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Mortality Risk within 14 Days after Coronavirus Disease 2019 Diagnosis in Dementia Patients: A Nationwide Analysis

Yi-Jun Kim[a] Yongho Jee[b] Sholhui Park[c] Eun-Hee Ha[d, e] Inho Jo[e, f] Hyang Woon Lee[e, g] Myung Seon Song[h]

[a]Institute of Convergence Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea; [b]Advanced Biomedical Research Institute, Ewha Womans University Seoul Hospital, Seoul, Republic of Korea; [c]Department of Laboratory Medicine, Ewha Womans University Seoul Hospital, Seoul, Republic of Korea; [d]Department of Occupational and Environmental Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea; [e]System Health Science & Engineering, Ewha Womans University, Seoul, Republic of Korea; [f]Department of Molecular Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea; [g]Departments of Neurology, Medical Science, and Computational Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea; [h]Department of Psychiatry, Keyo Hospital, Uiwang, Republic of Korea

Keywords
Dementia · COVID-19 · Early death · Propensity score matching · General logistic regression

Abstract
Introduction: The study evaluated the increased mortality risk within 14 days of coronavirus disease 2019 (COVID-19) diagnosis in dementia patients. ***Methods:*** This retrospective study was conducted from February to April 2020 using the COVID-19 patients' database from the Korea Disease Control and Prevention Agency. The risk factors for early death within 14 days were determined using generalized logistic regression performed in a stepwise manner. Dementia patients diagnosed with COVID-19 were used for the study. The propensity score-matched cohort was included as controls. The differences in mortality within 14 days after COVID-19 diagnosis between the dementia patients and controls were evaluated. ***Results:*** We enrolled 5,349 COVID-19 patients from the database; 224 had dementia as comorbidity. The mortality rate within 14 days after COVID-19 diagnosis in dementia patients and the controls was 23.7% versus 1.7%, respectively, before propensity score matching (PSM) ($p < 0.001$), and 23.7% versus 9.2% after PSM ($p < 0.001$). The hazard ratio (HR) for mortality within 14 days in COVID-19 patients with dementia was significant even after PSM (HR 5.104, 95% confidence interval 2.889–5.673, $p < 0.001$). The survival curve of dementia patients was steeply inclined within 14 days after COVID-19 diagnosis, resulting in 70.7% of all deaths in dementia patients. ***Conclusions:*** COVID-19 patients with dementia had a higher risk of early death within 14 days. Thus, prompt intervention is necessary for dementia patients after COVID-19 diagnosis.

Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 infection is hitting the world. In August 2021, 204 million cases and 4.31 million deaths were reported worldwide [1].

Yi-Jun Kim and Yongho Jee contributed equally to this work.

Correspondence to:
Yi-Jun Kim, kimyj.ro@gmail.com

karger@karger.com
www.karger.com/dem

Since no herd immunity of this pandemic exists, COVID-19 rapid spread before the lockdown in many countries of the world was significantly higher than influenza, or even measles spread [2]. On December 11, 2020, the US Food and Drug Administration issued the first authorization for emergency vaccination to prevent COVID-19 [3, 4]. Although vaccine distribution has begun, it will take years to get enough vaccines worldwide [1, 5]. Therefore, efficient patient treatment will continually be necessary amidst limited medical resources.

To date, several studies have analyzed poor COVID-19 prognostic risk factors [6, 7]. However, survivor and nonsurvivor characteristics are most merely analyzed and compared [6, 7]. Early intensive care intervention is possible for more emergency patients with death possibility within a few weeks (within 14 days) after diagnoses. To date, no papers have reported on mortality within a specific period after COVID-19 diagnosis.

Individuals with *APOE ε4/ε4* homozygotes were more likely to test positive for COVID-19, with higher mortality than other genotypes [8]. This variant is a common risk factor for Alzheimer's disease, the most common form of dementia [9, 10]. This suggests higher COVID-19 susceptibility, and fatality in dementia patients is not only social but also genetic. Therefore, dementia patients' mortality pattern in COVID-19 may differ from other deaths. Several studies have shown dementia as a poor COVID-19 risk factor. However, none has shown dementia's association with early death within a few weeks of COVID-19 diagnosis [11, 12].

The Korea Disease Control and Prevention Agency (KDCA) released COVID-19 patients' data from February to April 2020 across the country for research purposes. Thus, we characterized the death cases within 14 and 30 days of COVID-19 diagnosis to determine early mortality risk factors among dementia patients. The aim of this study was to elucidate risk factors for early death after COVID-19 infection and to identify dementia as one of the independent risk factors for early death after COVID-19 infection.

Materials and Methods

Study Design and Setting

Patients

The KDCA provided COVID-19 patients' data from February to April 30, 2020. The anonymized data were available to authorized researchers using a virtual server. All patients were hospitalized, treated, quarantined, and finally discharged as dead or alive. Patients diagnosed with COVID-19 after death and patients with missing data were excluded from the study. Demographic information, initial examination findings, clinical results on admission, comorbid diseases, clinical severity, and general blood test results were provided.

Study Variable Description

The study variables include demographics characteristics, such as age, sex, and body mass index (BMI), and patients' vital signs, including systolic blood pressure, diastolic blood pressure, heart rate, and temperature. COVID-19 symptoms (fever, cough, sputum, sore throat, runny nose, myalgia, fatigue, shortness of breath, headache, change of consciousness, vomiting/nausea, and diarrhea) and comorbid diseases (diabetes mellitus, hypertension, heart failure, other chronic heart diseases, asthma, chronic obstructive pulmonary disease, chronic kidney disease, cancer, chronic liver disease, rheumatoid disease/autoimmune disease, and dementia) were included in the study. The use of the intensive care unit during hospitalization and blood test results (hemoglobin, hematocrit, lymphocyte, platelets, and white blood cell) were analyzed.

Statistical Analysis

Pearson's χ^2 test was used to compare the differences between categorical variables and prognostic outcomes between dementia patients and the control. Blood test results were classified according to the normal and abnormal ranges of the test [13]. Generalized logistic regression was performed in a stepwise manner after incorporating all variables to determine the risk factors for early mortality within 30 days. Variables incorporated were demographics, vital sign, COVID-19 symptoms, comorbid diseases, and blood test results. Subgroups with normal or normal-low variable values were selected as reference groups. The same analysis was performed for early death within 14 days.

To further analyze the difference in early mortality according to the prevalence of dementia, propensity score matching (PSM) was performed. A 2:1 control:dementia ratio using "optimal" matching was conducted. We analyzed the differences between the matched control and dementia patients' mortality at 14 and 30 days after COVID-19 diagnosis. A well-balanced match was defined as a standardized mean difference of <0.25 and a statistically insignificant p value of the χ^2 test between the matched control and the dementia patients. Survival estimate was performed using the Kaplan-Meier estimate and compared by a log-rank test. Two-tailed p value <0.05 was considered statistically significant. All analyses were performed using R programming software (ver. 4.0.2). The "MatchIt" R package was used for PSM.

Results

Patient Characteristics

A total of 5,628 COVID-19 patients were diagnosed. Of these, 7 patients with COVID-19 diagnosis after death were excluded; 5,349 patients remained after excluding patients aged <20 years old. Patient characteristics are summarized in Table 1. Patients over 70 years of age were 16.2%, and females were 59.4%. The most common symptoms at the time of COVID-19 diagnosis were fever

Table 1. Patient characteristics at the time of COVID-19 diagnosis

Patient characteristics	Values
Demographics and vital sign, *n* (%)	
Age, years	
<50	2,425 (45.3)
≥50 and <70	2,059 (38.5)
≥70	865 (16.2)
Sex	
Male	2,172 (40.6)
Female	3,177 (59.4)
BMI	
Low (<18.5)	193 (3.6)
Normal low (≥18.5 and <23.0)	1,762 (32.9)
Normal high (≥23.0 and <25.0)	1,012 (18.9)
High (≥25.0 and <30.0)	1,021 (19.1)
Higher (≥30.0)	194 (3.6)
Unknown	1,167 (21.8)
Systolic blood pressure, mm Hg	
Low (<120)	1,220 (22.8)
Normal low (≥120 and <130)	1,090 (20.4)
Normal high (≥130 and <140)	1,048 (19.6)
High (≥140 and <160)	1,385 (25.9)
Higher (≥160)	507 (9.5)
Unknown	99 (1.9)
Diastolic blood pressure, mm Hg	
Low (<80)	1,990 (37.2)
Normal low (≥80 and <90)	1,735 (32.4)
Normal high (≥90 and <100)	1,032 (19.3)
High (≥100)	493 (9.2)
Unknown	99 (1.9)
Heart rate, beats per min	
Low (<60)	107 (2.0)
Normal low (≥60 and <80)	1,811 (33.9)
Normal high (≥80 and <100)	2,439 (45.6)
High (≥100)	882(16.5)
Unknown	110 (2.1)
Temperature, °C	
Low (<36.0)	22 (0.4)
Normal low (≥36.0 and <37.0)	2,883 (53.9)
Normal high (≥37.0 and <38.0)	2,131 (39.8)
High (≥38.0)	277 (5.2)
Unknown	36 (0.7)
Symptoms at the time of COVID-19 diagnosis, *n* (%)	
Fever	
No	4,098 (76.6)
Yes	1,247 (23.3)
Unknown	4 (0.1)
Cough	
No	3,099 (57.9)
Yes	2,246 (42.0)
Unknown	4 (0.1)
Sputum	
No	3,783 (70.7)
Yes	1,562 (29.2)
Unknown	4 (0.1)
Sore throat	
No	4,497 (84.1)
Yes	848 (15.9)
Unknown	4 (0.1)
Runny nose	
No	4,769 (89.2)
Yes	576 (10.8)
Unknown	4 (0.1)
Myalgia	
No	4,433 (82.9)
Yes	912 (17.0)
Unknown	4 (0.1)
Fatigue	
No	5,115 (95.6)
Yes	230 (4.3)
Unknown	4 (0.1)
Shortness of breath	
No	4,689 (87.7)
Yes	656 (12.3)
Unknown	4 (0.1)
Headache	
No	4,399 (82.2)
Yes	946 (17.7)
Unknown	4 (0.1)
Change of consciousness	
No	5,313 (99.3)
Yes	32 (0.6)
Unknown	4 (0.1)
Vomiting/nausea	
No	5,106 (95.5)
Yes	239 (4.5)
Unknown	4 (0.1)
Diarrhea	
No	4,838 (90.4)
Yes	507 (9.5)
Unknown	4 (0.1)
Comorbidity at the time of COVID-19 diagnosis, *n* (%)	
Diabetes mellitus	
No	4,660 (87.1)
Yes	686 (12.8)
Unknown	3 (0.1)
Hypertension	
No	4,148 (77.5)
Yes	1,198 (22.4)
Unknown	3 (0.1)
Heart failure	
No	5,288 (98.9)
Yes	58 (1.1)
Unknown	3 (0.1)
Other chronic heart disease	
No	5,151 (96.3)
Yes	179 (3.3)
Unknown	19 (0.4)
Asthma	
No	5,220 (97.6)
Yes	126 (2.4)
Unknown	3 (0.1)
Chronic obstructive pulmonary disease	
No	5,308 (99.2)
Yes	38 (0.7)
Unknown	3 (0.1)
Chronic kidney disease	
No	5,291 (98.9)
Yes	55 (1.0)
Unknown	3 (0.1)
Cancer	
No	5,202 (97.3)
Yes	143 (2.7)
Unknown	4 (0.1)
Chronic liver disease	
No	4,952 (92.6)
Yes	82 (1.5)
Unknown	315 (5.9)
Rheumatoid disease/autoimmune disease	
No	4,990 (93.3)
Yes	38 (0.7)
Unknown	321 (6.0)
Dementia	
No	4,807 (89.9)
Yes	224 (4.2)
Unknown	318 (5.9)

Table 1 (continued)

Patient characteristics	Values
Blood test, *n* (%)	
Hemoglobin, g/dL	
Lower (men <12.3; women <10.8)	197 (3.7)
Low (men ≥12.3–14.0; women ≥10.8 and <12.3)	807 (15.1)
Normal low (men ≥14.0 and <15.7; women ≥12.3 and <13.8)	2,073 (38.8)
Normal high (men ≥15.7 and <17.5; women ≥13.8 and <15.3)	760 (14.2)
High (men ≥17.5; women ≥15.3)	58 (1.1)
Unknown	1,454 (27.2)
Hematocrit, %	
Low (men <41.5; women <35.9)	1,332 (24.9)
Normal low (men ≥41.5 and <45.9; women ≥35.9 and <40.2)	1,613 (30.2)
Normal high (men ≥45.9 and <50.4; women ≥40.2 and <44.6)	839 (15.7)
High (men ≥50.4; women ≥44.6)	105 (2.0)
Unknown	1,460 (27.3)
Lymphocyte, %	
Low (<20)	868 (16.2)
Normal low (≥20 and <32)	1,545 (28.9)
Normal high (≥32 and <44)	1,147 (21.4)
High (≥44)	311(5.8)
Unknown	1,478 (27.6)
Platelets, μL	
Low (<150K)	486 (9.1)
Normal low (≥150K and <300K)	2,678 (50.1)
Normal high (≥300K and <450K)	669 (12.5)
High (≥450K)	63 (1.2)
Unknown	1,453 (27.2)
White blood cell, μL	
Low (<4,500)	1,017 (19.0)
Normal (≥4,500 and <11,000)	2,727 (51.0)
High (≥11,000)	152 (2.8)
Unknown	1,453 (27.2)
Outcomes, *n* (%)	
Using the intensive care unit during hospitalization	
No	5,135 (96.0)
Yes	187 (3.5)
Unknown	27 (0.5)
Death, *N*	
No	5,115 (95.6)
Yes	234 (4.4)
Death within 30 days	
No	5,152 (96.3)
Yes	197 (3.7)
Death within 14 days	
No	5,208 (97.4)
Yes	141 (2.6)

COVID-19, coronavirus disease 2019; BMI, body mass index.

(23.3%), cough (42.0%), and sputum (29.2%), while some presented with shortness of breath (12.3%) and change of consciousness (0.6%). Among the patients, 3.5% received intensive care during the hospitalization. Death occurred in 234 (4.4%) of 5,349 patients, 197 (3.7%) within 30 days, and 141 (2.6%) within 14 days.

At COVID-19 diagnosis, 224 patients (4.2%) had dementia (Table 2). Most dementia patients were older than 70 years (85.7%), compared to 86.9% of the control group younger than 70 years. Dementia patients were more likely women (59.0% vs. 68.3%). The underweight population in the dementia group was 2.5 times that of the control group (3.4% vs. 8.9%), and the proportions of low diastolic blood pressure and low heart rate were higher than those of the control group (diastolic blood pressure <80 mm Hg, 36.8% vs. 46.9%; heart rate <60 beats per min, 1.7% vs. 8.0%, respectively). The rates of underlying diseases including diabetes, high blood pressure, heart disease, lung disease, and kidney disease were higher than those of the control group. In contrast, dementia patients had significantly fewer complaints of symptoms such as cough, sputum, sore throat, runny nose, myalgia, and headache than the control group. The rate of loss of consciousness symptoms was higher in dementia patients (0.5% vs. 3.6%). In blood test, dementia patients had a higher percentage of below normal levels of hemoglobin, hematocrit, lymphocyte, platelet, and white blood cells than the control group.

Dementia Was a Significant Mortality Risk Factor within 30 and 14 Days after COVID-19 Diagnosis

General logistic regression analysis for death within 30 days after COVID-19 diagnosis shows that dementia was a significant risk factor (hazard ratio [HR] 4.543, 95% confidence interval [CI] 2.788–5.031, $p < 0.001$) (Table 3). Old age, low BMI, low or high body temperature, shortness of breath, change of consciousness, diabetes mellitus, cancer, low hemoglobin, low lymphocyte, low platelets, and high white blood cell were also significant risk factors for mortality within 30 days. On the other hand, female sex, sore throat, and headache were favorable prognostic factors.

Factors related to death within 14 days were also confirmed by the same analysis, and dementia was still a significant risk factor (HR 5.175, 95% CI 3.073–5.696, $p < 0.001$) (Table 4). Low BMI and cancer, which were significant risk factors for death within 30 days, were excluded from significant risk factors for mortality within 14 days. Old age, low or high body temperature, shortness of breath, change of consciousness, diabetes mellitus, low hemoglobin, low lymphocyte, low platelet, and high white blood cell were identified as significant risk factors for death within 14 days, while headache was a significantly good prognostic factor.

Early Mortality Between Dementia Patients and Matched Control

Of the 224 dementia patients, 75 (33.5%) deaths occurred (Table 2). This accounts for 32.1% of 234 deaths.

Table 2. Patient characteristics before and after PSM according to dementia in COVID-19

Characteristics	Before PSM				After PSM			
	control (*N* = 5,125)	dementia (*N* = 224)	*p* value	SMD	control (*N* = 448)	dementia (*N* = 224)	*p* value	SMD
Demographics and vital sign, *n* (%)								
Age, years								
<50	2,424 (47.3)	1 (0.4)	<0.001	23.076	2(0.4)	1 (0.4)	0.623	<0.001
≥50 and <70	2,028 (39.6)	31 (13.8)		2.113	75 (16.7)	31 (13.8)		0.063
≥70	673 (13.1)	192 (85.7)		1.746	371 (82.8)	192 (85.7)		0.061
Sex								
Male	2,101 (41.0)	71 (31.7)	0.007	0.523	171 (38.2)	71 (31.7)	0.118	0.142
Female	3,024 (59.0)	153 (68.3)		0.434	277 (61.8)	153 (68.3)		0.135
BMI								
Low (<18.5)	173 (3.4)	20 (8.9)		0.182	34 (7.6)	20 (8.9)		0.027
Normal low (≥18.5 and <23.0)	1,697 (33.1)	65 (29.0)		0.217	138 (30.8)	65 (29.0)		0.038
Normal high (≥23.0 and <25.0)	992 (19.4)	20 (8.9)	<0.001	0.749	54 (12.1)	20 (8.9)	0.345	0.070
High (≥25.0 and <30.0)	1,005 (19.6)	16 (7.1)		1.003	46 (10.3)	16 (7.1)		0.071
Higher (≥30.0)	194 (3.8)	0 (0.0)		NA	1 (0.2)	0 (0.0)		NA
Unknown	1,064 (20.8)	103 (46)		0.889	175 (39.1)	103 (46.0)		0.143
Systolic blood pressure, mm Hg								
Low (<120)	1,166 (22.8)	54 (24.1)		0.066	84 (18.8)	54 (24.1)		0.109
Normal low (≥120 and <130)	1,053 (20.5)	37 (16.5)		0.222	75 (16.7)	37 (16.5)		0.005
Normal high (≥130 and <140)	1,013 (19.8)	35 (15.6)	0.119	0.230	71 (15.8)	35 (15.6)	0.705	0.005
High (≥140 and <160)	1,320 (25.8)	65 (29.0)		0.154	146 (32.6)	65 (29.0)		0.077
Higher (≥160)	477 (9.3)	30 (13.4)		0.173	64 (14.3)	30 (13.4)		0.019
Unknown	96 (1.9)	3 (1.3)		0.031	8 (1.8)	3 (1.3)		0.010
Diastolic blood pressure, mm Hg								
Low (<80)	1,885 (36.8)	105 (46.9)		0.451	192 (42.9)	105 (46.9)		0.084
Normal low (≥80 and <90)	1,667 (32.5)	68 (30.4)	0.025	0.112	138 (30.8)	68 (30.4)	0.850	0.009
Normal high (≥90 and <100)	997 (19.5)	35 (15.6)		0.211	81 (18.1)	35 (15.6)		0.053
High (≥100)	480 (9.4)	13 (5.8)		0.222	29 (6.5)	13 (5.8)		0.014
Unknown	96 (1.9)	3 (1.3)		0.031	8 (1.8)	3 (1.3)		0.010
Heart rate, beats per min								
Low (<60)	89 (1.7)	18 (8.0)		0.168	20 (4.5)	18 (8.0)		0.071
Normal low (≥60 and <80)	1,720 (33.6)	91 (40.6)	<0.001	0.323	164 (36.6)	91 (40.6)	0.189	0.084
Normal high (≥80 and <100)	2,351 (45.9)	88 (39.3)		0.353	192 (42.9)	88 (39.3)		0.077
High (≥100)	858 (16.7)	24 (10.7)		0.370	65 (14.5)	24 (10.7)		0.085
Unknown	107 (2.1)	3 (1.3)		0.046	7 (1.6)	3 (1.3)		0.005
Temperature, °C								
Low (<36.0)	20 (0.4)	2 (0.9)		0.017	5 (1.1)	2 (0.9)		0.005
Normal low (≥36.0 and <37.0)	2,733 (53.3)	150 (67.0)	<0.001	0.614	290 (64.7)	150 (67.0)	0.968	0.047
Normal high (≥37.0 and <38.0)	2,073 (40.4)	58 (25.9)		0.894	120 (26.8)	58 (25.9)		0.019
High (≥38.0)	266 (5.2)	11 (4.9)		0.014	27 (6.0)	11 (4.9)		0.024
Unknown	33 (0.6)	3 (1.3)		0.025	6 (1.3)	3 (1.3)		<0.001
Symptoms at the time of COVID-19 diagnosis, *n* (%)								
Fever								
No/unknown	3,923 (76.5)	179 (79.9)	0.278	0.165	363 (81)	179 (79.9)	0.809	0.024
Yes	1,202 (23.5)	45 (20.1)		0.180	85 (19)	45 (20.1)		0.023
Cough								
No/unknown	2,920 (57.0)	183 (81.7)	<0.001	1.049	344 (76.8)	183 (81.7)	0.174	0.103
Yes	2,205 (43.0)	41 (18.3)		1.846	104 (23.2)	41 (18.3)		0.109
Sputum								
No/unknown	3,591 (70.1)	196 (87.5)	<0.001	0.787	374 (83.5)	196 (87.5)	0.210	0.085
Yes	1,534 (29.9)	28 (12.5)		1.312	74 (16.5)	28 (12.5)		0.090
Sore throat								
No/unknown	4,281 (83.5)	220 (98.2)	<0.001	0.681	434 (96.9)	220 (98.2)	0.447	0.028
Yes	844 (16.5)	4 (1.8)		2.142	14 (3.1)	4 (1.8)		0.031
Runny nose								
No/unknown	4,551 (88.8)	222 (99.1)	<0.001	0.489	439 (98.0)	222 (99.1)	0.452	0.024
Yes	574 (11.2)	2 (0.9)		1.751	9 (2.0)	2 (0.9)		0.028
Myalgia								
No/unknown	4,219 (82.3)	218 (97.3)	<0.001	0.694	374 (83.5)	196 (87.5)	0.814	0.085
Yes	906 (17.7)	6 (2.7)		1.854	74 (16.5)	28 (12.5)		0.087
Fatigue								
No/unknown	4,906 (95.7)	213 (95.1)	0.770	0.032	425 (94.9)	213 (95.1)	1.000	0.005
Yes	219 (4.3)	11 (4.9)		0.030	23 (5.1)	11 (4.9)		0.005
Shortness of breath								
No/unknown	4,506 (87.9)	187 (83.5)	0.060	0.227	362 (80.8)	187 (83.5)	0.459	0.056
Yes	619 (12.1)	37 (16.5)		0.192	86 (19.2)	37 (16.5)		0.058
Headache								
No/unknown	4,186 (81.7)	217 (96.9)	<0.001	0.702	429 (95.8)	217 (96.9)	0.621	0.024
Yes	939 (18.3)	7 (3.1)		1.772	19 (4.2)	7 (3.1)		0.025

Table 2 (continued)

Characteristics	Before PSM				After PSM			
	control (*N* = 5,125)	dementia (*N* = 224)	*p* value	SMD	control (*N* = 448)	dementia (*N* = 224)	*p* value	SMD
Change of consciousness								
No/unknown	5,101 (99.5)	216 (96.4)	<0.001	0.157	436 (97.3)	216 (96.4)	0.688	0.019
Yes	24 (0.5)	8 (3.6)		0.071	12 (2.7)	8 (3.6)		0.018
Vomiting/nausea								
No/unknown	4,893 (95.5)	217 (96.9)	0.407	0.070	424 (94.6)	217 (96.9)	0.269	0.047
Yes	232 (4.5)	7 (3.1)		0.083	24 (5.4)	7 (3.1)		0.053
Diarrhea								
No/unknown	4,631 (90.4)	211 (94.2)	0.072	0.188	416 (92.9)	211 (94.2)	0.623	0.028
Yes	494 (9.6)	13 (5.8)		0.242	32 (7.1)	13 (5.8)		0.029
Comorbidity at the time of COVID-19 diagnosis, *n* (%)								
Diabetes mellitus								
No/unknown	4,502 (87.8)	161 (71.9)	<0.001	0.875	312 (69.6)	161 (71.9)	0.612	0.047
Yes	623 (12.2)	63 (28.1)		0.553	136 (30.4)	63 (28.1)		0.048
Hypertension								
No/unknown	4,053 (79.1)	98 (43.8)	<0.001	2.327	210 (46.9)	98 (43.8)	0.494	0.067
Yes	1,072 (20.9)	126 (56.3)		1.151	238 (53.1)	126 (56.3)		0.066
Heart failure								
No/unknown	5,079 (99.1)	212 (94.6)	<0.001	0.227	426 (95.1)	212 (94.6)	0.950	0.009
Yes	46 (0.9)	12 (5.4)		0.109	22 (4.9)	12 (5.4)		0.009
Other chronic heart disease								
No/unknown	4,961 (96.8)	209 (93.3)	0.008	0.178	416 (92.9)	209 (93.3)	0.957	0.009
Yes	164 (3.2)	15 (6.7)		0.126	32 (7.1)	15 (6.7)		0.009
Asthma								
No/unknown	5,007 (97.7)	216 (96.4)	0.317	0.064	434 (96.9)	216 (96.4)	0.939	0.009
Yes	118 (2.3)	8 (3.6)		0.052	14 (3.1)	8 (3.6)		0.009
Chronic obstructive pulmonary disease								
No/unknown	5,095 (99.4)	216 (96.4)	<0.001	0.151	437 (97.5)	216 (96.4)	0.565	0.024
Yes	30 (0.6)	8 (3.6)		0.072	11 (2.5)	8 (3.6)		0.022
Chronic kidney disease								
No/unknown	5,080 (99.1)	214 (95.5)	<0.001	0.182	432 (96.4)	214 (95.5)	0.724	0.019
Yes	45 (0.9)	10 (4.5)		0.092	16 (3.6)	10 (4.5)		0.018
Cancer								
No/unknown	4,987 (97.3)	219 (97.8)	0.839	0.027	438 (97.8)	219 (97.8)	1.000	0.000
Yes	138 (2.7)	5 (2.2)		0.025	10 (2.2)	5 (2.2)		0.000
Chronic liver disease								
No/unknown	5,049 (98.5)	218 (97.3)	0.251	0.060	438 (97.8)	218 (97.3)	0.929	0.009
Yes	76 (1.5)	6 (2.7)		0.046	10 (2.2)	6 (2.7)		0.009
Rheumatoid disease/autoimmune disease								
No/unknown	5,087 (99.3)	224 (100)	0.375	0.037	447 (99.8)	224 (100)	1.000	0.005
Yes	38 (0.7)	0 (0.0)		NA	1 (0.2)	0 (0.0)		NA
Blood test, *n* (%)								
Hemoglobin, g/dL								
Lower (men <12.3; women <10.8)	338 (6.6)	67 (29.9)		0.627	126 (28.1)	67 (29.9)		0.037
Low (men ≥12.3–14.0; women ≥10.8 and <12.3)	911 (17.8)	67 (29.9)		0.480	130 (29)	67 (29.9)		0.019
Normal low (men ≥14.0 and <15.7; women ≥12.3 and <13.8)	1,634 (31.9)	60 (26.8)	<0.001	0.276	128 (28.6)	60 (26.8)	0.993	0.037
Normal high (men ≥15.7 and <17.5; women ≥13.8 and <15.3)	743 (14.5)	17 (7.6)		0.467	36 (8.0)	17 (7.6)		0.009
High (men ≥17.5; women ≥15.3)	55 (1.1)	3 (1.3)		0.012	6 (1.3)	3 (1.3)		0.000
Unknown	1,444 (28.2)	10 (4.5)		2.868	22 (4.9)	10 (4.5)		0.009
Hematocrit, %								
Low (men<41.5; women<35.9)	1,200 (23.4)	132 (58.9)		1.188	254 (56.7)	132 (58.9)		0.047
Normal low (men ≥41.5 and <45.9; women ≥35.9 and <40.2)	1,558 (30.4)	55 (24.6)	<0.001	0.322	121 (27)	55 (24.6)	0.950	0.053
Normal high (men ≥45.9 and <50.4; women ≥40.2 and <44.6)	818 (16.0)	21 (9.4)		0.421	39 (8.7)	21 (9.4)		0.014
High (men ≥50.4; women ≥44.6)	99 (1.9)	6 (2.7)		0.032	11 (2.5)	6 (2.7)		0.005
Unknown	1,450 (28.3)	10 (4.5)		2.888	23 (5.1)	10 (4.5)		0.014
Lymphocyte, %								
Low (<20)	780 (15.2)	88 (39.3)		0.797	173 (38.6)	88 (39.3)		0.014
Normal low (≥20 and <32)	1,482 (28.9)	63 (28.1)	<0.001	0.040	142 (31.7)	63 (28.1)	0.651	0.073
Normal high (≥32 and <44)	1,102 (21.5)	45 (20.1)		0.073	75 (16.7)	45 (20.1)		0.069
High (≥44)	294 (5.7)	17 (7.6)		0.081	29 (6.5)	17 (7.6)		0.023
Unknown	1,467 (28.6)	11 (4.9)		2.758	29 (6.5)	11 (4.9)		0.035
Platelets, μL								
Low (<150K)	434 (8.5)	52 (23.2)		0.477	90 (20.1)	52 (23.2)		0.065
Normal low (≥150K and <300K)	2,541 (49.6)	137 (61.2)	<0.001	0.526	273 (60.9)	137 (61.2)	0.799	0.005
Normal high (≥300K and <450K)	646 (12.6)	23 (10.3)		0.128	57 (12.7)	23 (10.3)		0.054
High (≥450K)	61 (1.2)	2 (0.9)		0.017	5 (1.1)	2 (0.9)		0.005
Unknown	1,443 (28.2)	10 (4.5)		2.865	23 (5.1)	10 (4.5)		0.014

Table 2 (continued)

Characteristics	Before PSM				After PSM			
	control (*N* = 5,125)	dementia (*N* = 224)	*p* value	SMD	control (*N* = 448)	dementia (*N* = 224)	*p* value	SMD
White blood cell, μL								
Low (<4,500)	948 (18.5)	69 (30.8)		0.489	119 (26.6)	69 (30.8)		0.088
Normal (≥4,500 and <11,000)	2,593 (50.6)	134 (59.8)	<0.001	0.427	281 (62.7)	134 (59.8)	0.692	0.062
High (≥11,000)	141 (2.8)	11 (4.9)		0.083	24 (5.4)	11 (4.9)		0.009
Unknown	1,443 (28.2)	10 (4.5)		2.865	24 (5.4)	10 (4.5)		0.019
Outcomes, *n* (%)								
Using the intensive care unit during hospitalization								
No/unknown	4,954 (96.7)	208 (92.9)	0.004		404 (90.2)	208 (92.9)	0.315	
Yes	171 (3.3)	16 (7.1)			44 (9.8)	16 (7.1)		
Death, *N*								
No	4,966 (96.9)	149 (66.5)	<0.001		376 (83.9)	149 (66.5)	<0.001	
Yes	159 (3.1)	75 (33.5)			72 (16.1)	75 (33.5)		
Death within 30 days								
No	4,995 (97.5)	157 (70.1)	<0.001		385 (85.9)	157 (70.1)	<0.001	
Yes	130 (2.5)	67 (29.9)			63 (14.1)	67 (29.9)		
Death within 14 days								
No	5,037 (98.3)	171 (76.3)	<0.001		407 (90.8)	171 (76.3)	<0.001	
Yes	88 (1.7)	53 (23.7)			41 (9.2)	53 (23.7)		

SMD, standardized mean difference; NA, not applicable; PSM, propensity score matching; COVID-19, coronavirus disease 2019; BMI, body mass index.

Among the dementia patients, 53 (23.7%) died within 14 days and 67 (29.9%) within 30 days after COVID-19 diagnosis. That is, 70.7% (53/75) of the deaths occurred within 14 days in dementia. Of the 5,125 control patients, 159 (3.1%) died. Among them, 88 patients (1.7%) died within 14 days, and 130 (2.5%) died within 30 days after COVID-19 diagnosis. Among the controls, 55.3% (88/159) of the deaths occurred within 14 days. Of the 141 deaths within 14 days after COVID-19 diagnosis, 53 (37.6%) patients had dementia.

To analyze the effect of dementia on early death after COVID-19 diagnosis more accurately by minimizing effects of other variables, PSM between dementia patients and controls was performed (Table 2). The PSM showed that patients over 70 years old were corrected from 13.1% to 85.7% in the control and dementia groups before correction and to 82.8% and 85.7% after correction. There were no significant differences between the control and dementia groups in all variables after PSM (all p values >0.05; all standardized mean differences <0.25). The Kaplan-Meier survival estimate between the control and dementia patients showed a downward slope of the survival curve, showing that death within 14 days in dementia patients was more pronounced than the control (Fig. 1). Even after PSM, survival curve showed that patients with dementia had a significantly lower survival rate than the control ($p < 0.001$). The mortality rate within 14 days after COVID-19 diagnosis of the dementia patients was significantly higher than that of controls before PSM ($p < 0.001$) and even after PSM (23.7% vs. 9.2%, $p < 0.001$) (Table 2).

After adjustment of all covariates in dementia-based matched cohort, the HRs of dementia for death within 30 days and 14 days after COVID-19 infection were 3.757 (95% CI, 2.281–4.255, $p < 0.001$) and 5.104 (95% CI, 2.889–5.673, $p < 0.001$), respectively. These high and significant HRs suggest that dementia itself is an independent risk factor for early death after COVID-19 infection.

Discussion

Our study showed dementia as a major risk factor for early death after COVID-19 infection diagnosis. Our study provides insight that comparable with emergency symptoms, such as dyspnea and loss of conscious, dementia is an independent risk factor for early death, indicating the need for intensive monitoring and urgent and active intervention for dementia the point of COVID-19 diagnosis.

Dementia patients were older and underweight, and had a higher rate of underlying disease than the control group. In addition, the population rates of lower-than-normal levels of hemoglobin, lymphocyte, and platelets were higher than the control group, and these were risk factors for early death after COVID-19 infection. In com-

Table 3. General logistic regression of death within 30 days after COVID-19 diagnosis

Characteristics	HR	95% CI	*p* value
Age, years			
<50	Reference		
≥50 and <70	7.797	(2.128–9.096)	0.002
≥70	34.497	(9.480–35.789)	<0.001
Sex – female	0.632	(0.419–1.045)	0.030
BMI			
Low (<18.5)	3.212	(1.389–4.051)	0.006
Normal low (≥18.5 and <23.0)	Reference		
Unknown	4.045	(2.384–4.574)	<0.001
Temperature, °C			
Low (<36.0)	6.423	(1.396–7.949)	0.017
Normal low (≥36.0 and <37.0)	Reference		
Normal high (≥37.0 and <38.0)	1.710	(1.098–2.154)	0.018
High (≥38.0)	2.421	(1.275–3.062)	0.007
Unknown	6.958	(1.073–8.827)	0.042
Sore throat	0.360	(0.137–1.326)	0.038
Shortness of breath	2.658	(1.724–3.091)	<0.001
Headache	0.276	(0.111–1.188)	0.006
Change of consciousness	8.395	(2.795–9.495)	<0.001
Diabetes mellitus	1.906	(1.264–2.317)	0.002
Cancer	3.109	(1.440–3.878)	0.004
Dementia	4.543	(2.788–5.031)	<0.001
Hemoglobin, g/dL			
Lower (men <12.3; women <10.8)	1.917	(1.134–2.441)	0.015
Normal low (men ≥14.0 and <15.7; women ≥12.3 and <13.8)	Reference		
Lymphocyte, %			
Low (<20)	3.812	(2.233–4.347)	<0.001
Normal low (≥20 and <32)	Reference		
Unknown	5.265	(1.339–6.634)	0.017
Platelets, μL			
Low (<150K)	2.537	(1.566–3.019)	<0.001
Normal low (≥150K and <300K)	Reference		
White blood cell, μL			
Normal (≥4,500 and <11,000)	Reference		
High (≥11,000)	3.595	(1.970–4.196)	<0.001

HR, hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; BMI, body mass index.

parison, the number of common symptom complaints caused by COVID-19 was lower than that of the control group, which is thought to decrease the early diagnosis rate of COVID-19 in dementia patients, which may cause an increase in mortality. The reason for the low number of complaints may be due to the decreased communication ability of dementia patients, but may also be a specific biological characteristic of dementia patients. Therefore, in dementia patients, even if the complaints are not serious, it is advisable to conduct a thorough diagnostic test when exposed to risk factors. However, even after PSM of all differences with the control group, dementia patients still showed a higher early mortality rate than the control group, suggesting that another pathological cause of dementia increases the mortality rate.

The *APOE ε4/ε4* genotype increases the risk of Alzheimer's disease by amyloid β-peptide deposition in senile plagues and cerebral vessels [9]. In an analysis using the UK Biobank, *APOE ε4/ε4* homozygotes have 2.2-fold higher risk for COVID-19 positivity and 4.3-fold increase in mortality after COVID-19 than in *ε3/ε3* homozygotes [8]. Apoprotein E4 (APOE4) isoform links to various viral infections [14, 15]. It facilitates entry of herpes simplex virus type-1 particles into the cell and promotes the viral colonization in the brain with higher efficiency than APOE3 [14]. Also, APOE4 increased the rate of human

Table 4. General logistic regression of death within 14 days after COVID-19 diagnosis

Characteristics	HR	95% CI	*p* value
Age (years)			
<50	Reference		
≥50 and <70	14.533	(1.882–16.577)	0.010
≥70	53.959	(6.995–56.002)	<0.001
BMI			
Normal low (≥18.5 and <23.0)	Reference		
Unknown	3.246	(1.820–3.825)	<0.001
Temperature, °C			
Low (<36.0)	7.319	(1.490–8.911)	0.014
Normal low (≥36.0 &<37.0)	Reference		
Normal high (≥37.0 and <38.0)	2.014	(1.230–2.507)	0.005
High (≥38.0)	3.575	(1.810–4.255)	<0.001
Unknown	17.292	(4.658–18.604)	<0.001
Shortness of breath	2.478	(1.549–2.947)	<0.001
Headache	0.299	(0.107–1.324)	0.021
Change of consciousness	9.858	(3.494–10.896)	<0.001
Diabetes mellitus	2.210	(1.416–2.654)	<0.001
Dementia	5.175	(3.073–5.696)	<0.001
Hemoglobin, g/dL			
Lower (men <12.3; women <10.8)	2.248	(1.270–2.819)	0.005
Normal low (men ≥14.0 and <15.7; women ≥12.3 and <13.8)	Reference		
Unknown	33.019	(1.757–35.952)	0.019
Lymphocyte, %			
Low (<20)	3.492	(1.871–4.116)	<0.001
Normal low (≥20 and <32)	Reference		
Unknown	6.585	(1.590–8.006)	0.009
Platelets, μL			
Low (<150K)	2.411	(1.417–2.942)	0.001
Normal low (≥150K and <300K)	Reference		
White blood cell, μL			
Normal (≥4,500 and <11,000)	Reference		
High (≥11,000)	3.571	(1.881–4.212)	<0.001

HR, hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; BMI, body mass index.

immunodeficiency virus cell entry and disease progression [15]. One study speculated that coronavirus might bind to the APOE protein and *APOE* cluster genes and neighboring genes, which mediate inflammation and may interact with COVID-19, resulting in high susceptibility and poor prognosis in dementia patients [16]. APOE may relate to angiotensin-converting enzyme 2 (ACE2), an entry receptor of severe acute respiratory syndrome coronavirus 2. In mouse Alzheimer's disease model, the ACE2 gene highly expresses in brain [17]. The majority of the ACE2-expressing cells in the lung are type II alveolar cells, and *APOE* gene is one of the highly expressed viral process-related genes in ACE2-expressing type II alveolar cells [18].

Increased inflammatory response after COVID-19 infection might have resulted in the early death in dementia patients due to various causes. The APOE4 affects pro-/anti-inflammatory actions by moderating macrophage [19]. A previous study showed that viral exacerbations of asthma and increased APOE concentrations from bronchoalveolar lavage fluid macrophages amplify pulmonary inflammatory responses [20]. Inflammatory cytokine plasma level, including interleukin-6 (IL-6), is higher in dementia patients than their age-matched controls. The serum IL-6 level positively correlated with dementia progression and inversely related to the immune response in other studies [21, 22]. An elevated serum IL-6 level and increased fatality were observed in critically ill COVID-19 patients [23]. Elevated IL-6 is central to the development of macrophage activation syndrome cytokine storm [24]. Cytokine storm causes acute respiratory distress syndrome and multi-organ failure, leading to death [25].

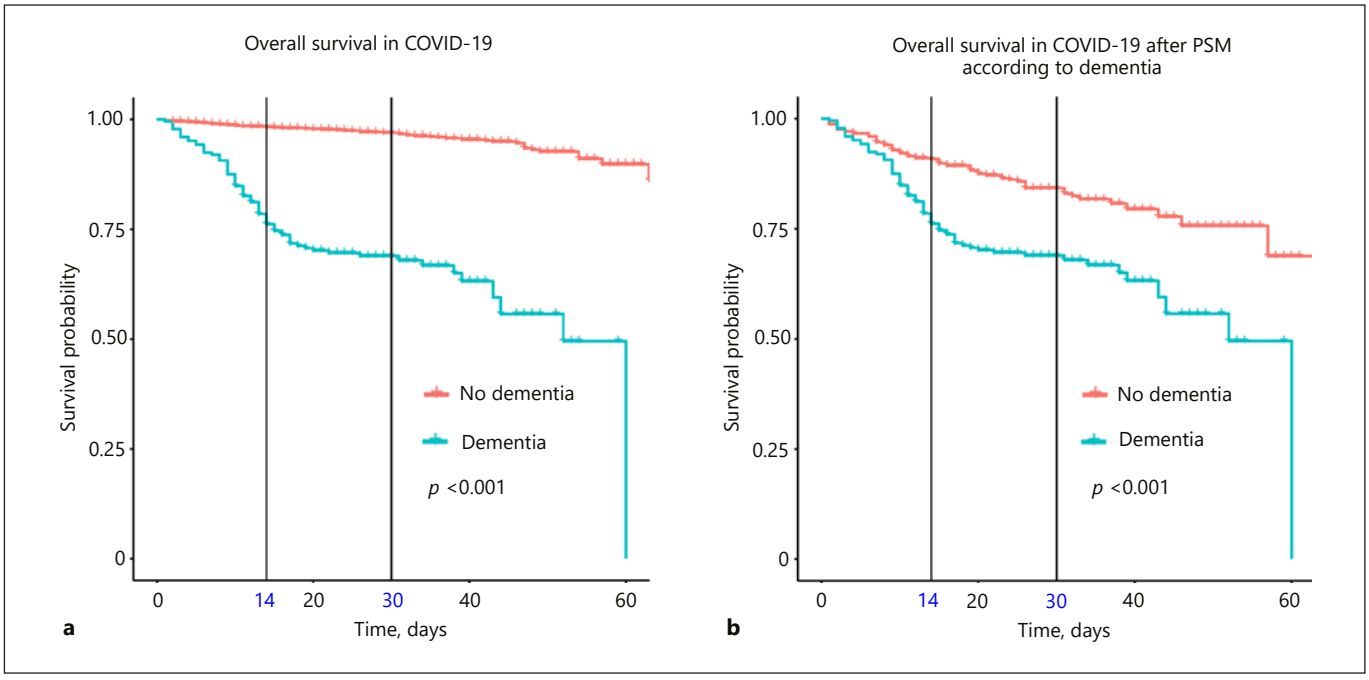

Fig. 1. Kaplan-Meier overall survival estimate according to the dementia comorbidity after COVID-19 diagnosis. **a** Before PSM. **b** After PSM *p* value, log-rank test. PSM, propensity score matching; COVID-19, coronavirus disease 2019.

The premature early death of dementia patients might be influenced by other socio-clinical factors; for example, the loss of communication ability can delay COVID-19 diagnosis and underestimate the disease severity [11]. In addition, it is difficult to prepare medical and human resources for COVID-19 dementia patients. Particularly, a resident COVID-19-negative caregiver who will accept quarantine conditions is needed for dementia patients [26]. Finally, cohort quarantine policies for nursing hospitals with confirmed COVID-19 infections may hinder timely intervention in patients with dementia [27]. All these COVID-19 quarantine policies and conditions can cause undue difficulty for dementia patients, leading to early mortality within 14 days of COVID-19 diagnosis. To prevent premature dementia patients' death after COVID-19 infection, close monitoring, prompt isolation, and active treatments are necessary.

Among the underlying diseases, diabetes, as well as dementia, was analyzed as a major risk factor for early death after COVID-19 infection. Several studies have demonstrated heterogeneous results regarding the impact of diabetes medications on the prognosis of COVID-19 patients. Metformin reduced mortality from COVID-19 infection [28], whereas dipeptidyl peptidase 4 inhibitors did not affect the outcome of COVID-19 [29]. KDCA did not provide information on the patient's diabetes medications. Further research is essential to evaluate the effect of diabetes as an underlying disease and each diabetes drug on early death in COVID-19.

Our study also showed that low hemoglobin, lymphocytes, and platelets were significantly correlated with early death from COVID-19. Anemia [30], lymphopenia [31], and thrombocytopenia [32] were reported as risk factors for severe COVID-19 infection, respectively. In the case of hemoglobin, a study insisted that COVID-19 should be regarded as an oxygen-deprived blood disease and improvement of hemoglobin dysfunction could be a therapeutic approach for this disease.

This study has limitations as a retrospective study. For example, patients with missing values (category of "unknown") on BMI, body temperature, and blood tests showed a much worse prognosis than the reference groups with normal range values, suggesting that information input may have been omitted in patients who needed emergency treatment due to severe symptoms at the time of COVID-19 diagnosis. As the COVID-19 pandemic prolongs, a systematic prospective study will help to define risk factors of a poor prognosis more accurately in COVID-19.

Conclusion

Dementia patients are at higher risk of early death within 14 days of COVID-19 diagnosis. It is necessary to prevent COVID-19 in dementia patients thoroughly, and intensive monitoring is necessary to prevent early death of dementia patients after COVID-19 diagnosis. Further randomized controlled studies are needed to confirm the finding of this study that dementia is an independent risk factor for early death from COVID-19.

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by the Institutional Review Board of Ewha Womans University Medical Center, approval number [SEUMC 2020-09-009]. Consent to participate statement: This study has been granted an exemption from requiring written informed consent by the Institutional Review Board of Ewha Womans University Medical Center.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Y.J. Kim planned the study, performed all statistical analyses, supervised the data analysis, and wrote the paper. Y. Jee performed data acquisition and contributed to revising the paper. E. H. Ha, I. Jo, H.W. Lee, and M.S. Song helped to plan the study and to revise the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the KDCA, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of KDCA.

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