Predictors of COVID-19-associated mortality among hospitalized elderly patients with dementia

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Abstract. The mortality of elderly patients with dementia hospitalized with coronavirus disease 2019 (COVID-19)-associated pneumonia is high. The mortality rate of these patients continues to be high following their discharge. However, data on the outcomes of these patients in all phases of the pandemic are limited. The aim of the present study was to examine the clinical characteristics and the in-hospital and 90-day mortality rates of elderly patients with dementia hospitalized due to COVID-19-associated pneumonia during all phases of the pandemic. During the time period between February 15, 2021 to July 15, 2022, 105 elderly patients (≥65 years old) with dementia of various etiologies were hospitalized due to COVID-19-associated pneumonia. The patient characteristics and in-hospital outcomes within 90 days of admission were recorded. The mean age of the patients was 84.03±7.61 years and 60 (57.1%) patients were females. A total of 52 (49.5%) patients were hospitalized during the omicron variant period, 27 (25.7%) were fully vaccinated (three doses) and 38 (36.2%) patients succumbed during their hospitalization. In total, 52 (49.5%) patients succumbed within the first 90 days of admission. According to the univariate regression analysis, the omicron variant [hazard ratio (HR), 2.126; 95% confidence interval (CI), 1.073-4.213; P=0.031] and the absence of full vaccination (HR, 6.231; 95% CI, 1.500-25.87; P=0.012) were associated with a higher in-hospital mortality. In the multivariate regression analysis, only the absence of complete vaccination was an independent predictor of mortality (HR, 5.182; 95% CI, 1.205-22.28; P=0.027). According to the univariate regression analysis, age (HR, 1.045; 95% CI, 1.006-1.085; P=0.023) and the lack of complete vaccination (HR, 3.254; 95% CI, 1.294-8.181; P=0.012) were associated with 90-day mortality; in addition, by multivariate regression analysis, age (HR, 1.047; 95% CI, 1.007-1.048; P=0.021) and the absence of full vaccination (HR, 3.286; 95% CI, 1.307-8.265; P=0.011) exhibited an independent association with the 90-day mortality rate. Based on the findings presented herein, the in-hospital and 90-day mortality rates of elderly patients with dementia and COVID-19-associated pneumonia is high. An older age and the lack of complete vaccination are independently associated with poor outcomes.

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Introduction

As of May 3, 2023, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic had resulted in >764 million cases and 6.9 million deaths, with the omicron variant dominating worldwide [https://covid19.who.int/]. Fortunately, with the advancements of the vaccination campaign and the succession of SARS-CoV-2 mutations, the percentage of patients admitted to hospitals due to coronavirus disease 2019 (COVID-19) and the COVID-19-associated mortality rates changed significantly over the course of the pandemic, and the current trend in confirmed cases and mortality rates continues to decrease globally [https://covid19.who.int/].

Multiple contributors to severe outcomes due to COVID-19 infection (e.g., diabetes mellitus, arterial hypertension, cardiovascular and oncological burden) have been identified (1). Dementia is a well-established predictor of a higher mortality rate globally (2), and individuals with dementia may be a particularly high-risk subgroup for both infection (2,3) and negative consequences due to COVID-19 infection (4,5). This

is most likely attributed to a larger comorbidity burden (6), a greater vulnerability to pneumonia (7), and an inability to adhere to safety measures, such as social isolation (3). However, during the early stages of the pandemic, the associations between dementia and the risk of mortality of patients with COVID-19 were less consistent (1,8).

The impact of dementia on COVID-19-related mortality has shifted over time, particularly as vaccinations became widely available and were widely administered, and as new strains of SARS-CoV-2 developed (9). The association of dementia with the risk of COVID-19-related mortality has now been confirmed in a large number of patients treated over a lengthy period of time during the pandemic (10).

However, data on the prognostic factors for the poor outcomes of patients with dementia hospitalized due to COVID-19-associated pneumonia in all pandemic waves are limited. The aim of the present study was to shed light on the factors associated with the mortality of elderly patients with dementia hospitalized due to COVID-19-associated pneumonia over a long period of time during the pandemic.

Patients and methods

Study design. The present study was a prospective study on elderly (≥65 years old) patients with dementia and COVID-19-associsated pneumonia hospitalized in the Department of Infectious Diseases and COVID-19 Unit of Laiko General Hospital (Athens, Greece), between February 15, 2021 and July 15, 2022. The diagnosis of dementia was already confirmed according to the DSM-5 diagnosis of Major Neurocognitive Disorder, which corresponds to dementia and requires substantial impairment to be present in one or (usually) more cognitive domains (11). The research was conducted in line with the Declaration of Helsinki and obtained approval from the Institutional Review Board of Laiko General Hospital. Written informed consent was obtained from the patients. The following criteria for inclusion were applied: i) An age ≥65 years; ii) a prior diagnosis of dementia; iii) a confirmation of COVID-19 infection by polymerase chain reaction; iv) severe or critical disease according to the clinical spectrum of SARS-CoV-2 infection (https://www.covid19treatmentguidelines.nih.gov/). The exclusion criterion was the lack of data on 90-day survival post-diagnosis.

Data collection. The patients' demographic characteristics, clinical symptoms, vaccination status against COVID-19 and the Charlson comorbidity index (CCI) values were recorded. Hemoglobin and hematocrit levels, white blood cell (WBC), neutrophil, lymphocyte, platelet and immature granulocyte counts, C-reactive protein (CRP), the levels of serum albumin and lactate dehydrogenase, as well as d-dimer, ferritin, liver and cholestatic enzyme levels were recorded upon admission. Charts were assessed for the implementation of in-hospital and all-cause mortality rates at 90 days.

Statistical analysis. The Kolmogorov-Smirnov test was used to assess the normal distribution of the parameters. Continuous parameters exhibiting a normal distribution are displayed as the mean (standard deviation), and those with a non-normal distribution are displayed as the median (range). To detect predictive factors of the event(s) (event=in-hospital mortality or mortality at 90 days), statistically significant variables were evaluated using Cox proportional hazards univariate and multivariate regression analyses. Statistical analysis was conducted using IBM SPSS-Statistics version 26.0 (IBM Corp.). Values of $P<0.05$ were considered to indicate statistically significant differences.

Table I. Demographics and clinical characteristics of the study population.

Variable	Value
Sex, n (%)	
Females	60 (57.1)
Males	45 (42.9)
Variant, n (%)	
Wild-type	8 (7.6)
Alpha	24 (22.9)
Delta	21 (20)
Omicron	52 (49.5)
Vaccination status, n (%)	
Fully vaccinated (at least three doses)	27 (25.7)
Unvaccinated or partially vaccinated	78 (74.3)
In-hospital mortality, n (%)	
No	67 (63.8)
Yes	38 (36.2)
90-day mortality, n (%)	
No	53 (50.5)
Yes	52 (49.5)
Age (years), mean (SD)	84.03 (7.61)
CCI, median (range)	5 (3-9)

CCI, Charlson comorbidity index; SD, standard deviation.

Results

During the study period, a total of 1,144 elderly individuals were hospitalized in COVID-19 Unit, Laiko General Hospital (Athens, Greece) due to COVID-19-associated pneumonia, of whom 105 (9.2%) patients (60 females, 57.1%) were suffering from dementia. The mean age of the patients was 84.03±7.61 years, and the median value of the CCI was 5 (range, 3-9). A total of 8 patients (7.6%) were hospitalized during the period of wild-type variant predominance period, 24 (22.9%) patients were hospitalized during the alpha variant predominance period, 21 (20%) patients were hospitalized during the delta variant predominance period, and 52 (49.5%) patients were hospitalized during the omicron variant predominance period.

As regards the vaccination status, only 27 (25.7%) patients were fully vaccinated (at least three doses). In total, 38 (36.2%) patients succumbed during their hospitalization, while a total of 52 (49.5%) patients succumbed during the first 90 days following diagnosis. The demographics and clinical characteristics of the study population are presented in Table I.

Table II. Univariate Cox regression analysis (outcome: In-hospital mortality).

			95% CI	
Variable	P-value	HR	Lower	Upper
Age (years)	0.326	1.022	0.979	1,066
Male sex	0.815	1.079	0.569	2.046
Absence of full vaccination	**0.012**	6.231	1.500	25.878
Omicron variant	**0.031**	2.126	1.073	4.213
CCI	0.225	0.240	0.602	1.127
Hb (g/dl)	0.702	0.680	0.819	1.144
Hct (%)	0.581	0.840	0.931	1.041
WBC (K/μl)	0.636	1.015	0.954	1.080
Neu (K/μl)	0.677	1.015	0.945	1.090
Lym (K/μl)	0.546	1.176	0.695	1.992
IGs (10^9/l)	0.603	2.879	0.053	15.22
PLTs (K/μl)	0.868	1.000	0.997	1.040
FIB (mg/dl)	0.538	1.001	0.998	1.003
Creatinine (mg/dl)	0.333	1.214	0.820	1.799
AST (U/l)	0.254	1.001	0.999	1.004
ALT (U/l)	0.284	1.003	0.997	1.009
ALP (U/l)	0.648	1.002	0.993	1.011
GGT (U/l)	0.768	0.999	0.990	1.007
LDH (U/l)	0.185	1.001	0.999	1.003
CRP (mg/l)	0.212	1.003	0.998	1.007
Fer (ng/ml)	0.106	1.000	1.001	1.004
d-dimer (μg/ml)	0.350	1.036	0.962	1.115
Albumin (g/l)	0.529	0.984	0.937	1.034
NLR	0.637	1.007	0.979	1.034
PLR	0.933	1.000	0.998	1.002
CAR	0.574	1.051	0.884	1.249

Values in bold font indicate statistically significant differences (P<0.05). HR, hazard ratio; CI, confidence interval; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CCI, Charlson comorbidity index; CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; Fer, ferritin; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, hemoglobin; Hct, hematocrit; HR, hazard ratio; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; Neu, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLTs, platelets; WBC, white blood cell.

Table III. Multivariate Cox regression analysis (outcome: In-hospital mortality).

			95% CI	
Variable	P-value	HR	Lower	Upper
Absence of full vaccination	**0.027**	5.182	1.205	22.28
Omicron variant	0.245	1.515	0.752	3.054

Values in bold font indicate statistically significant differences (P<0.05). HR, hazard ratio; CI, confidence interval.

According to the univariate regression analysis, the period of omicron variant prevalence [hazard ratio (HR), 2.126; 95% confidence interval (CI), 1.073-4.213; P=0.031] and the absence of full vaccination (HR, 6.231; 95% CI, 1.500-25.87; P=0.012) were associated with in-hospital mortality (Table II); however, in the multivariate regression analysis, only the absence of complete vaccination exhibited an independent association with in-hospital mortality (HR, 5.182; 95% CI, 1.205-22.28; P=0.027) (Table III).

According to the univariate regression analysis, age (HR, 1.045; 95% CI, 1.006-1.085; P=0.023) and the absence of full vaccination (HR, 3.254; 95% CI, 1.294-8.181; P=0.012)

Table IV. Univariate Cox regression analysis (outcome: 90-day mortality).

			95% CI	
Variable	P-value	HR	Lower	Upper
Age (years)	**0.023**	1.045	1.006	1.085
Male sex	0.359	1.303	0.741	2.291
Omicron variant	0.114	0.637	0.364	1.114
CCI	0.545	0.924	0.715	1.194
Absence of full vaccination	**0.012**	3.254	1.294	8.181
Hb (g/dl)	0.155	0.905	0.788	1.038
Hct (%)	0.147	0.966	0.923	1.012
WBC (K/μl)	0.221	1.029	0.983	1.078
Neu (K/μl)	0.210	1.034	0.981	1.089
Lym (K/μl)	0.526	1.158	0.736	1.820
IGs (10^9/l)	0.133	10.031	0.497	20.26
PLTs (K/μl)	0.846	1.000	0.997	1.003
FIB (mg/dl)	0.985	1.000	0.998	1.002
Creatinine (mg/dl)	0.643	1.092	0.753	1.584
AST (U/l)	0.486	1.001	0.999	1.003
ALT (U/l)	0.521	1.002	0.996	1.008
ALP (U/l)	0.583	1.002	0.995	1.010
GGT (U/l)	0.847	0.999	0.993	1.006
LDH (U/l)	0.295	1.001	0.999	1.003
CRP (mg/l)	0.110	1.003	0.999	1.007
Fer (ng/ml)	0.054	1.001	1.000	1.003
d-dimer (μg/ml)	0.539	1.021	0.955	1.093
Albumin (g/l)	0.080	0.965	0.927	1.004
NLR	0.489	1.008	0.986	1.031
PLR	0.899	1.000	0.998	1.001
CAR	0.123	1.113	0.971	1.275

Values in bold font indicate statistically significant differences (P<0.05). HR, hazard ratio; CI, confidence interval; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CCI, Charlson comorbidity index; CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; Fer, ferritin; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, hemoglobin; Hct, hematocrit; HR, hazard ratio; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; Neu, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLTs, platelets; WBC, white blood cell.

Table V. Multivariate Cox regression analysis (outcome: 90-day mortality).

			95% CI	
Variable	P-value	HR	Lower	Upper
Absence of full vaccination	**0.011**	3.286	1.307	8.265
Age (years)	**0.021**	1.047	1.007	1.088

Values in bold font indicate statistically significant differences (P<0.05). HR, hazard ratio; CI, confidence interval.

were associated with the 90-day mortality (Table IV). In addition, by multivariate regression analysis, age (HR, 1.047; 95% CI, 1.007-1.048; P=0.021) and the absence of full vaccination (HR, 3.286; 95% CI, 1.307-8.265; P=0.011) exhibited an independent association with the 90-day mortality (Table V).

Discussion

According to some studies from the first pandemic waves, the mortality rate of patients with dementia hospitalized due to COVID-19-associated pneumonia ranges between 22.4-37.5% (12-14). In their study, Kostev *et al* (10) reported

that in patients with dementia and COVID-19 from all the pandemic waves, the in-hospital mortality rate was 26.5%, while in the present study, the in-hospital mortality rate was 36.2%. This difference may be attributed to different health systems and geographical settings.

In the present study, the 90-day mortality rate was 49.5%. The post-discharge out-of-hospital mortality among patients with dementia with COVID-19 has been reported to be considerably higher than that among non-dementia patients (15). Patients with dementia are an older, more vulnerable population, having a higher CCI value than elderly patients without dementia (15). As a result, patients with dementia will have a higher mortality rate, despite the fact that the majority did not meet the severity requirements at the time of admission. As a result, patients with dementia who are discharged need to be monitored closely, since they are at a high risk of mortality.

Studies from the first pandemic waves have reported comorbidities, such as chronic kidney disease, medications such as antipsychotics and benzodiazepines, and laboratory biomarkers such as CRP, WBC, neutrophil count, serum sodium and calcium as prognostic factors for the mortality of patients with dementia and COVID-19 (9,12,16). The study by Kostev *et al* (10), which included patients with dementia diagnosed with COVID-19 across a long time period of the pandemic, identified age, the non-omicron variant, obesity, liver cirrhosis and cancer as prognostic factors for mortality. However, that study did not take into account the vaccination status, as it is already mentioned in its limitations (10).

In the present study, age was an independent prognostic factor for the 90-day mortality rate, while the absence of full vaccination was an independent prognostic factor for both in-hospital and 90-day mortality among patients with dementia with COVID-19-assocaited pneumonia. An older age is a recognized prognostic factor for COVID-19-associated mortality, and COVID-19 is responsible for disproportionately high rates of mortality among the elderly, particularly those with multiple comorbidities (17-20). The absence of vaccination is a known risk factor for the mortality of patients with COVID-19 (21). Moreover, it has been demonstrated that vaccines against COVID-19 are highly effective in preventing hospitalization and mortality among the elderly (22,23).

To the best of our knowledge, the present study is the first to report the protective role of full vaccination in elderly patients with dementia hospitalized due to COVID-19 in all the pandemic waves. However, the present study is also subject to some limitations. Although the CCI was used for adjustment in the regression analysis, other entities, such as anemia, that were not included could have affected the study outcomes. No detailed data are available regarding the causes of mortality for those individuals who did not survive. In addition, no medications regarding COVID-19 or other medications for the underlying disease were included in the analysis. Furthermore, considering that the present study only enrolled hospitalized patients, the association between dementia and a fatal course of COVID-19 cannot be generalized to indicate an association between dementia and COVID-19 severity in individuals treated as outpatients. Finally, viral variants were not identified individually for patients. The assignment of variants was based on the predominant variant at the time the patient was diagnosed with SARS-CoV2 infection, and a distinction was only made based on whether patients were diagnosed before or since the omicron variant emerged.

In conclusion, the present study demonstrates that in-hospital and the 90-day mortality rates of elderly patients with dementia and COVID-19-associated pneumonia are high. An older age and a lack of full vaccination are independently associated with poor outcomes.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AB and VEG conceptualized the study. VEG, AT, DB, DAS, SM, AG, GK, PMV, IE, EA, AB, PS and NVS made a substantial contribution to data interpretation and analysis, and wrote and prepared the draft of the manuscript. VEG and NVS analyzed the data and provided critical revisions. VEG and NVS confirm the authenticity of all the data. All authors contributed to manuscript revision and have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in line with the Declaration of Helsinki and obtained approval from the regional Institutional Review Board (approval no. 765/12-2021).

Patient consent for publication

Written informed consent was obtained from the patients.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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