Association between Dementia and Clinical Outcome after COVID-19: A Nationwide Cohort Study with Propensity Score Matched Control in South Korea

Sheng-Min Wang[1]*, See Hyun Park[2]*, Nak-Young Kim[3], Dong Woo Kang[4], Hae-Ran Na[1], Yoo Hyun Um[5], Seunghoon Han[2], Sung-Soo Park[6]✉, and Hyun Kook Lim[1]✉

[1]Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[2]Department of Pharmacology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[3]Department of Psychiatry, Keyo Hospital, Uiwang, Republic of Korea
[4]Department of Psychiatry, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[5]Department of Psychiatry, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Suwon, Republic of Korea
[6]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Objective Despite a high prevalence of dementia in older adults hospitalized with severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2), or so called COVID-19, research investigating association between preexisting diagnoses of dementia and prognosis of COVID-19 is scarce. We aimed to investigate treatment outcome of patients with dementia after COVID-19.

Methods We explored a nationwide cohort with a total of 2,800 subjects older than 50 years who were diagnosed with COVID-19 between January and April 2020. Among them, 223 patients had underlying dementia (dementia group). We matched 1:1 for each dementia-non-dementia group pair yielding 223 patients without dementia (no dementia group) using propensity score matching.

Results Mortality rate after COVID-19 was higher in dementia group than in no dementia group (33.6% vs. 20.2%, p=0.002). Dementia group had higher proportion of patients requiring invasive ventilatory support than no dementia group (34.1% vs. 22.0%, p=0.006). Multivariable analysis showed that dementia group had a higher risk of mortality than no dementia group (odds ratio=3.05, p<0.001). We also found that patients in dementia group had a higher risk of needing invasive ventilatory support than those in no dementia group.

Conclusion Our results suggest that system including strengthen quarantines are required for patients with dementia during the COVID-19 pandemic.
Psychiatry Investig 2021;18(6):523-529

Key Words SARS-CoV-2, COVID-19, Dementia, Mortality.

INTRODUCTION

An outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or so called COVID-19, first oc-

curred in Wuhan, Hubei Province, China at the end of 2019.[1] Thereafter, COVID-19 has spread worldwide and become global pandemic. Numerous studies identified diverse risk factors associated with severity and mortality after SARS-CoV-2 infections.[2,3] Risk factors varied depending on the studies, but it is generally acknowledged that history of chronic medical diseases and conditions reducing general immunity are associated worse treatment outcome in patients with COVID-19. Studies showed that older age (>65), cigarette smoking, use of anti-inflammatory biological agents, and having pre-existing disease including pulmonary disease, allergic rhinitis, asthma, hypertension, cardiovascular disease, chronic kidney disease, diabetes, obesity, malignancy, chronic HIV infection, and transplantation could be possible risk factors for severe COVID-19.[3-5]

Patients with dementia are known to have a higher risk of

developing respiratory infection. Pneumonia is one of the leading causes of acute care hospitalization in patients with dementia.[6] Moreover, pneumonia is the most common cause of death in patients with dementia.[7] More than 50 million people worldwide are suffering from dementia, and one new case occurs every 3 seconds.[8] Thus, the "double hit" of dementia and COVID-19 pandemic could result in a more detrimental effect in people living with dementia.[9] In line with this, Alzheimer's Disease International (ADI) recently reported that 85 percent of all COVID-19 deaths in Canada occurred in long term care facilities, where two thirds of people had dementia.[10]

There have been limited research investigating association between preexisting diagnoses of dementia and prognosis of COVID-19. A recent study based on UK Biobank Community Cohort showed that dementia was associated with the largest risk increase [Odds ratio (OR)=7.30] for COVID-19 hospitalization and death.[11] However, among 507 patients included in the COVID-19 group, the number of patients diagnosed with dementia were very small (n=14). Another study identified that dementia was associated with increased hospital mortality,[12] but the main objective of the research was to characterize the clinical features of patients admitted to hospital with COVID-19 rather than focusing on the impact of dementia in the treatment outcome of COVID-19.

We aimed to investigate treatment outcome of patients with dementia after COVID-19. Using a nationwide cohort in South Korea (hereafter Korea), we compared treatment outcome after COVID-19 infection between patients having underlying dementia with those not having dementia. We hypothesized that underlying dementia might increase the risk of patients having more severe outcomes after COVID-19 infection.

METHODS

Data source

Korea Disease Control & Prevention Agency (KDCA), a public organization under the South Korean Ministry of Welfare and Health, is responsible for performing defense and monitoring activities to contain and prevent COVID-19.[13] All patients who were diagnosed with COVID-19 received mandatory and complimentary care either at a hospital or a medical facility.[14] While patients received medical care, the KDCA was able to collect all medical data related to diagnosis and treatment of COVID-19. In addition, all physicians in charge of patient care were required to complete a case report form developed by the KDCA which contained patients' demographic and epidemiological characteristics and their detailed medical, surgical, and psychiatric histories (http://icreat.

nih.go.kr/). The final consolidated COVID-19 data, which were provided by the KDCA, consisted of 42 clinical variables and 5,628 observations.

Study population

The study population was defined as all individuals aged older than 50 years who were confirmed to have COVID-19 infection between January and April 2020. COVID-19 infection was defined as laboratory confirmation of a positive result using real-time reverse transcriptase polymerase chain reaction assay using the Korean Ministry of Food and Drug Safety approved kit.[15,16] Nasal and pharyngeal swabs were assessed for diagnosis of COVID-19, which was in accordance with World Health Organization guidelines.[17] Presence of dementia was defined based on the information collected from the case report form, which was completed by the physicians who treated patients. To ensure confidentiality, all patient-related data were anonymized. Consent from individual subjects were waived because current study used publicly open, anonymous data. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, Seoul, Korea (KC20ZADI0654).

Outcome measurements

The primary outcome measure of this study was mortality difference after COVID-19 between patients with underlying dementia (dementia group) and patients without dementia (no dementia group). As secondary outcome measures, we also compared days from admission to death, length of hospital stay before discharge, rate of patients requiring any oxygen supply, and rate of patients requiring invasive ventilatory support including mechanical ventilatory care and tracheostomy.

Propensity matching score

To account for the non-randomized treatment allocation, the propensity score was used to select a matching patient among patients not diagnosed with dementia. The missing values of all continuous dependent variables need to be calculated prior to applying the propensity score matching. Data was imputed by regressing each variable in turn against all other variables and then predicting missing data for the dependent variable using the fitted forest. Nearest neighbor matching was used to match patients in a non-dementia cohort with the closest propensity score for each patient in the dementia group. Age, gender, systolic blood pressure, diastolic blood pressure, comorbidity, and baseline hematological variables were used as covariates for matching to generate a mother cohort with a 1:1 ratio for the dementia and non-dementia groups.

Statistical analysis

Continuous and categorical variables were denoted by mean±standard deviation and n (%) in each dementia and non-dementia group, respectively. Difference between the dementia and non-depression group in baseline demographic and clinical characteristics were compared using Student's-T test for continuous and χ^2 test for categorical variables. Multivariable logistics regression model was used to explore the risk factor for all variables that has p-value <0.05 in univariate analysis. A two tailed test with alpha <0.05 was considered to be statistically significant for overall analysis. For all statistical analysis, we used R statistical software (ver. 3.6.1, R Foundation for Statistical Computing, Vienna, Austria, 2019-07-05).

RESULTS

Baseline characteristics

A total of 5,628 subjects were diagnosed with SARS-CoV-2 between January and April 2020. After excluding seven patients who were diagnosed with SARS-CoV-2 after death, 27 patients who did not have disease course after SARS-CoV-2, and 2,794 patients who were younger than age of 50 years, a total of 2,800 patients were initially available for analysis. Among them, we identified 223 patients (dementia group) with dementia and 2,577 patients without dementia. Subsequently, we matched 1:1 for each dementia-non-dementia group pair yielding 223

patients in non-dementia group (Figure 1). After matching propensity score of the dementia group with that of the no dementia group, the two groups did not differ in their baseline patient characteristics (Table 1).

Primary and secondary outcomes

Mortality rate after SARS-CoV-2 infection were significantly higher in dementia group than in no dementia group (33.6% vs. 20.2%, p=0.002). In addition, dementia group had higher proportion of patients requiring invasive ventilatory support than no dementia group (34.1% vs. 22.0%, p=0.006). However, time from to admission to death, length of hospitalization, and rate of patients needing oxygen supply did not significantly differ between the two groups (Table 2).

Prognostic parameters for mortality of COVID-19

Univariable analysis showed that age, baseline heart rate, presentations including dyspnea and altered mental status, and baseline blood cell examination including hemoglobin and absolute lymphocyte counts were potential factors associated with mortality. In addition, comorbidities including dementia, diabetes, hypertension, and chronic renal disease were also identified as potential factors (Supplementary Table 1 in the online-only Data Supplement). In multivariable analysis using potential variables derived from the univariate analysis, we observed that dementia had significant impacts on surviv-
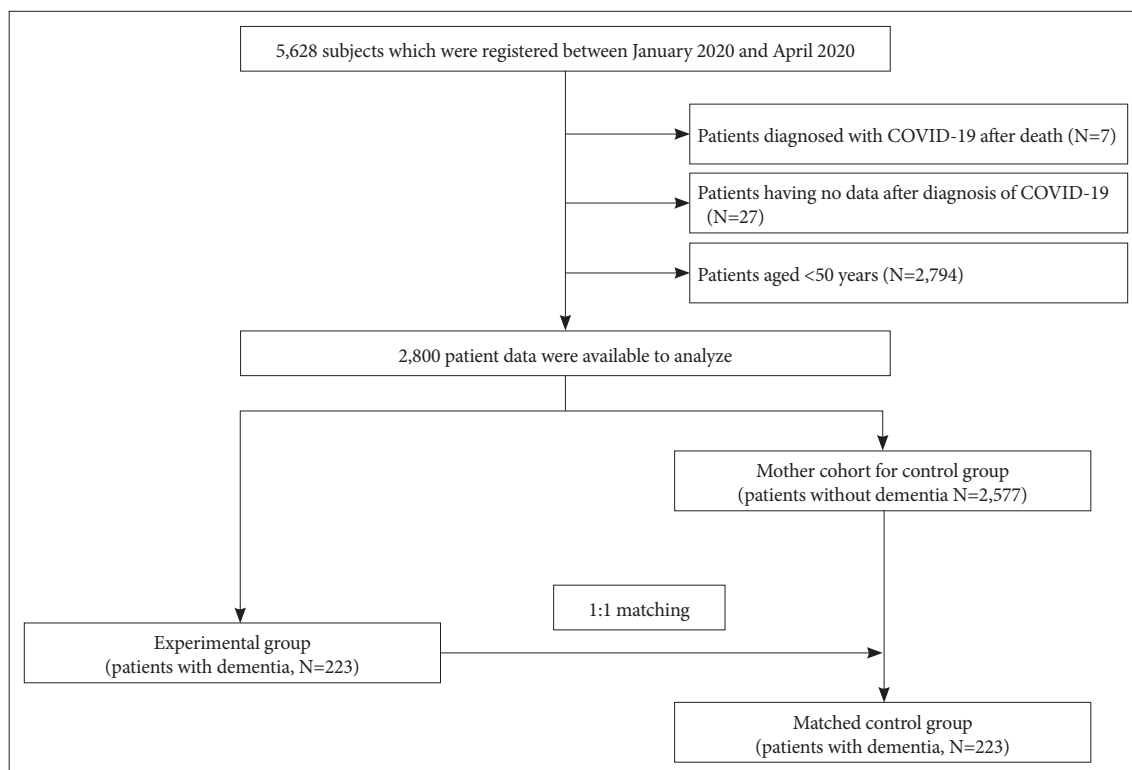

Figure 1. Flow chart depicting creation of study cohorts.

Table 1. Baseline demographic and clinical characteristics

Variables	Groups		p-value
	Dementia (N=223)	No dementia (N=223)	
Age (yr)			0.949
50−59	9 (4.0)	7 (3.1)	
60−69	22 (9.9)	21 (9.4)	
70−79	52 (23.3)	55 (24.7)	
≥80	140 (62.8)	140 (62.8)	
Gender			0.272
Female	153 (68.6)	141 (63.2)	
Male	70 (31.4)	82 (36.8)	
Systolic blood pressure (mm Hg)			0.686
<120	54 (24.2)	51 (22.9)	
120−129	36 (16.1)	26 (11.7)	
130−139	35 (15.7)	32 (14.3)	
140−159	65 (29.1)	75 (33.6)	
≥160	30 (13.5)	36 (16.1)	
Diastolic blood pressure (mm Hg)			0.829
<80	105 (47.1)	110 (49.3)	
80−89	67 (30.0)	59 (26.5)	
90−99	35 (15.7)	33 (14.8)	
≥100	13 (5.8)	18 (8.1)	
Heart rate (bests/min)	80.7±17.5	82.3±15.3	0.326
Body temperature (°C)	36.8±0.6	36.8±0.5	0.765
Baseline presentation			
Sputum (+)	27 (12.1)	33 (14.8)	0.422
Fatigue (+)	11 (4.9)	10 (4.5)	0.592
Dyspnea (+)	37 (16.6)	43 (19.3)	0.453
Altered mental status (+)	8 (3.6)	4 (1.8)	0.308
Nausea/vomiting (+)	7 (3.1)	7 (3.1)	0.606
Diarrhea (+)	13 (5.8)	21 (9.4)	0.214
Comorbidity			
Diabetes (+)	63 (28.3)	69 (30.9)	0.604
Hypertension (+)	126 (56.5)	124 (55.6)	0.924
Heart failure (+)	12 (5.4)	14 (6.3)	0.840
Cardiac disease (+)	15 (6.7)	20 (9.0)	0.416
Asthma (+)	8 (3.6)	10 (4.5)	0.810
Chronic obstructive lung disease (+)	8 (3.6)	6 (2.7)	0.786
Chronic renal disease (+)	10 (4.5)	13 (5.8)	0.668
Previous malignant disease* (+)	5 (2.2)	6 (2.7)	0.999
Chronic hepatic disease (+)	6 (2.7)	5 (2.7)	0.999
Autoimmune disease (+)	0 (0.0)	0 (0.0)	
Baseline hemogram			
Hemoglobin (g/dL)	12.1±1.9	12.1±1.8	0.855
Whole blood cell counts (/mm^3)	6,130±2,907	6,487±3,169	0.216
Absolute lymphocyte counts (/mm^3)	1,322±691	1,336±627	0.827
Platelet (/mm^3)	207,468±80,951	215,027±79,296	0.320

Data are presented as mean±standard deviation or N (%). *patients' whose malignancy were completely cured not needing treatment were not accounted. SD: standard deviation

Table 2. Treatment outcomes of SARS-CoV-2

Outcomes	Groups		p-value
	Dementia (N=223)	No dementia (N=223)	
Death	75 (33.6)	45 (20.2)	0.002[†]
Days alive from admission to death in those who died	14.0±11.5	15.5±11.9	0.483
Days needing hospitalization in those who recovered	29.6±10.8	29.1±120	0.714
Requiring oxygen supply*	117 (52.5)	102 (45.7)	0.185
Requiring invasive ventilative support	76 (34.1)	49 (22.0)	0.006[†]

Data are presented as mean±standard deviation or N (%). *any oxygen support more intensive than nasal cannula, [†]p<0.05. SD: standard deviation, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
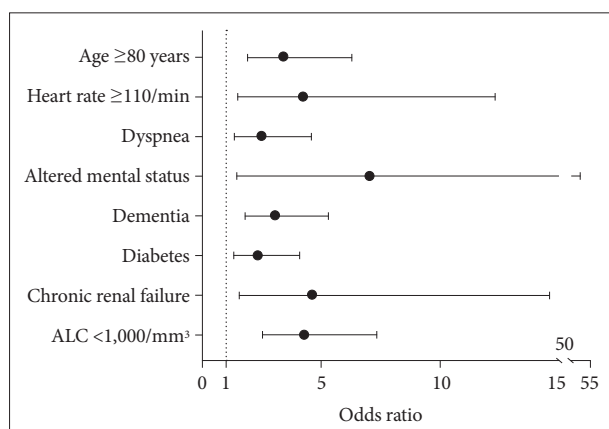

Figure 2. Multivariable analysis of factors associated with event of death after SARS-CoV-2 infection. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ALC: absolute lymphocyte count.

al (OR=3.05, 95% CI: 1.80–5.4, p<0.001) (Figure 2). Other factors including age, heart rate, dyspnea, altered mental status, diabetes, chronic renal disease, and absolute lymphocyte counts were also significant factors associated with higher mortality after SARS-CoV-2 (Table 3).

DISCUSSION

We compared patients who had underlying dementia with those propensity score-matched patients not having dementia and analyzed their disease severity and survival outcome after SARS-CoV-2 infection. Our study showed that patients diagnosed with dementia have three times higher risk of mortality than patients without dementia in a nationwide cohort from Korea. In addition, higher proportion of dementia group required invasive ventilatory support than no dementia group.

In line with our findings, a previous study showed that dementia has the largest effect risk of mortality in adults aged older than 65 who were diagnosed with COVID-19.[11] However, it is still unclear how underlying dementia could affect mortality and severity after COVID-19. Patients with dementia have a more difficulty expressing his or her somatic symp-

Table 3. Multivariable analysis of factors associated with event of death after SARS-CoV-2 infection

Variable	Odd ratio (95% CI)	p-value
Age (yr)		
<80	1	
≥80	3.40 (1.91–6.28)	<0.001*
Heart rate, baseline		
<110/min	1	
≥110/min	4.22 (1.49–12.32)	0.007*
Dyspnea at presentation		
Not present	1	
Present	2.49 (1.35–4.59)	0.004*
Altered mental status at presentation		
Not present	1	
Present	7.03 (1.45–52.48)	0.026*
Comorbidity		
Dementia, no	1	
Dementia, yes	3.05 (1.80–5.3)	<0.001*
Diabetes, no	1	
Diabetes, yes	2.32 (1.32–4.1)	0.004
Hypertension, no	1	
Hypertension, yes	1.13 (0.65–1.96)	0.675
Chronic renal disease, no	1	
Chronic renal disease, yes	4.62 (1.56–14.61)	0.007*
Hemoglobin at presentation		
≥12.5 g/dL	1	
<12.5 g/dL	1.63 (0.96–2.81)	0.073
Absolute lymphocyte counts at presentation		
≥1,000 /mm³	1	
<1,000 /mm³	4.27 (2.53–7.34)	<0.001*

*p<0.05. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, CI: confidence interval

toms, and clinicians could easily mis-interpret them as cognitive or behavior symptoms of dementia.[18] Thus, important signs and symptoms associated with aggravation of COVID-19 could be unnoticed which could have delayed them

from receiving timely treatment. In line with this hypothesis, in the elderly with dementia, delirium was one of the most frequent early presentation of COVID-19.[19] In addition, dementia is the most important and leading risk factor for delirium,[20] and delirium is known to increase the risk of mortality during an acute hospital admission.[21] Likewise, delirium was found to be independently associated with increased mortality in elderly adults diagnosed with COVID-19.[19]

Although the pathogenic mechanism of dementia on severe course of COVID-19 is still unexplainable, immune dysregulation might be one of important pathophysiology.[22] Evidence indicated that an uncontrolled over-production of soluble markers of inflammation, following immunologic alteration, is a major cause of acute respiratory distress syndrome in patients with COVID-19.[23] Recent researches highlighted that aberrant activities of astrocytes and microglia could be important mediators of SARS-CoV-2-induced neurological damage and cytokine storm.[24] Microglia and astrocyte activation are important hall marks in the pathophysiology Alzheimer's disease (the most common cause of dementia).[25,26] Thus, patients with dementia might be at increased risk of excessive production of cytokines than those without dementia. However, further work is needed to elucidate exact pathophysiological association between dementia and clinical outcome after COVID-19.

Days alive from admission to death, days of hospitalization before discharge, and rate of patients needing oxygen supply did not show significant differences between dementia and no dementia groups. A study comprising COVID-19 patients over 60 years of age showed that rapid disease progress was noted in the dead regardless of underlying conditions.[27] Moreover, almost all of the dead patients were initially critically ill (92.3%). Thus, patients who died in our study might have also shown similarly rapid progress regardless of dementia presence. In line with this hypothesis, in both dementia and no dementia group, almost all of the dead patients were severely ill requiring invasive ventilatory support (>92% for both groups).

In the other perspective, SARS-CoV-2 infection may accentuate pre-existing dementia.[28] SARS-CoV-2 may have both direct effects on the brain via viral infection and vascular cascade within in the brain indirect effects on the brain via immunological response of the host.[29] Recent findings showed that up to one third of COVID-19 patients have demonstrated neurological sequelae.[30] Thus, our results might justify that additional attention is needed when patients with COVID-19 have underlying dementia.

Our study has several strengths. Despite observational data confirming that there is a high prevalence of dementia in older adults hospitalized with COVID-19,[31] no controlled study so far has specifically investigated effect of dementia in the clinical outcome of COVID-19. Dementia is a disease of old age and is also associated with a variety of comorbidities, so creating a study cohort and finding appropriate control could have been more difficult than other medical conditions.[11] We conducted a nationwide cohort study and first included all patients who were diagnosed with COVID-19 and received admission care at a designated hospital. Thereafter, patients who were diagnosed with dementia before COVID-19 were selected among the mother cohort. By doing so, we were also able to include 223 patients (all aged 50 years or above) having both dementia and COVID-19 and minimize selection bias and treatment setting effect. In addition, by using propensity score matching via multivariable methods, we were also able to find equal number of patients having similar baseline demographic and clinical characteristics to no dementia group.

This study contains several limitations. First, presence of underlying dementia was based on reports of the patients and/or the guardians (family members), so it is subject to recall bias. Likewise, patients with dementia group might have under-reported their other comorbidities which could have confounded our results by influencing propensity score. Second, we were unable to undertake cerebral imaging studies and objective cognitive testing. Therefore, it was not possible to investigate whether dementia subtype or severity of cognitive impairment had an effect in mortality or clinical outcome after COVID-19. Lastly, other important risk factors such as obesity, cigarette smoking, and chronic neurological disorders other than dementia were not included as parts of covariates.

In conclusion, using a large nationwide, propensity score matched cohort, we found that patients diagnosed with dementia have a higher risk of needing invasive ventilatory support and mortality than patients without dementia after COVID-19. Additional research are needed to confirm our findings and investigate pathophysiological association between dementia and COVID-19. Lastly, our results suggest additional attentions are required for patients with dementia during the course of COVID-19 treatment.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2021.0064.

Conflicts of Interest

Author Contributions

Conceptualization: Sheng-Min Wang, Sung-Soo Park. Data curation: See Hyun Park. Formal analysis: See Hyun Park, Sung-Soo Park. Funding acquisition: Sheng-Min Wang. Investigation: Nak-Young Kim, Dong Woo Kang. Methodology: Sheng-Min Wang, See Hyun Park, Sung-Soo Park. Project: Nak-Young Kim, Dong Woo Kang. Administration: Hae-Ran Na, Yoo Hyun Um. Resources: See Hyun Park. Software: See Hyun Park. Supervision: Hyun Kook Lim, Seunghoon Han. Validation: Hae-Ran Na, Yoo Hyun Um. Visualization: Hae-Ran Na, Yoo Hyun Um. Writing—original draft: Sheng-Min Wang, Sung-Soo Park. Writing—review & editing: Sheng-Min Wang, See Hyun Park, Sung-Soo Park, Hyun Kook Lim.

ORCID iDs

Sheng-Min Wang   https://orcid.org/0000-0003-2521-1413
See Hyun Park   https://orcid.org/0000-0002-7278-7469
Nak-Young Kim   https://orcid.org/0000-0003-0116-6283
Dong Woo Kang   https://orcid.org/0000-0003-3289-075X
Hae-Ran Na   https://orcid.org/0000-0002-7960-8603
Yoo Hyun Um   https://orcid.org/0000-0002-3403-4140
Seunghoon Han   https://orcid.org/0000-0002-9976-5120
Sung-Soo Park   https://orcid.org/0000-0002-8826-4136
Hyun Kook Lim   https://orcid.org/0000-0001-8742-3409

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Supplementary Table 1. Univariable analysis of factors associated with survival

Variable	Survival		p-value
	Death (N=120)	Alive (N=326)	
Age (yr)			<0.001
50−60	2 (1.7)	14 (4.3)	
60−70	2 (1.7)	41 (12.6)	
70−80	20 (16.7)	87 (26.7)	
≥80	96 (80.0)	184 (56.4)	
Gender			0.207
Female	73 (60.8)	221 (67.8%)	
Male	47 (39.2)	105 (32.2)	
Systolic blood pressure, baseline (mm Hg)			0.701
<140	61 (51.3)	173 (53.9)	
≥140	58 (48.7)	148 (46.1)	
Diastolic blood pressure, baseline (mm Hg)			0.940
<80	59 (49.6)	156 (48.6)	
≥80	60 (50.4)	165 (51.4)	
Heart rate, baseline (/min)			0.001
<110	106 (89.1)	331 (97.2)	
≥110	13 (10.9)	9 (2.8)	
Body temperature, baseline (°C)			0.380
<38.0	112 (94.1)	309 (96.6)	
≥38.0	7 (5.9)	11 (3.4)	
Baseline presentation			
Sputum (+)	19 (15.8)	41 (12.6)	0.468
Fatigue (+)	5 (4.2)	16 (4.9)	0.935
Dyspnea (+)	39 (32.5)	41 (12.6)	<0.001
Altered mental status (+)	8 (6.7)	4 (1.2)	0.005
Nausea/vomiting (+)	3 (2.5)	11 (3.4)	0.866
Diarrhea (+)	8 (6.7)	26 (8.0)	0.788
Comorbidity			
Dementia (+)	75 (62.5)	148 (45.4)	0.002
Diabetes (+)	47 (39.2)	85 (26.1)	0.01
Hypertension (+)	79 (65.8)	171 (52.5)	0.01
Chronic cardiac disease (+)	19 (15.8)	36 (11.0)	0.229
Chronic pulmonary disease (+)	9 (7.5)	19 (5.8)	0.671
Chronic renal disease (+)	12 (10.0)	11 (3.4)	0.01
Malignant disease (+)	4 (3.3)	7 (2.1)	0.71
Chronic hepatic disease (+)	2 (1.7)	9 (2.8)	0.75
Autoimmune disease (+)	0 (0.0)	0 (0.0)	0.999
Baseline hemogram			
Hemoglobin (g/dL)			<0.001
≥12.5	35 (29.9)	157 (50.3)	
<12.5	82 (70.1)	155 (49.7)	
Absolute lymphocyte counts (/mm³)			<0.001
≥1,000	42 (36.5)	211 (68.7)	
<1,000	73 (63.5)	96 (31.3)	
Platelet (/mm³)			0.22
≥100,000	109 (93.2)	301 (96.5)	
<100,000	8 (6.8)	11 (3.5)	