.4)	0.264
Cardiovascular Disease (%)	470 (18.2)	274 (23.9)	< 0.001*	640 (20.6)	57 (15.7)	47 (18.1)	0.067†
Positive Contact History (%)	1203 (46.5)	537 (46.9)	0.876	1452 (46.7)	170 (46.8)	118 (45.6)	0.937
Mean (SD) Start of symptoms before admission (days)	5.6 (3.9)	5.3 (4.1)	0.042*	5.5 (3.9)	5.4 (4.4)	5.7 (4.5)	0.594
COV (%)	2191 (84.7)	919 (80.2)	< 0.001*				
COV + AD (%)	227 (8.8)	136 (11.9)	0.004*				
COV + PD (%)	168 (6.5)	91 (7.9)	0.127				

Categorical variables were compared with χ^2 , and continuous variables were compared with t-test for independent samples between alive and dead groups, and with ANOVA test among COV, COV + AD, and COV + PD groups. SD: Standard Deviation; PaO₂: Partial Pressure of Oxygen; COV: Patient with a confirmed diagnosis of COVID-19 infection; AD: Alzheimer’s Disease; PD: Parkinson’s Disease.

* Significant at $p < 0.05$.

† Approaching significance.

mostly women. They comprised the largest percentage of O₂ therapy and loss of consciousness on admission. The COV group showed the largest percentage of myalgia, cough, nausea, and headache. Of the measured predictors, intubation on admission was highly significant in predicting the poor outcome of hospitalization (Table 1). Fig. 2 shows the mosaic plot for comparing not intubated with intubated patients in the proportion of mortality. The odds ratio of intubation for in-hospital mortality was 27.2 with the 95%CI of 21.1 to 35.2. We excluded intubation from further analyses as it highly influenced the process of modeling.

3.2. Survival analysis

The median hospital stay was 6, 6, and 7 days for COV, COV + AD, and COV + PD groups (Kruskal-Wallis $\chi^2(2) = 5.4429$, $p = 0.066$). Pairwise Wilcoxon rank sum test showed that there is a significant difference between COV + AD and COV + PD in median hospital stay ($W = 42,008$, $p = 0.023$). Fig. 3 illustrates Kaplan-Meier curves for survival probability. Early at admission, the curves are parallel, however, they separate gradually with a steeper decline in the COV + AD group. The Cox

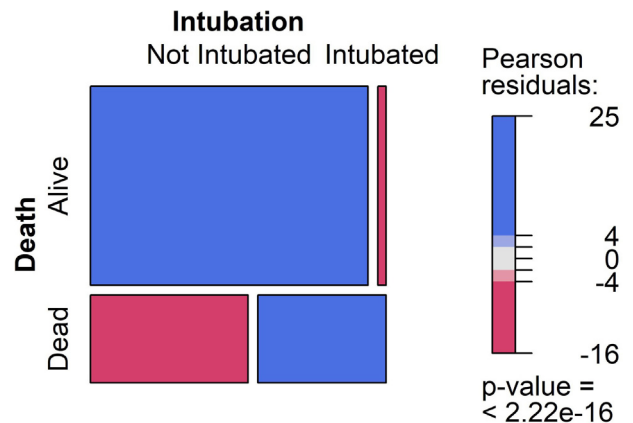


Fig. 2 – Mosaic plot for death vs. intubation. The column widths indicate the relative proportions of the corresponding values at each variable. The blue color means there are more observations in that cell than would have been expected under the null hypothesis of independence. The red color indicates that there are fewer observations than would have been expected.

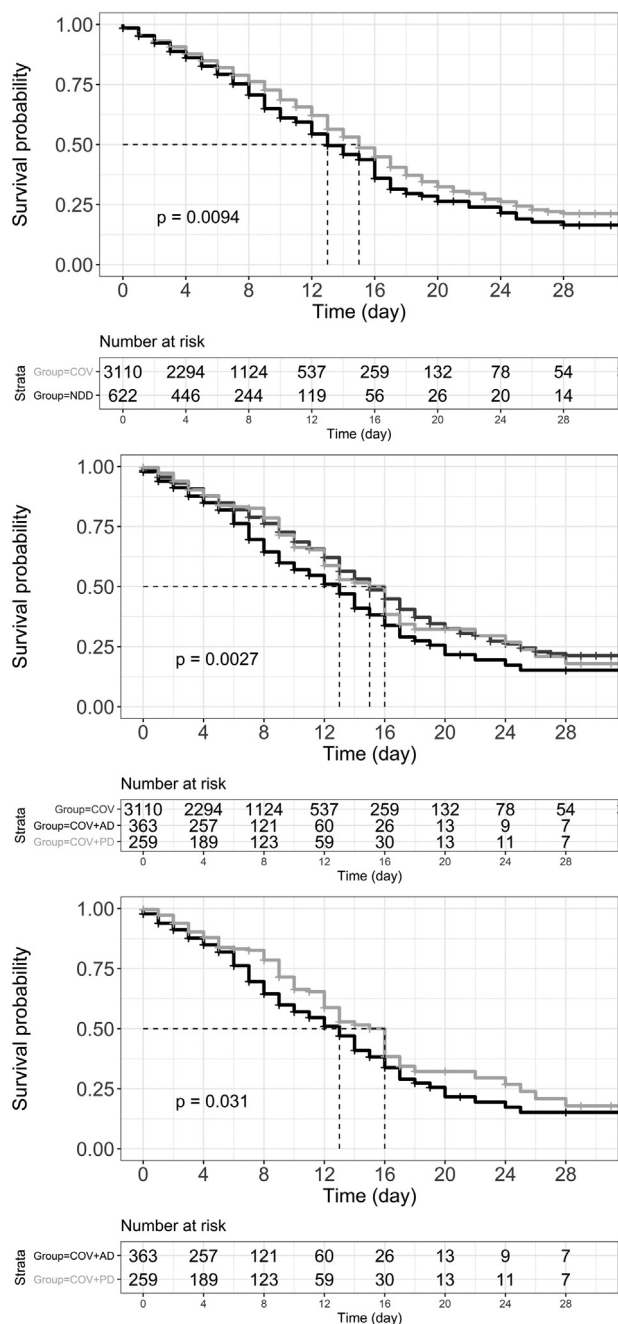


Fig. 3 – Kaplan-Meier curve of survival probability. The dashed lines represent median survival and p values show if there is a difference between the survival curves using rank tests. Top: COV (light gray) and NDD (black) groups. Middle: COV (dark gray), COV + AD (black), and COV + PD (light gray). Bottom: COV + AD (black) and COV + PD (light gray). COV: Patient with a confirmed diagnosis of COVID-19 infection; AD: Alzheimer’s Disease; PD: Parkinson’s Disease.

proportional-hazards model incorporating fixed (non-time-dependent) covariates significantly predicted the risk for mortality; Wald $\chi^2(8) = 122.8, p < 0.001$ (Table 2). Hazard ratios showed that AD is a significant predictor of mortality in patients with COVID-19 infection.

4. Discussion

This study was conducted to investigate the effects of AD and PD on the prognosis of hospitalized patients with COVID-19 infection. We included patients diagnosed as having COVID-19 infection using both RT-PCR and chest CT findings and evaluated their risk of mortality within 28 days of admission. A large number of predictors were recorded including demographic features, clinical manifestations, and comorbidities.

Our data showed that patients who died were older and presented to the healthcare centers with more critical symptoms such as loss of consciousness, respiratory distress, systolic hypertension, and lower PaO₂. They had diabetes or cardiovascular disease more frequently and needed early intubation and O₂ therapy more than patients with good prognoses. Also, dead people showed relatively faster progress of symptoms before admission. Meanwhile, patients who remained alive during the first 28 days of hospitalization experienced myalgia and headache more frequently. We found that AD significantly affects the risk for mortality. Patients with COV + AD were older than the other groups and were mostly women. They also were frequently presented to hospitals with more serious manifestations such as loss of consciousness and needed more serious care such as early intubation and O₂ therapy compared with COV and COV + PD groups. In contrast, patients without NDD experienced myalgia, cough, nausea, and headache more commonly compared with the NDD group.

Matias-Guiu et al. carried out a case series study to evaluate the frequency and mortality of COVID-19 in patients with AD and frontotemporal dementia. They included 204 individuals; 147 patients with AD and 57 with frontotemporal dementia. Overall, 22 (15.0%) of patients had COVID-19 and AD. They reported that in patients with COVID-19, 12 out of 22 (54.5%) patients with AD died and concluded that AD is associated with a higher risk for mortality than frontotemporal dementia. Also, they suggested that increasing age might be associated with a higher mortality rate while their logistic model did not assign a significant role to age [14]. Our study was longitudinal and quite larger; we found significant and independent effects for age and AD on mortality of COVID-19. Similarly, our AD group was older and mostly female. Of the 363 patients with COV + AD in our study, 136 (37.5% of AD patients) died which is smaller than the mortality rate of patients with AD in Matias-Guiu’s study. Inclusion of patients with AD without stratification of severity and residency (home and care home) might have diluted our percentage.

Similar pathological changes in AD and COVID-19 might increase the risk for mortality in a synergistic manner. Commonly, AD affects patients more than 65 years of age with a prevalence that doubles every 5 years [30]. Also, aging is a known risk factor for mortality of COVID-19 [4]. In addition, the excessive expression of viral receptor angiotensin-converting enzyme 2 and pro-inflammatory molecules, the comorbidities of AD complications such as diabetes, lifestyle alterations in AD, and behavioral changes imposed by COVID-19 have been suggested to increase the risk for mortality of COVID-19 in patients with AD [11]. Inflammatory mediators

Table 2 – Cox proportional-hazards regression for the survival data.

Feature	Hazard	95% CI		p
		Lower Limit	Upper Limit	
PD	1.17	0.94	1.46	0.171
AD	1.27	1.06	1.53	0.010*
Age (year)	1.04	1.03	1.05	< 0.001*
Sex (male)	1.07	0.95	1.21	0.254
Diabetes	1.15	0.99	1.33	0.057†
Cardiovascular Disease	1.12	0.98	1.29	0.105
Contact History	0.98	0.87	1.10	0.679
Start of symptoms before admission (days)	0.97	0.96	0.99	0.005*

AD: Alzheimer's Disease; PD: Parkinson's Disease.
 * Significant at $p < 0.05$.
 † Approaching significance.

have been suggested to induce CNS manifestations and immunological processes in the peripheral nervous system of patients with COVID-19 infection. Interleukin 6 and 1, cytoskeleton-associated protein 4, and galectin 9 are thought as the common links between COVID-19 and AD manifestations [31].

Scherbaum et al. carried out a cross-sectional nationwide assessment of hospitalized patients with PD in Germany and evaluated the impact of the COVID-19 pandemic. They reported that patients with PD aged 65 years or older were at higher risk of COVID-19 and that advanced age and male sex were more frequent in COVID-19. The COVID-19 inpatient mortality rate was higher in PD than in non-PD patients (35.4% vs. 20.7%, $p < 0.001$), particularly in patients aged 75–79 years. They concluded that PD inpatients are more frequently affected by COVID-19 and had increased COVID-19-associated mortality compared with non-PD patients. Meanwhile, they warranted that more studies are needed to assess the significance of associated comorbidities for COVID-19 risk and mortality in PD [32]. In our study, the mortality of the COV + PD group was 35.1% — similar to the Scherbaum study — and the mortality of COV was 29.5% — higher than the Scherbaum study. The mean (SD) age was 73 (10.5) years in our COV + PD group. They focused on age ranges, while we investigated the effects of a large number of predictors (including age). They conducted a cross-sectional study, but we carried out longitudinal research. They estimated a higher mortality for PD compared with the non-PD group. Our Kaplan-Meier curves showed that the COV + PD group had slightly less survival probability than the COV group. However, adjustments showed that in the presence of other predictors the difference was not significant. Considering the results of the two studies the discrepancy might be related to the higher mortality in our COV group rather than less mortality in our COV + PD group.

Nevertheless, another study performed by Vignatelli et al. indicated that PD per se is not a risk factor for COVID-19 hospitalization. They included patients with the clinical diagnosis of PD ($n = 696$) or Parkinsonism ($n = 184$) and people anonymously matched (ratio 1:10) for sex, age, district, and Charlson Index ($n = 8590$) in a historical cohort. The adjusted hazard ratio was 0.8 (95% CI, 0.3–2.3, $p = 0.74$) in PD. They also reported that the 30-day fatality rate was 35.1%, without difference among the 3 groups [33]. Our results are compatible

with the Vignatelli study concerning mortality (35.1% for 28-day mortality in our study) and the PD hazard ratio of 1.17 (95% CI, 0.94–1.46, $p = 0.171$). In another study on health records of 13,338 UK individuals tested for COVID-19, Yu et al. showed that AD predicts the highest risk for mortality among elderly individuals; however, PD patients did not have a higher risk for mortality from COVID-19 [19]. It has been suggested that CoV-2 binds to the ACE2 receptors of the dopaminergic neurons of the striatum, which are degenerated by PD-related neuropathology [34]. This reduces neuroinvasion in those patients. Also, some PD medications have been thought to play therapeutic roles in COVID-19 [19].

We selected strict inclusion criteria (positive RT-PCR test result plus CT findings). This allowed us to be more confident regarding the diagnosis of COVID-19 infection. We assessed a large number of predictors including clinical manifestations and comorbidities. Our analyses were straightforward and we incorporated features that are quickly obtained by interview or physical examination upon admission of the patient. Meanwhile, we had some limitations in our study. We did not include lab tests in our predictor list. Recording binary variables prevented errors in data entry and led to a bit of ease in filling forms but we lost information by not recording details of medical history for each patient. Moreover, we did not record the severity and the stages of NDD for each patient. Therefore, we were not able to do subgroup analyses within AD or PD groups. A larger sample size with plenty of medical details is needed to allow discovering more knowledge from data. The pathophysiologic bases of the findings can be investigated in further and more basic biomedical research.

5. Conclusion

The current study showed that inpatients with AD have an increased risk for 28-day mortality from COVID-19. However, PD does not significantly predict higher mortality of COVID-19 infection compared with other hospitalized patients. Typically, patients with AD are elderly women and are more likely to have serious manifestations such as loss of consciousness on admission. They should be considered as high-risk patients and healthcare settings should be ready to provide more critical care for them such as early intubation and immediate O₂ therapy.

Author contributions

MF contributed to the concept and interpretation of the results and helped with administrative affair. NMM and FT contributed to the design and to decision on eligibility, and carried out literature review. HM participated in designing the study, coordinated data record and performed statistical analyses. SZBJ guided development of the study protocol and contributed to the interpretation of the results and coordinated the research process. All the authors participated in drafting and its final approval.

Disclosure of interest

The authors declare that they have no competing interest.

Funding support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics code

Shahid Beheshti University of Medical Sciences with the ethics code of IR.SBMU.RETECH.REC.1399.499.

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