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

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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.

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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

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 ± SD	78.51±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.

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

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 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).

	In-hospital mortality		
Variable	No	Yes	P-value
Omicron variant			
No	468	242	0.513
Yes	281	133	
Variant			
Wuhan	66	38	**0.014**
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/μl)	No	6.24	0.40-105.81	-0.300	-0.052	**0.001**
	Yes	7.32	1.23-43.82			
Neu (K/μl)	No	4.70	0.20-97.30	-0.376	-0.127	**0.001**
	Yes	6.10	0.10-33.09			
Lym (K/μl)	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/μl)	No	183	8-608	-0.052	0.196	0.156
	Yes	184	11-467			
D-dimers (μg/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/μl)	0.174	0.854	0.681	1.072
Neu (K/μl)	0.091	1.234	0.967	1.575
Lym (K/μl)	0.341	1.119	0.888	1.411
IGs (10^9/l)	**0.043**	0.727	0.533	0.990
D-dimers (μg/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: No	1-year mortality: Yes	P-value
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	
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/μl)	No	6.01	2.36-11.29	-0.383	-0.146	**0.001**
	Yes	7.85	3.32-24.52			
Neu (K/μl)	No	4.70	1.50-9.70	-0.450	-0.213	**0.001**
	Yes	6.10	2.1-21.1			
Lym (K/μl)	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/μl)	No	163	112-416	-0.106	0.130	0.668
	Yes	160	65-443			
D-dimers (μg/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
Dypsnea	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/μl)	0.261	0.879	0.702	1.101
Neu (normal range 1.5-6.6 K/μl)	0.142	1.201	0.940	1.535
Lym (normal range 1.2-3.4 K/μl)	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 μg/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.

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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

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.

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