

Risk factors for the in-hospital and 1-year mortality of elderly patients hospitalized due to COVID-19-related pneumonia

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Received August 24, 2023; Accepted November 9, 2023

DOI: 10.3892/etm.2023.12310

Abstract. Coronavirus disease 2019 (COVID-19) is characterized by poor outcomes and a high mortality rate, particularly among elderly patients. Since the beginning of the pandemic, an older age has been recognized as a critical risk factor for disease severity, with increasing mortality rates in each decade of life. This phenomenon may be a consequence of a poor previous health status, with a higher prevalence of pre-existing comorbidities and a higher degree of frailty. The majority of studies on the outcomes and risk factors of elderly patients refer to the first waves of the pandemic and the predictors of in-hospital mortality in these patients. The aim of the present study was to provide a detailed description of the clinical characteristics and management of a cohort of elderly patients (≥ 65 years of age) who were hospitalized with COVID-19-related pneumonia in all phases of the pandemic, presenting their outcomes, and investigating predictors of in-hospital and out-of-hospital mortality over a period of 1 year in this particularly vulnerable population. A total of 1,124 elderly patients (603 males, 53.7%) with a mean age of 78.51 ± 7.42 years and a median Charlson comorbidity index (CCI) of 5 were included in the study. Of these patients, 104 (9.3%) were hospitalized during the period of prevalence

of the original strain Wuhan, 385 (34.3%) were hospitalized during the period of prevalence of the Alpha variant, 221 (19.7%) were hospitalized during the period of prevalence of the Delta variant, and 414 (36.8%) were hospitalized during the period of prevalence of the Omicron variant. Overall, the in-hospital mortality rate was 33.4% (375 patients), and the 1-year mortality rate was 44.7% (502 patients). The majority of patients had not been vaccinated or had not completed full vaccination against severe acute respiratory syndrome coronavirus-2 (843 patients, 75%), given the period of infection. Age, immature granulocytes, lactate dehydrogenase (LDH) levels, ferritin levels, chest X-ray score, as well as the absence of full vaccination, cough and fatigue, were statistically significantly and independently associated with in-hospital mortality, while age, LDH levels, ferritin levels, alanine aminotransferase levels, CCI, chest X-ray score, the absence of cough and fatigue, and a history of dementia were statistically significantly and independently associated with 1-year mortality. On the whole, the present study demonstrates that both the in-hospital mortality and 1-year mortality rates of elderly patients hospitalized due to COVID-19-related pneumonia are high.

Introduction

On March 11, 2020, the World Health Organization (WHO) characterized the coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as a pandemic (1). As of May 24, 2023, 766,895,075 confirmed cases of COVID-19 and 6,935,889 related deaths were recorded worldwide, according to the WHO (2). With the progress of the vaccination campaign and the succession of SARS-CoV-2 mutations, the proportion of patients with COVID-19

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Key words: COVID-19, pneumonia, mortality, elderly, risk factors

requiring hospitalization and the mortality associated with COVID-19 have markedly changed during the pandemic, and the incidence of confirmed cases and deaths continues to decline worldwide (2).

Patients with COVID-19 present with a wide range of respiratory manifestations, ranging from mild clinical course to severe and potentially life-threatening pneumonia (3). In addition, some patients experience gastrointestinal symptoms, such as vomiting, diarrhea, abdominal pain and nausea in addition to the respiratory symptoms (4,5), as well as cardiovascular and neurological symptoms (6).

Multiple risk factors for severe COVID-19 infection have been identified since the beginning of the pandemic, such as diabetes mellitus, arterial hypertension, cardiovascular disease and malignancies (7). COVID-19 is characterized by poor outcomes and high mortality rates, particularly among elderly patients. Since the beginning of the pandemic, an older age has been recognized as a critical risk factor for disease severity, with increasing mortality rates in each decade of life (8). This phenomenon may be a consequence of a poor previous health status, with a higher prevalence of pre-existing comorbidities and a higher degree of frailty. It is unclear whether the poorer quality of service provided in health care systems collapsed worldwide by the unprecedented pandemic contributes to the observed poor prognosis of the elderly (9).

The majority of studies on the outcomes and risk factors of elderly patients refer to the first waves of the pandemic and predictors of in-hospital mortality in these patients. A previous systematic review of these studies reported that an increasing age, body mass index, male sex, dementia, reduced functionality or dependence for daily activities, the presence of infiltrates on chest X-ray, hypoxemic respiratory failure and a lower saturation of oxygen upon admission were risk factors for mortality due to COVID-19 (10). High levels of D-dimers, 25-hydroxyvitamin D deficiency, high levels of C-reactive protein (CRP) plus any other lymphocyte abnormalities, higher blood urea or lactate dehydrogenase (LDH) levels, and higher platelet count (PLTs) have been established as predictors of poor outcomes in the elderly (10). It has been reported that prior treatment with renin-angiotensin-aldosterone system inhibitors, pharmacological treatments for respiratory diseases and other medications, such as antibiotics, corticosteroids, vitamin K antagonists and antihistamines in combination with other antivirals reduces the likelihood of severe COVID-19 infection and mortality. Seasonal influenza vaccination may also reduce mortality from COVID-19, according to that previous systematic review.

As elderly patients represent a vulnerable population even in the era of omicron mutation prevalence and as the infection becomes endemic, data are required to improve healthcare pathways in the context of COVID-19 (11). The aim of the present study was to provide a detailed description of the clinical characteristics and management of a cohort of elderly patients (≥ 65 years of age) who were hospitalized with COVID-19-related pneumonia in all phases of the pandemic, to present their outcomes, and to investigate predictors of in-hospital and 1-year mortality rates in this particularly vulnerable population.

Patients and methods

Study design. For the purposes of the present study, a retrospective recording of data was carried out on consecutive elderly patients aged ≥ 65 years who were hospitalized with COVID-19-related pneumonia at the Infectious Diseases Unit of Laiko General Hospital during the period October 1, 2020 to July 15, 2022, including patients who were infected from the initial strain and from the Alpha, Delta, and Omicron variants. The study was conducted in line with the Declaration of Helsinki and obtained approval by the Institutional Review Board of Laiko General Hospital, Athens, Greece (protocol no. 7950/08.06.2023). Written informed was obtained from all the included the patients.

Data collection. The demographic characteristics (sex, age), clinical symptoms, the extent of pneumonia on the chest X-ray with the chest X-ray score (12), the vaccination status against SARS-CoV-2, any comorbidities and the Charlson Comorbidity Index (CCI) were recorded. The following admission laboratory findings were also recorded: Hemoglobin (Hb) and hematocrit (Hct) levels; white blood cells (WBC); neutrophils (Neu); lymphocytes (Lym); PLTs and immature granulocytes (IGs); CRP; serum albumin and LDH levels; D-dimer levels; fibrinogen (FIB); creatinine; ferritin; the levels of liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT); and cholestatic enzymes gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). The patients were treated according to the WHO recommendations which represent the standard clinical practice (13) and these treatments received by the patients for the treatment of COVID-19 pneumonia were recorded.

Recording of outcomes. In-hospital mortality rates were recorded, as well as mortality rates within 1 year of admission. Predictors of mortality were also investigated. Patients without a reliable follow-up at 1 year were excluded from the study.

Statistical analysis. Statistical analysis was performed using IBM SPSS-Statistics version 29.0 (IBM Corp.). The Kolmogorov-Smirnov test was used to examine the normal distribution of parameters. Continuous parameters with a normal distribution are shown as the mean (standard deviation), and those with a non-normal distribution are shown as the median (range). For the analysis of categorical variables, the Chi-squared or the Fisher's exact tests were used. To detect predictors of events (event=in-hospital mortality or mortality at 1 year), statistically significant variables were assessed using univariate and multivariate Cox proportional hazards regression analysis. Values of $P < 0.05$ were considered to indicate statistically significant differences.

Results

A total of 1,124 elderly patients (603 males, 53.7%) with a mean age of 78.51 ± 7.42 years and a median CCI of 5 were included in the study. Of these patients, 104 (9.3%) were hospitalized during the period of prevalence of the original Wuhan strain, 385 (34.3%) were hospitalized during the period of prevalence of the

Table I. Demographics of the study population.

| Parameter | Value |
|------------------------------|------------------|
| Age (years), mean \pm SD | 78.51 \pm 7.42 |
| CCI, median (range) | 5 (2-8) |
| Sex, n (%) | |
| Females | 520 (46.3) |
| Males | 604 (53.7) |
| In-hospital mortality, n (%) | |
| No | 749 (66.6) |
| Yes | 375 (33.4) |
| 1-year mortality, n (%) | |
| No | 622 (55.3) |
| Yes | 502 (44.7) |
| Variant, n (%) | |
| Alpha | 385 (34.3) |
| Delta | 221 (19.7) |
| Omicron | 414 (36.8) |
| Wuhan | 104 (9.3) |
| Omicron variant, n (%) | |
| No | 710 (63.2) |
| Yes | 414 (36.8) |
| Fully vaccinated, n (%) | |
| No | 843 (75) |
| Yes | 281 (25) |
| Vaccination doses, n (%) | |
| 0 | 704 (62.6) |
| 1 | 66 (5.9) |
| 2 | 162 (14.4) |
| 3 | 179 (15.9) |
| 4 | 13 (1.2) |

CCI, Charlson comorbidity index.

Alpha variant, 221 (19.7%) were hospitalized during the period of prevalence of the Delta variant, and 414 (36.8%) were hospitalized during the period of prevalence of the Omicron variant. Overall, the in-hospital mortality rate was 33.4% (375 patients) and the 1-year mortality was 44.7% (502 patients). The majority of patients had not been vaccinated or had not completed full vaccination against SARS-CoV-2 (843 patients, 75%), given the time period of infection. The demographics of the total study population are summarized in Table I.

The most common symptom upon admission was fever (755 patients, 67.2%), followed by dyspnea (619 patients, 55.1%) and cough (312 patients, 27.8%) (Table II). The most common comorbidity was arterial hypertension (558 patients, 49.6%), followed by cardiovascular disease, which included stroke, coronary artery disease, valvular diseases, arrhythmias and cardiomyopathy (433 patients, 38.5%), and diabetes mellitus (305 patients, 27.1%) (Table III).

The majority of the patients were treated with anticoagulants, dexamethasone and remdesivir; 83 (7.4%) patients received tocilizumab; 12 (1.1%) patients received

Table II. Symptoms of patients upon admission.

| Symptom | Frequency (no. of patients) | Percentage |
|----------------------------|--------------------------------|------------|
| Fever | | |
| No | 369 | 32.8 |
| Yes | 755 | 67.2 |
| Sore throat | | |
| No | 1,086 | 96.6 |
| Yes | 38 | 3.4 |
| Disruptions in smell/taste | | |
| No | 1,110 | 98.8 |
| Yes | 14 | 1.2 |
| Dyspnea | | |
| No | 505 | 44.9 |
| Yes | 619 | 55.1 |
| Cough | | |
| No | 812 | 72.2 |
| Yes | 312 | 27.8 |
| Fatigue | | |
| No | 990 | 88.1 |
| Yes | 134 | 11.9 |
| Gastrointestinal symptoms | | |
| No | 1,024 | 91.1 |
| Yes | 100 | 8.9 |
| Altered mental status | | |
| No | 1,061 | 94.4 |
| Yes | 63 | 5.6 |

baricitinib; and 9 (0.8%) patients received anakinra. In 138 (12.3%) patients, oxygen therapy with a high-flow nasal cannula was applied; in 18 (1.6%) patients, non-invasive mechanical ventilation was applied; and 134 (11.9%) patients were intubated (received invasive mechanical ventilation) (Table IV).

In total, 3 (0.2%) patients had received prophylactic intravenous remdesivir; 4 (0.4%) patients had received the combination of monoclonal antibodies casirivimab/imdevimab; and 24 (2.1%) patients had received the combination of antiviral agents nirmatrelvir/ritonavir (Table V).

The univariate analysis of categorical variables for the outcome of in-hospital mortality revealed that patients who succumbed to the disease in the hospital were significantly more likely to be in the Delta variant prevalence period (in-hospital mortality rate: 92/129 patients, 41.6%); these patients also had a statistically higher proportion of cardiovascular disease, heart failure, renal disease and a history of nursing home residency. In addition, the lack of complete vaccination, dyspnea and an altered mental status were significantly associated with the in-hospital mortality rate, and fever, cough, sore throat, disruptions in taste/smell and fatigue were significantly associated with the in-hospital survival rate ($P < 0.05$; Table VI).

Table III. Comorbidities of the study population.

| Comorbidity | Frequency (no. of patients) | Percentage |
|--|--------------------------------|------------|
| Lung disease (COPD, asthma, pulmonary fibrosis) | | |
| No | 969 | 86.2 |
| Yes | 155 | 13.8 |
| Obesity (BMI >30kg/m ²) | | |
| No | 1,088 | 96.8 |
| Yes | 36 | 3.2 |
| Diabetes mellitus | | |
| No | 819 | 72.9 |
| Yes | 305 | 27.1 |
| Arterial hypertension | | |
| No | 566 | 50.4 |
| Yes | 558 | 49.6 |
| Cardiovascular disease (stroke, coronary artery disease, valvular disease, arrhythmias, cardiomyopathy) | | |
| No | 691 | 61.5 |
| Yes | 433 | 38.5 |
| Heart failure | | |
| No | 1,023 | 91 |
| Yes | 101 | 9 |
| Renal disease | | |
| No | 1,019 | 90.7 |
| Yes | 105 | 9.3 |
| Liver disease | | |
| No | 1,103 | 98.1 |
| Yes | 21 | 1.9 |
| Autoimmune disease | | |
| No | 1,055 | 93.9 |
| Yes | 69 | 6.1 |
| Hematological malignancy | | |
| No | 1,060 | 94.3 |
| Yes | 64 | 5.7 |
| Solid organ malignancy | | |
| No | 1,042 | 92.7 |
| Yes | 82 | 7.3 |
| Solid organ transplantation | | |
| No | 1,112 | 98.9 |
| Yes | 12 | 1.1 |
| Parkinson's disease | | |
| No | 1,089 | 96.9 |
| Yes | 35 | 3.1 |
| Dementia | | |
| No | 1,020 | 90.7 |
| Yes | 104 | 9.3 |
| Nursing home resident | | |
| No | 1,084 | 96.4 |
| Yes | 40 | 3.6 |

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table IV. Medication that was administrated to the study population during the hospitalization period.

| Medication | Frequency (no. of patients) | Percentage |
|---------------------------------|--------------------------------|------------|
| Remdesivir | | |
| No | 116 | 10.3 |
| Yes | 1,008 | 89.7 |
| Dexamethasone | | |
| No | 47 | 4.2 |
| Yes | 1,077 | 95.8 |
| Tocilizumab | | |
| No | 1,041 | 92.6 |
| Yes | 83 | 7.4 |
| Anticoagulants | | |
| No | 44 | 3.9 |
| Yes | 1,080 | 96.1 |
| Anakinra | | |
| No | 1,115 | 99.2 |
| Yes | 9 | 0.8 |
| Baricitinib | | |
| No | 1,112 | 98.9 |
| Yes | 12 | 1.1 |
| High flow nasal cannula | | |
| No | 986 | 87.7 |
| Yes | 138 | 12.3 |
| Non-invasive ventilation | | |
| No | 1,106 | 98.4 |
| Yes | 18 | 1.6 |
| Invasive mechanical ventilation | | |
| No | 990 | 88.1 |
| Yes | 134 | 11.9 |

The univariate analysis of continuous variables for the outcome, in-hospital mortality, revealed that the patients who succumbed in hospital had a significantly older age, lower Hb and lower Hct levels, higher CCI, higher WBC, higher Neu count, higher IG count, higher value of D-dimers, higher value of creatinine, higher values of AST, ALP, GGT, LDH, CRP, ferritin and chest X-ray score, and a lower value of Lym count compared to the survivors ($P<0.05$; Table VII).

From the multivariate analysis for the outcome of in-hospital mortality, it emerged that age, IGs, LDH, ferritin, chest X-ray score, as well as the absence of full vaccination, cough and fatigue, were significantly and independently associated with the in-hospital mortality rate ($P<0.05$; Table VIII).

The univariate analysis of continuous variables for the outcome of 1-year mortality revealed that patients who succumbed within 1 year were significantly more likely to have been ill in the period of prevalence of the Alpha variant (mortality within 1 year, 52%); these patients also

Table V. Prophylactic therapy that patients received for COVID-19 prior to their admission to the hospital.

| Therapy | Frequency (no. of patients) | Percentage |
|------------------------|--------------------------------|------------|
| Remdesivir | | |
| No | 1,121 | 99.8 |
| Yes | 3 | 0.2 |
| Casirivimab/imdevimab | | |
| No | 1,119 | 99.6 |
| Yes | 5 | 0.4 |
| Nirmatrelvir/ritonavir | | |
| No | 1,100 | 97.9 |
| Yes | 24 | 2.1 |

had a significantly greater proportion of arterial hypertension, cardiovascular disease, heart failure, renal disease, dementia, Parkinson's disease, hematological malignancy, solid organ malignancy and a history of nursing home residency. Furthermore, dyspnea and an altered mental status were statistically significantly associated with mortality, and fever, cough, sore throat, disruptions in taste/smell and fatigue were statistically significantly associated with the 1-year survival ($P<0.05$; Table IX).

The univariate analysis of categorical variables for the outcome of 1-year mortality revealed that patients who succumbed within 1 year had a significantly older age, lower Hb and lower Hct levels, higher CCI, higher WBC value, higher Neu value, higher value of IGs, higher value of D-dimers, higher value of creatinine, higher value of ALP, LDH, CRP, ferritin and chest X-ray score, and a lower value of Lym, ALT and GGT compared to the survivors ($P<0.05$; Table X).

From the multivariate analysis for the outcome of 1-year mortality, it was found that age, LDH, ferritin, ALT, CCI, chest X-ray score, the absence of cough and fatigue, and a history of dementia were significantly and independently associated with mortality within 1 year ($P<0.05$; Table XI).

As shown in Table I, an additional 127 elderly patients succumbed within 1 year of admission. As regards the causes of death, the majority of patients succumbed due to cardiac events, including acute myocardial infarction, arrhythmia, cardiogenic shock, or pulmonary edema. The second cause of death was septic shock (36 patients, 28.3%); in 13 patients, the cause of death was not specified, while it is noteworthy that 3 patients (2.4%) succumbed due to a new SARS-CoV-2 infection (Table XII).

Discussion

According to the present study, the in-hospital and out-of-hospital mortality of elderly patients with COVID-19 was high. Overall, the in-hospital mortality rate was 33.4% (375 patients), and the 1-year mortality rate was 44.7% (502 patients). As regards in-hospital mortality, the findings of the present study are in agreement with those of previous

Table VI. Univariate analysis for categorical variables (outcome: In-hospital mortality).

| Variable | In-hospital mortality | | P-value |
|--------------------------------------|-----------------------|-----|--------------|
| | No | Yes | |
| Omicron variant | | | |
| No | 468 | 242 | 0.513 |
| Yes | 281 | 133 | |
| Variant | | | 0.014 |
| Wuhan | 66 | 38 | |
| Alpha | 272 | 112 | |
| Delta | 129 | 92 | |
| Omicron | 281 | 133 | |
| Sex | | | |
| Female | 361 | 159 | 0.076 |
| Male | 388 | 216 | |
| Lung disease | | | |
| No | 636 | 333 | 0.081 |
| Yes | 113 | 42 | |
| Obesity (BMI >30 kg/m ²) | | | |
| No | 721 | 367 | 0.208 |
| Yes | 28 | 8 | |
| Diabetes mellitus | | | |
| No | 545 | 274 | 0.943 |
| Yes | 204 | 101 | |
| Arterial hypertension | | | |
| No | 362 | 204 | 0.058 |
| Yes | 387 | 171 | |
| Cardiovascular disease | | | |
| No | 481 | 210 | 0.009 |
| Yes | 268 | 165 | |
| Heart failure | | | |
| No | 695 | 328 | 0.004 |
| Yes | 54 | 47 | |
| Renal disease | | | |
| No | 692 | 327 | 0.006 |
| Yes | 57 | 48 | |
| Liver disease | | | |
| No | 735 | 368 | 0.998 |
| Yes | 14 | 7 | |
| Autoimmune disease | | | |
| No | 704 | 351 | 0.793 |
| Yes | 45 | 24 | |
| Hematological malignancy | | | |
| No | 707 | 353 | 0.892 |
| Yes | 42 | 22 | |
| Solid organ malignancy | | | |
| No | 702 | 340 | 0.068 |
| Yes | 47 | 35 | |
| Solid organ transplantation | | | |
| No | 742 | 370 | 0.540 |
| Yes | 7 | 5 | |

Table VI. Continued.

| Variable | In-hospital mortality | | P-value |
|----------------------------|-----------------------|-----|--------------|
| | No | Yes | |
| Parkinson's disease | | | |
| No | 731 | 358 | 0.067 |
| Yes | 18 | 17 | |
| Dementia | | | |
| No | 684 | 336 | 0.383 |
| Yes | 65 | 39 | |
| Nursing home residency | | | |
| No | 731 | 353 | 0.006 |
| Yes | 18 | 22 | |
| Fully vaccinated | | | |
| No | 544 | 299 | 0.010 |
| Yes | 205 | 76 | |
| Vaccination doses | | | |
| 0 | 462 | 242 | 0.001 |
| 1 | 42 | 24 | |
| 2 | 94 | 68 | |
| 3 | 140 | 39 | |
| 4 | 11 | 2 | |
| Fever | | | |
| No | 220 | 149 | 0.001 |
| Yes | 529 | 226 | |
| Sore throat | | | |
| No | 717 | 369 | 0.022 |
| Yes | 32 | 6 | |
| Disruptions in smell/taste | | | |
| No | 735 | 375 | 0.007 |
| Yes | 14 | 0 | |
| Dyspnea | | | |
| No | 366 | 139 | 0.001 |
| Yes | 383 | 236 | |
| Cough | | | |
| No | 504 | 308 | 0.001 |
| Yes | 245 | 67 | |
| Fatigue | | | |
| No | 646 | 344 | 0.008 |
| Yes | 103 | 31 | |
| Gastrointestinal symptoms | | | |
| No | 676 | 348 | 0.182 |
| Yes | 73 | 27 | |
| Altered mental status | | | |
| No | 718 | 343 | 0.004 |
| Yes | 31 | 32 | |

P-values in bold font indicate statistically significant differences ($P < 0.05$). BMI, body mass index.

studies (14-18), reporting on the in-hospital mortality of elderly patients from the first waves of the pandemic. The present study is one of the few studies reporting on in-hospital mortality of elderly patients over a long period of the pandemic, including the period of prevalence of the Omicron variant. It is also the first study, to the best of our knowledge, to present the 1-year mortality for elderly patients who were hospitalized during all periods of the pandemic.

The majority of the patients who succumbed within 1 year did not survive mainly due to cardiac events. It has been documented that after COVID-19, there is an increased risk of cardiovascular events such as arrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, acute heart failure and thromboembolic events. Mechanisms underlying the association between COVID-19 and the development of cardiac complications include the prolonged damage from direct viral invasion of myocardial cells and cell death, endothelial cell infection and subsequent endothelitis, the activation of the complement and complement-mediated coagulation and microangiopathy, transcriptional alteration of multiple cell types in cardiac tissue, ACE2 downregulation and renin-angiotensin-aldosterone system dysfunction, autonomic nervous system dysfunction, increased levels of pro-inflammatory cytokines, and activation of TGF- β signaling through the Smad pathway leading to fibrosis and scarring of cardiac tissue. In addition, a possible factor explaining cardiac complications is an abnormal, persistent hyperactivated immune response, either autoimmune or in the context of the persistence of the virus in immunologically privileged sites. The integration of their SARS-CoV-2 genome into the DNA of infected human cells, which can then express some transcripts containing viral and cellular human sequences, has also been reported as a putative mechanism for the sustained activation of the immune-inflammatory procoagulant cascade (19,20).

The second cause of death within 1 year was septic shock. No association was observed with the administration of immunosuppressive agents, such as corticosteroids and tocilizumab. It is likely that the emergence of new infections and septic shock after COVID-19 are due to the dysfunction of the immune system combined with the impaired immune response of the elderly following COVID-19 infection (21,22).

Of note, 3 patients succumbed due to a new SARS-CoV-2 infection, and 2 of these patients were hospitalized during the time period of the prevalence of the Omicron variant. Protection against reinfection by the original strain and the Alpha and Delta variants was found to decrease over time, but remained at 78.6% (49.8-93.6) at 40 weeks. Protection against reinfection by the Omicron BA.1 subvariant declined more rapidly and was estimated at 36.1% (24.4-51.3) at 40 weeks. However, protection against severe disease has been reported to remain high for all variants, with 90.2% (69.7-97.5) for the original strain and the Alpha and Delta variants and 88.9% (84.7-90.9) for the Omicron BA.1 subvariant at 40 weeks (23).

In the present study, age, IGS, LDH, ferritin, chest X-ray score and the absence of full vaccination, cough and fatigue were significantly and independently associated with the in-hospital mortality of this older population.

Table VII. Univariate analysis for continuous variables (outcome: In-hospital mortality).

| Variable | In-hospital mortality | Mean/ median | Standard deviation/range | 95% CI for the mean difference Lower | 95% CI for the mean difference Upper | P-value |
|--------------------------|-----------------------|-----------------|-----------------------------|--|--|--------------|
| Age (years) | No | 77.56 | 8.23 | -0.536 | -0.286 | 0.001 |
| | Yes | 80.99 | 8.54 | | | |
| Hb (g/dl) | No | 12.57 | 2.06 | 0.152 | 0.401 | 0.001 |
| | Yes | 11.96 | 2.49 | | | |
| Hct (%) | No | 37.84 | 5.86 | 0.159 | 0.409 | 0.001 |
| | Yes | 36.04 | 7.25 | | | |
| Albumin (g/dl) | No | 38.81 | 4.53 | -0.182 | 1.143 | 0.155 |
| | Yes | 36.20 | 7.02 | | | |
| CCI | No | 4 | 2-11 | -0.515 | -0.265 | 0.001 |
| | Yes | 5 | 2-12 | | | |
| WBC (K/ μ l) | No | 6.24 | 0.40-105.81 | -0.300 | -0.052 | 0.001 |
| | Yes | 7.32 | 1.23-43.82 | | | |
| Neu (K/ μ l) | No | 4.70 | 0.20-97.30 | -0.376 | -0.127 | 0.001 |
| | Yes | 6.10 | 0.10-33.09 | | | |
| Lym (K/ μ l) | No | 0.99 | 0.060-69.19 | -0.045 | 0.204 | 0.001 |
| | Yes | 0.77 | 0.180-31.21 | | | |
| IGs (10 ⁹ /l) | No | 0.04 | 0.01-21.58 | -0.204 | 0.045 | 0.001 |
| | Yes | 0.06 | 0.01-5.62 | | | |
| PLTs (K/ μ l) | No | 183 | 8-608 | -0.052 | 0.196 | 0.156 |
| | Yes | 184 | 11-467 | | | |
| D-dimers (μ g/ml) | No | 1.07 | 0.01-35.40 | -0.417 | -0.151 | 0.001 |
| | Yes | 1.74 | 0.01-20 | | | |
| FIB (mg/dl) | No | 521 | 223-1367 | -0.197 | 0.058 | 0.062 |
| | Yes | 562 | 256-1133 | | | |
| Creat (mg/dl) | No | 0.94 | 0.30-14.98 | -0.225 | 0.024 | 0.001 |
| | Yes | 1.11 | 0.29-971 | | | |
| AST (U/l) | No | 30 | 17-499 | -0.367 | -0.117 | 0.002 |
| | Yes | 36 | 8-1222 | | | |
| ALT (U/l) | No | 21 | 13-433 | -0.178 | 0.071 | 0.376 |
| | Yes | 21 | 13-772 | | | |
| ALP (U/l) | No | 69 | 26-377 | -0.316 | -0.066 | 0.010 |
| | Yes | 75 | 23-1238 | | | |
| GGT (U/l) | No | 27 | 22-746 | -0.273 | -0.022 | 0.001 |
| | Yes | 34 | 4-1060 | | | |
| LDH (U/l) | No | 295 | 152-1991 | -0.514 | -0.262 | 0.001 |
| | Yes | 349.5 | 101-3091 | | | |
| CRP (mg/l) | No | 46.08 | 0.40-320.76 | -0.615 | -0.363 | 0.001 |
| | Yes | 82.03 | 0.68-444.60 | | | |
| Ferr (ng/ml) | No | 383 | 13-7709 | -0.546 | -0.283 | 0.001 |
| | Yes | 657 | 25.20-33341 | | | |
| Chest X-ray score | No | 5 | 1-6 | -0.574 | -0.321 | 0.001 |
| | Yes | 6 | 1-6 | | | |

P-values in bold font indicate statistically significant differences (P<0.05). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CCI, Charlson comorbidity index; CRP, C-reactive protein; Ferr, ferritin; Creat, creatinine; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, hemoglobin; Hct, hematocrit; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; Neu, neutrophils; PLTs, platelets; WBC, white blood cell.

Table VIII. Multivariate analysis (outcome: In-hospital mortality).

| Variable | P-value | HR | 95% CI lower | 95% CI upper |
|------------------------------------|--------------|-------|--------------|--------------|
| Age per year | 0.001 | 1.039 | 1.016 | 1.061 |
| CCI | 0.232 | 1.080 | 0.952 | 1.226 |
| Hb (g/dl) | 0.737 | 1.052 | 0.782 | 1.415 |
| Hct (%) | 0.435 | 0.960 | 0.867 | 1.063 |
| WBC (K/ μ l) | 0.174 | 0.854 | 0.681 | 1.072 |
| Neu (K/ μ l) | 0.091 | 1.234 | 0.967 | 1.575 |
| Lym (K/ μ l) | 0.341 | 1.119 | 0.888 | 1.411 |
| IGs (10 ⁹ /l) | 0.043 | 0.727 | 0.533 | 0.990 |
| D-dimers (μ g/ml) | 0.834 | 0.995 | 0.950 | 1.042 |
| Creat (mg/dl) | 0.364 | 1.063 | 0.931 | 1.214 |
| AST (U/l) | 0.930 | 2.000 | 0.996 | 1.003 |
| ALP (U/l) | 0.419 | 1.002 | 0.998 | 1.005 |
| GGT (U/l) | 0.428 | 0.999 | 0.996 | 1.002 |
| LDH (U/l) | 0.003 | 1.002 | 1.001 | 1.003 |
| CRP (mg/l) | 0.097 | 1.002 | 1.000 | 1.005 |
| Ferr (ng/ml) | 0.003 | 1.000 | 1.000 | 1.000 |
| Chest X-ray score | 0.005 | 1.200 | 1.058 | 1.362 |
| Cardiovascular disease | 0.629 | 1.092 | 0.763 | 1.563 |
| Heart failure | 0.056 | 1.728 | 0.985 | 3.031 |
| Renal disease | 0.240 | 1.514 | 0.758 | 3.025 |
| Nursing home resident | 0.203 | 1.693 | 0.753 | 3.805 |
| Absence of full vaccination | 0.003 | 1.972 | 1.257 | 3.093 |
| Absence of fever | 0.507 | 1.131 | 0.786 | 1.630 |
| Absence of sore throat | 0.365 | 1.714 | 0.534 | 5.500 |
| Absence of smell/taste disruptions | 0.999 | 3.207 | 0.042 | 4.281 |
| Dyspnea | 0.324 | 1.199 | 0.836 | 1.720 |
| Absence of cough | 0.001 | 1.974 | 1.325 | 2.940 |
| Absence of fatigue | 0.029 | 1.874 | 1.067 | 3.292 |
| Altered mental status | 0.540 | 1.231 | 0.633 | 2.395 |
| Variant | | | | |
| Wuhan | Ref | Ref | Ref | Ref |
| Alpha | 0.223 | 0.706 | 0.403 | 1.237 |
| Delta | 0.362 | 1.352 | 0.707 | 2.588 |
| Omicron | 0.329 | 0.742 | 0.407 | 1.351 |

P-values in bold font indicate statistically significant differences ($P < 0.05$). HR, hazard ratio; CI, confidence interval; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; CCI, Charlson comorbidity index; Creat, creatinine; CRP, C-reactive protein; Ferr, ferritin; GGT, gamma glutamyl-transferase; Hb, hemoglobin; Hct, hematocrit; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; Neu, neutrophils; WBC, white blood cell; Ref, reference for calculation of the hazard ratio.

The majority of these findings are consistent with those of previous studies of the in-hospital mortality of elderly patients with COVID-19 (14,16,24-27). Among studies in the general population, age has been reported as an independent predictor of mortality within 1 year after COVID-19 (28,29). It has also been reported that in the general population, chronic obstructive pulmonary disease, chronic cardiovascular disease and active malignancy are also independent predictors of 1-year mortality following infection with SARS-CoV-2 (29). However, there are no data to date, as mentioned above, on mortality within 1 year for elderly patients, and the present study is the first (at

least to the best of our knowledge) to report that age, LDH, ferritin, ALT, CCI, chest X-ray score, the absence of cough and fatigue, and a history of dementia were statistically significantly and independently associated with mortality within 1 year.

Several factors accompanying aging, including the altered expression of the ACE2 receptor, the increased production of reactive oxygen species, the increased activity of senescent adipocytes, altered autophagy and mitophagy, immunosenescence, as well as vitamin D deficiency, may be involved in the pathophysiology of severe disease and poor outcomes in elderly patients with COVID-19 (30).

Table IX. Univariate analysis for categorical variables (outcome: 1-Year mortality).

| Variable | 1-year mortality | | P-value |
|--------------------------------------|------------------|-----|--------------|
| | No | Yes | |
| Omicron variant | | | |
| No | 411 | 299 | 0.025 |
| Yes | 211 | 203 | |
| Variant | | | |
| Wuhan | 60 | 44 | 0.001 |
| Alpha | 245 | 140 | |
| Delta | 106 | 115 | |
| Omicron | 211 | 203 | |
| Sex | | | |
| Female | 299 | 221 | 0.186 |
| Male | 323 | 281 | |
| Lung disease | | | |
| No | 532 | 437 | 0.487 |
| Yes | 90 | 65 | |
| Obesity (BMI >30 kg/m ²) | | | |
| No | 598 | 490 | 0.177 |
| Yes | 24 | 12 | |
| Diabetes mellitus | | | |
| No | 454 | 365 | 0.946 |
| Yes | 168 | 137 | |
| Arterial hypertension | | | |
| No | 295 | 271 | 0.031 |
| Yes | 327 | 231 | |
| Cardiovascular disease | | | |
| No | 407 | 284 | 0.003 |
| Yes | 215 | 218 | |
| Heart failure | | | |
| No | 580 | 443 | 0.004 |
| Yes | 42 | 59 | |
| Renal disease | | | |
| No | 583 | 436 | 0.001 |
| Yes | 39 | 66 | |
| Liver disease | | | |
| No | 612 | 491 | 0.512 |
| Yes | 10 | 11 | |
| Autoimmune disease | | | |
| No | 581 | 474 | 0.533 |
| Yes | 41 | 28 | |
| Hematological malignancy | | | |
| No | 595 | 465 | 0.032 |
| Yes | 27 | 37 | |
| Solid organ malignancy | | | |
| No | 592 | 450 | 0.001 |
| Yes | 30 | 52 | |
| Solid organ transplantation | | | |
| No | 617 | 495 | 0.390 |
| Yes | 5 | 7 | |

Table IX. Continued.

| Variable | 1-year mortality | | P-value |
|----------------------------|------------------|-----|--------------|
| | No | Yes | |
| Parkinson's disease | | | |
| No | 611 | 478 | 0.005 |
| Yes | 11 | 24 | |
| Dementia | | | |
| No | 584 | 436 | 0.001 |
| Yes | 38 | 66 | |
| Nursing home residency | | | |
| No | 610 | 474 | 0.001 |
| Yes | 12 | 28 | |
| Fully vaccinated | | | |
| No | 469 | 374 | 0.730 |
| Yes | 153 | 128 | |
| Vaccination doses | | | |
| 0 | 404 | 300 | 0.061 |
| 1 | 34 | 32 | |
| 2 | 75 | 87 | |
| 3 | 104 | 75 | |
| 4 | 5 | 8 | |
| Fever | | | |
| No | 164 | 205 | 0.001 |
| Yes | 458 | 297 | |
| Sore throat | | | |
| No | 591 | 495 | 0.001 |
| Yes | 31 | 7 | |
| Disruptions in smell/taste | | | |
| No | 609 | 501 | 0.005 |
| Yes | 13 | 1 | |
| Dyspnea | | | |
| No | 314 | 191 | 0.001 |
| Yes | 308 | 311 | |
| Cough | | | |
| No | 405 | 407 | 0.001 |
| Yes | 217 | 95 | |
| Fatigue | | | |
| No | 532 | 458 | 0.004 |
| Yes | 90 | 44 | |
| Gastrointestinal symptoms | | | |
| No | 562 | 462 | 0.344 |
| Yes | 60 | 40 | |
| Altered mental status | | | |
| No | 601 | 460 | 0.001 |
| Yes | 21 | 42 | |

P-values in bold font indicate statistically significant differences (P<0.05). BMI, body mass index.

Table X. Univariate analysis for continuous variables (outcome: 1-year mortality).

| Variable | 1-Year mortality | Mean/median | Standard deviation/range | 95% CI for the mean difference Lower | 95% CI for the mean difference Upper | P-value |
|--------------------------|------------------|-------------|--------------------------|---|---|--------------|
| Age (years) | No | 76.68 | 7.82 | -0.674 | -0.435 | 0.002 |
| | Yes | 81.22 | 8.62 | | | |
| Hb (g/dl) | No | 12.78 | 2.01 | 0.303 | 0.541 | 0.001 |
| | Yes | 11.85 | 2.39 | | | |
| Hct (%) | No | 38.37 | 5.67 | 0.283 | 0.521 | 0.001 |
| | Yes | 35.84 | 6.98 | | | |
| Albumin (g/dl) | No | 39.58 | 4.52 | 0.067 | 1.327 | 0.721 |
| | Yes | 35.91 | 6.04 | | | |
| CCI | No | 4 | 2-7 | -0.44 | -0.503 | 0.001 |
| | Yes | 6 | 3-8 | | | |
| WBC (K/ μ l) | No | 6.01 | 2.36-11.29 | -0.383 | -0.146 | 0.001 |
| | Yes | 7.85 | 3.32-24.52 | | | |
| Neu (K/ μ l) | No | 4.70 | 1.50-9.70 | -0.450 | -0.213 | 0.001 |
| | Yes | 6.10 | 2.1-21.1 | | | |
| Lym (K/ μ l) | No | 1.12 | 0.58-2.61 | -0.019 | 0.217 | 0.001 |
| | Yes | 1.03 | 0.33-5.17 | | | |
| IGs (10 ⁹ /l) | No | 0.04 | 0.02-0.13 | -0.091 | -0.055 | 0.001 |
| | Yes | 0.06 | 0.01-5.620 | | | |
| PLTs (K/ μ l) | No | 163 | 112-416 | -0.106 | 0.130 | 0.668 |
| | Yes | 160 | 65-443 | | | |
| D-dimers (μ g/ml) | No | 1.05 | 0.29-6.20 | -0.434 | -0.182 | 0.001 |
| | Yes | 1.92 | 0.48-6.88 | | | |
| FIB (mg/dl) | No | 538 | 43-860 | -0.103 | 0.138 | 0.783 |
| | Yes | 493 | 308-893 | | | |
| Creat (mg/dl) | No | 0.96 | 0.58-8.55 | -0.195 | 0.041 | 0.001 |
| | Yes | 1.20 | 0.56-6.57 | | | |
| AST (U/l) | No | 31 | 15-127 | -0.273 | -0.037 | 0.517 |
| | Yes | 30 | 14-297 | | | |
| ALT (U/l) | No | 23 | 7-65 | -0.095 | 0.140 | 0.001 |
| | Yes | 16 | 6-36 | | | |
| ALP (U/l) | No | 60 | 40-102 | -0.398 | -0.159 | 0.001 |
| | Yes | 71 | 25-279 | | | |
| GGT (U/l) | No | 35 | 12-204 | -0.313 | -0.075 | 0.003 |
| | Yes | 30 | 12-271 | | | |
| LDH (U/l) | No | 288 | 212-566 | -0.376 | -0.138 | 0.001 |
| | Yes | 307 | 151-966 | | | |
| CRP (mg/l) | No | 61.83 | 1.15-206 | -0.536 | -0.297 | 0.001 |
| | Yes | 94 | 0.93-414 | | | |
| Ferr (ng/ml) | No | 499 | 33-7510 | -0.461 | -0.214 | 0.001 |
| | Yes | 635 | 54.7-33341 | | | |
| Chest X-ray score | No | 4 | 1-6 | -0.550 | -0.310 | 0.001 |
| | Yes | 6 | 1-6 | | | |

P-values in bold font indicate statistically significant differences ($P < 0.05$). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson comorbidity index; CRP, C-reactive protein; Ferr, ferritin; Creat, creatinine; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, hemoglobin; Hct, hematocrit; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; Neu, neutrophils; PLTs, platelets; WBC, white blood cell.

Table XI. Multivariate analysis (outcome: I-year mortality)

| Variable | P-value | HR | 95% CI lower | 95% CI upper |
|---------------------------------------|--------------|-------|--------------|--------------|
| Age per year | 0.001 | 1.043 | 1.020 | 1.066 |
| Variant | | | | |
| Wuhan | Ref | Ref | Ref | Ref |
| Alpha | 0.318 | 0.754 | 0.434 | 1.312 |
| Delta | 0.832 | 1.070 | 0.574 | 1.995 |
| Omicron | 0.832 | 0.941 | 0.538 | 1.647 |
| Absence of fever | 0.169 | 1.282 | 0.900 | 1.828 |
| Absence of sore throat | 0.117 | 2.324 | 0.809 | 6.671 |
| Absence of disruptions in smell/taste | 0.187 | 4.436 | 0.486 | 40.48 |
| Dyspnea | 0.448 | 1.143 | 0.810 | 1.613 |
| Absence of cough | 0.012 | 1.605 | 1.108 | 2.327 |
| Absence of fatigue | 0.014 | 1.917 | 1.138 | 3.228 |
| Altered mental status | 0.343 | 1.391 | 0.703 | 2.751 |
| CCI | 0.002 | 1.264 | 1.086 | 1.471 |
| Arterial hypertension | 0.096 | 0.763 | 0.554 | 1.049 |
| Cardiovascular disease | 0.589 | 0.908 | 0.640 | 1.288 |
| Heart failure | 0.409 | 1.272 | 0.719 | 2.251 |
| Renal disease | 0.897 | 1.046 | 0.533 | 2.052 |
| Solid organ malignancy | 0.914 | 1.044 | 0.480 | 2.269 |
| Hematological malignancy | 0.443 | 1.407 | 0.588 | 3.367 |
| Parkinson's disease | 0.453 | 1.390 | 0.588 | 3.284 |
| Dementia | 0.008 | 2.065 | 1.213 | 3.513 |
| Nursing home residency | 0.235 | 1.714 | 0.704 | 4.173 |
| Hb (normal range 13-17 g/dl) | 0.696 | 0.943 | 0.703 | 1.265 |
| Hct (normal range 38-48%) | 0.793 | 0.986 | 0.891 | 1.092 |
| WBC (normal range 4.5-11 K/ μ l) | 0.261 | 0.879 | 0.702 | 1.101 |
| Neu (normal range 1.5-6.6 K/ μ l) | 0.142 | 1.201 | 0.940 | 1.535 |
| Lym (normal range 1.2-3.4 K/ μ l) | 0.750 | 1.038 | 0.826 | 1.304 |
| IGs (1 normal range 0-0.4 10^9 /l) | 0.354 | 1.778 | 0.526 | 6.011 |
| D-dimers (normal <0.5 μ g/ml) | 0.954 | 0.999 | 0.951 | 1.049 |
| Creat (normal range 0.7-1.2 mg/dl) | 0.122 | 1.111 | 0.972 | 1.269 |
| ALT (normal range <41 U/l) | 0.021 | 0.995 | 0.990 | 0.999 |
| ALP (normal range 40-129 U/l) | 0.166 | 1.003 | 0.999 | 1.008 |
| GGT (normal range 8-61 U/l) | 0.951 | 1.000 | 0.997 | 1.003 |
| LDH (normal range 135-225 U/l) | 0.004 | 1.002 | 1.001 | 1.003 |
| CRP (normal range 0-5 mg/l) | 0.147 | 1.002 | 0.999 | 1.005 |
| Ferr (normal range 30-400 ng/ml) | 0.029 | 1.000 | 1.000 | 1.000 |
| Chest X-ray score | 0.001 | 1.209 | 1.079 | 1.355 |

P-values in bold font indicate statistically significant differences ($P < 0.05$). HR, hazard ratio; CI, confidence interval; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CI, confidence interval; CCI, Charlson comorbidity index; Creat, creatinine; CRP, C-reactive protein; Ferr, ferritin; GGT, gamma glutamyl-transferase; Hb, hemoglobin; Hct, hematocrit; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; Neu, neutrophils; WBC, white blood cell; Ref, reference for calculation of the hazard ratio.

Increased IG counts detected in peripheral blood demonstrate an enhanced bone marrow activity and have been linked to poor outcomes in patients with COVID-19 (31). Increased LDH levels in the circulation could reflect either the direct SARS-CoV-2 infection of cells or marked tissue

damage secondary to an excessive systemic inflammatory response (32). Ferritin is known as an acute phase reactant, and its levels are increased in acute and chronic inflammation; in COVID-19, ferritin has been linked to disease severity (33). Elevated ALT levels have also been associated

Table XII. Causes of 1-year mortality.

| Cause of 1-year mortality | Frequency (no. of patients) | Percentage |
|-----------------------------|--------------------------------|------------|
| Unknown | 13 | 10.2 |
| Cardiac events | 41 | 32.3 |
| Septic shock | 36 | 28.3 |
| Pneumonia-ARDS | 10 | 7.9 |
| End-stage cancer | 10 | 7.9 |
| Ischemic stroke | 5 | 3.9 |
| Pulmonary embolism | 4 | 3.1 |
| Mesenteric ischemia | 1 | 0.8 |
| Gastrointestinal hemorrhage | 1 | 0.8 |
| Hepatic encephalopathy | 1 | 0.8 |
| Acute renal failure | 1 | 0.8 |
| COPD exacerbation | 1 | 0.8 |
| New SARS-CoV-2 infection | 3 | 2.4 |

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2.

with poor outcomes of patients with COVID-19, reflecting liver injury (34-36).

It has been reported that initial chest X-ray scores of patients with COVID-19 are linked to clinical outcomes, such as mortality, the length of hospitalization and the duration of invasive ventilation (37). Since the beginning of the pandemic, comorbidities have been known to affect the outcomes of patients with COVID-19. In the three stages of COVID-19, from the initial viral replication phase to the inflammatory tissue injury and long-term consequences, specific comorbidities can either exacerbate these pathological mechanisms that determine health outcomes or lower the patient's tolerance for organ injury (38). One established risk factor for the mortality of patients with COVID-19 is a lack of vaccination (39). Furthermore, vaccination against COVID-19 has been proven to be highly beneficial in reducing hospitalization and mortality among the elderly (40,41).

In addition, cough has been shown to be associated with better outcomes in patients with COVID-19 (42). As regards the symptom of fatigue, it has been linked to poor outcomes of patients with COVID-19 (43); however, in the present study, it was associated with in-hospital and with 1-year survival.

Dementia is also a well-established risk factor for the poor outcomes of elderly patients hospitalized due to COVID-19 (43,44) and according to the present study, it was an independent risk factor for 1-year mortality.

The present study has certain limitations which should be mentioned. The present study was a single-center study without a control group. In addition, medications that patients were receiving for underlying diseases were not included in the analysis. Finally, SARS-CoV-2 variants were not identified individually for patients. Variant assignment was based

on the prevalent variant at the time the patient was diagnosed with the infection, and distinction was made only based on whether patients were diagnosed before or after the appearance of the Omicron variant.

In conclusion, both the in-hospital and 1-year mortality of elderly patients hospitalized due to COVID-19 pneumonia is high. As regards the causes of death, the majority of patients succumbed due to cardiac events. Age, IGs, LDH, ferritin, chest X-ray score, as well as the absence of full vaccination, cough and fatigue were significantly and independently associated with in-hospital mortality, while age, LDH, ferritin, ALT, CCI, chest X-ray score, the absence of cough and fatigue, and a history of dementia were significantly and independently associated with 1-year mortality.

Acknowledgements

Not applicable.

Funding

No funding was received.

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

NVS and VEG conceptualized the study. VEG, AT, DB, DAS, SM, AG, GK, PMV, IrE, SS, MT, IoE, OK, CVP, AA, IT, NT, PP, PS and NVS made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. PS 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 version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in line with the Declaration of Helsinki and gained approval by the regional Institutional Review Board (protocol number protocol no. 7950/08.06.2023). Written informed was obtained from all the included patients.

Patient consent for publication

Not applicable.

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.

References

- World Health Organization: Emergencies. Coronavirus disease (COVID-19) pandemic. <https://www.who.int/europe/emergencies/situations/covid-19>. Accessed July 1, 2023.
- World Health Organization (WHO): WHO Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/>. Accessed July 1, 2023.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, *et al*: Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382: 1708-1720, 2020.
- Georgakopoulou VE, Gkoufa A, Damaskos C, Papalexis P, Pierrakou A, Makrodimetri S, Sypsa G, Apostolou A, Asimakopoulou S, Chlapoutakis S, *et al*: COVID-19-associated acute appendicitis in adults. A report of five cases and a review of the literature. *Exp Ther Med* 24: 482, 2022.
- Georgakopoulou VE, Gkoufa A, Garmis N, Makrodimetri S, Papageorgiou CV, Barlampa D, Garmis A, Chiapoutakis S, Sklapani P, Trakas N and Damaskos C: COVID-19 and acute pancreatitis: A systematic review of case reports and case series. *Ann Saudi Med* 42: 276-287, 2022.
- Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A and Hassanazadeh G: COVID-19 and multiorgan failure: A narrative review on potential mechanisms. *J Mol Histol* 51: 613-628, 2020.
- Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, *et al*: Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect* 81: e16-e25, 2020.
- Mueller AL, McNamara MS and Sinclair DA: Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)* 12: 9959-9981, 2020.
- Lee C and Frishman WH: Implications of frailty in COVID-19. *Cardiol Rev* 29: 285-288, 2021.
- Dadras O, SeyedAlinaghi S, Karimi A, Shamsabadi A, Qaderi K, Ramezani M, Mirghaderi SP, Mahdiabadi S, Vahedi F, Saeidi S, *et al*: COVID-19 mortality and its predictors in the elderly: A systematic review. *Health Sci Rep* 5: e657, 2022.
- Pericean RM, Oancea C, Reddyreddy AR, Rosca O, Bratosin F, Bloanca V, Citu C, Alambaram S, Vasamsetti NG and Dumitru C: Outcomes of elderly patients hospitalized with the SARS-CoV-2 omicron B.1.1.529 variant: A systematic review. *Int J Environ Res Public Health* 20: 2150, 2023.
- Setiawati R, Widyaningroem A, Handarini T, Hayati F, Basja AT, Putri ARDS, Jaya MG, Andriani J, Tanadi MR and Kamal IH: Modified chest X-ray scoring system in evaluating severity of COVID-19 patient in Dr. Soetomo General Hospital Surabaya, Indonesia. *Int J Gen Med* 14: 2407-2412, 2021.
- World Health Organization: Therapeutics and COVID-19: Living guideline. <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1>. Accessed January 13, 2023.
- Capdevila-Reniu A, Pellice M, Prieto-González S, Ventosa H, Ladino A, Naval J, Rodríguez-Núñez O, César Milisenda J, Moreno-Lozano PJ, Soriano A, *et al*: Clinical characteristics and outcome of patients aged over 80 years with covid-19. *Medicine (Baltimore)* 100: e24750, 2021.
- Zerah L, Baudouin É, Pépin M, Mary M, Krypciak S, Bianco C, Roux S, Gross A, Toméo C, Lemarié N, *et al*: Clinical characteristics and outcomes of 821 older patients with SARS-CoV-2 infection admitted to acute care geriatric wards. *J Gerontol A Biol Sci Med Sci* 76: e4-e12, 2021.
- Rodríguez-Sánchez I, Redondo-Martín M, Furones-Fernández L, Méndez-Hinojosa M, Chen-Chim Á, Saavedra-Palacios R and Gil-Gregorio P: Functional, clinical, and sociodemographic variables associated with risk of in-hospital mortality by COVID-19 in people over 80 years old. *J Nutr Health Aging* 25: 964-970, 2021.
- Mostaza JM, García-Iglesias F, González-Alegre T, Blanco F, Varas M, Hernández-Blanco C, Hontañón V, Jaras-Hernández MJ, Martínez-Prieto M, Menéndez-Saldaña A, *et al*: Clinical course and prognostic factors of COVID-19 infection in an elderly hospitalized population. *Arch Gerontol Geriatr*: July 27, 2020 (Epub ahead of print).
- Zhu X, Yuan W, Shao J, Huang K, Wang Q, Yao S, Lu W, Liu L and Fu T: Risk factors for mortality in patients over 70 years old with COVID-19 in Wuhan at the early break: Retrospective case series. *BMC Infect Dis* 21: 821, 2021.
- Xie Y, Xu E, Bowe B and Al-Aly Z: Long-term cardiovascular outcomes of COVID-19. *Nat Med* 28: 583-590, 2022.
- Abbasi J: The COVID heart-one year after SARS-CoV-2 infection, patients have an array of increased cardiovascular risks. *JAMA* 327: 1113-1114, 2022.
- Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsounou P, *et al*: Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 27: 992-1000.e3, 2020.
- Davitt E, Davitt C, Mazer MB, Areti SS, Hotchkiss RS and Remy KE: COVID-19 disease and immune dysregulation. *Best Pract Res Clin Haematol* 35: 101401, 2022.
- COVID-19 Forecasting Team: Past SARS-CoV-2 infection protection against re-infection: A systematic review and meta-analysis. *Lancet* 401: 833-842, 2023.
- Covino M, De Matteis G, Santoro M, Sabia L, Simeoni B, Candelli M, Ojetti V and Franceschi F: Clinical characteristics and prognostic factors in COVID-19 patients aged ≥80 years. *Geriatr Gerontol Int* 20: 704-708, 2020.
- Ulugerger Avci G, Bektan Kanat B, Suzan V, Can G, Korkmazer B, Karaali R, Tabak F, Borekci S, Aygun G, Yavuzer H and Doventas A: Clinical outcomes of geriatric patients with COVID-19: Review of one-year data. *Aging Clin Exp Res* 34: 465-474, 2022.
- Asaduzzaman M, Nazmul Alam ZHM, Zabeed Jillul Bari M, Jahangir Alam MM, Ranjan Chakraborty S and Ferdousi T: Clinical characteristics and predictors of mortality in elderly patients hospitalized with COVID-19 in Bangladesh: A multicenter, retrospective study. *Interdiscip Perspect Infect Dis* 2022: 5904332, 2022.
- Ramos-Rincon JM, Buonaiuto V, Ricci M, Martín-Carmona J, Paredes-Ruiz D, Calderón-Moreno M, Rubio-Rivas M, Beato-Pérez JL, Arnalich-Fernández F, Monge-Monge D, *et al*: Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. *J Gerontol A Biol Sci Med Sci* 76: e28-e37, 2021.
- Núñez-Cortés R, López-Bueno R, Torres-Castro R, Soto-Carmona C, Ortega-Palavecinos M, Pérez-Alenda S, Solís-Navarro L, Díaz-Cambronero Ó, Martínez-Arnau FM and Calatayud J: Risk factors for one-year mortality in hospitalized adults with severe COVID-19. *Aging Dis* 14: 14-20, 2023.
- Novelli L, Raimondi F, Carioli G, Carobbio A, Pappacena S, Biza R, Trapasso R, Anelli M, Amoruso M, Allegri C, *et al*: One-year mortality in COVID-19 is associated with patients' comorbidities rather than pneumonia severity. *Respir Med* 183: 100976, 2023.
- Meftahi GH, Jangravi Z, Sahraei H and Bahari Z: The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: The contribution of 'inflamm-aging'. *Inflamm Res* 69: 825-839, 2020.
- Georgakopoulou VE, Makrodimetri S, Triantafyllou M, Samara S, Voutsinas PM, Anastasopoulou A, Papageorgiou CV, Spandidos DA, Gkoufa A, Papalexis P, *et al*: Immature granulocytes: Innovative biomarker for SARS-CoV-2 infection. *Mol Med Rep* 26: 217, 2022.
- Georgakopoulou VE, Vlachogiannis NI, Basoulis D, Eliadi I, Georgiopoulos G, Karamanakis G, Makrodimetri S, Samara S, Triantafyllou M, Voutsinas PM, *et al*: A simple prognostic score for critical COVID-19 derived from patients without comorbidities performs well in unselected patients. *J Clin Med* 11: 1810, 2022.
- Kappert K, Jahić A and Tauber R: Assessment of serum ferritin as a biomarker in COVID-19: Bystander or participant? Insights by comparison with other infectious and non-infectious diseases. *Biomarkers* 25: 616-625, 2020.
- Bali T, Georgakopoulou VE, Kamiliou A, Vergos I, Adamantou M, Vlachos S, Ermidis G, Sipsas NV, Samarkos M and Cholongitas E: Abnormal liver function tests and coronavirus disease 2019: A close relationship. *J Viral Hepat* 30: 79-80, 2023.
- Georgakopoulou VE, Bali T, Adamantou M, Asimakopoulou S, Makrodimetri S, Samara S, Triantafyllou M, Voutsinas PM, Eliadi I, Karamanakis G, *et al*: Acute hepatitis and liver injury in hospitalized patients with COVID-19 infection. *Exp Ther Med* 24: 691, 2022.
- Cholongitas E, Bali T, Georgakopoulou VE, Giannakodimos A, Gyftopoulos A, Georgilaki V, Gerogiannis D, Basoulis D, Eliadi I, Karamanakis G, *et al*: Prevalence of abnormal liver biochemistry and its impact on COVID-19 patients' outcomes: A single-center Greek study. *Ann Gastroenterol* 35: 290-296, 2022.
- Shen B, Hou W, Jiang Z, Li H, Singer AJ, Hoshmand-Kochi M, Abbasi A, Glass S, Thode HC, Levsky J, *et al*: Longitudinal chest X-ray scores and their relations with clinical variables and outcomes in COVID-19 patients. *Diagnostics (Basel)* 13: 1107, 2023.

38. Russell CD, Lone NI and Baillie JK: Comorbidities, multimorbidity and COVID-19. *Nat Med* 29: 334-343, 2023.
39. Griffin JB, Haddix M, Danza P, Fisher R, Koo TH, Traub E, Gounder P, Jarashow C and Balter S: SARS-CoV-2 infections and hospitalizations among persons aged ≥ 16 years, by vaccination status-Los Angeles County, California, May 1-July 25, 2021. *MMWR Morb Mortal Wkly Rep* 70: 1170-1176, 2021.
40. Ellis RJ, Moffatt CR, Aaron LT, Beaverson G, Chaw K, Curtis C, Freeman-Lamb R, Judd D, Khatri K, Li YS, *et al*: Factors associated with hospitalisations and deaths of residential aged care residents with COVID-19 during the Omicron (BA.1) wave in Queensland. *Med J Aust* 218: 174-179, 2023.
41. Gomes D, Beyerlein A, Katz K, Hoelscher G, Nennstiel U, Liebl B, Überla K and von Kries R: Is the BNT162b2 COVID-19 vaccine effective in elderly populations? Results from population data from Bavaria, Germany. *PLoS One* 16: e0259370, 2021.
42. Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, Macho O, López GF, Robles MT, Dapena MD, Martínez S, Milà Ràfols N, Monaco EE, *et al*: Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. *PLoS One* 15: e0239571, 2020.
43. Verykokou G, Apollonatu V, Papaioannou AI, Vogiatzoglou A, Roukas K, Kyriakopoulos C, Chronis C, Aggelopoulou C, Gundogdu D, Schoini P, *et al*: Nursing home elderly patients hospitalized for COVID-19: Characteristics and predictors of outcomes. *Geriatr Gerontol Int* 23: 62-64, 2023.
44. Georgakopoulou VE, Gkoufa A, Tsakanikas A, Makrodimitri S, Karamanakis G, Basoulis D, Voutsinas PM, Eliadi I, Bougea A, Spandidos DA, *et al*: Predictors of COVID-19-associated mortality among hospitalized elderly patients with dementia. *Exp Ther Med* 26: 395, 2023.



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