Journal of Microbiology, Immunology and Infection 57 (2024) 257—268

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Clinical characteristics and treatment outcomes among the hospitalized elderly patients with COVID-19 during the late pandemic phase in central Taiwan

Chieh-Lung Chen [a,1], Chi-Kang Teng [a,1], Wei-Cheng Chen [a,b,c,d], Shinn-Jye Liang [a], Chih-Yen Tu [a,b], Hong-Mo Shih [b,e,f], Wan-Ju Cheng [f,g,h], Yu-Chao Lin [a,b,*], Po-Ren Hsueh [i,j,k,**]

[a] *Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[b] *School of Medicine, China Medical University, Taichung, Taiwan*
[c] *Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan*
[d] *Department of Education, China Medical University Hospital, Taichung, Taiwan*
[e] *Department of Emergency Medicine, China Medical University Hospital, Taichung, Taiwan*
[f] *Department of Public Health, China Medical University, Taichung, Taiwan*
[g] *Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan*
[h] *National Center for Geriatrics and Welfare Research, National Health Research Institutes, Miaoli, Taiwan*
[i] *Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[j] *PhD Program for Aging, School of Medicine, China Medical University, Taichung, Taiwan*
[k] *Department of Laboratory Medicine, School of Medicine, China Medical University, Taichung, Taiwan*

Received 4 January 2024; received in revised form 22 January 2024; accepted 23 January 2024
Available online 26 January 2024

KEYWORDS
Aged;
COVID-19;

Abstract *Background:* There is a lack of information regarding outcomes of elderly patients hospitalized with COVID-19 following the widespread use of COVID-19 vaccines and antiviral agents.

* Corresponding author. Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University Hospital, China Medical University, No. 2, Yude Road, North District, Taichung 40447, Taiwan.
** Corresponding author. Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, China Medical University, No. 2, Yude Road, North District, Taichung 40447, Taiwan.
E-mail addresses: cmchlyc@yahoo.com.tw (Y.-C. Lin), hsporen@gmail.com (P.-R. Hsueh).
[1] Chieh-Lung Chen and Chi-Kang Teng contributed equally to this article.

https://doi.org/10.1016/j.jmii.2024.01.006

Hospitalization;
Elderly;
Oldest-old;
Prognosis

Methods: A retrospective study was conducted between January and August 2022, enrolling patients aged 65 years or older. Patients were categorized into two groups: 'old' (65—79 years) and 'oldest-old' (80 years or more). Multivariate regression was employed to identify independent prognostic factors for in-hospital mortality.
Results: A total of 797 patients were enrolled, including 428 old and 369 oldest-old patients. In each subgroup, 66.6 % and 59.6 % of patients received at least one dose of the COVID-19 vaccine, respectively. Approximately 40 % of the patients received oral antiviral agents either before or upon hospital admission. A greater percentage of the oldest-old patients received remdesivir (53.4 % versus 39.7 %, $p < 0.001$), dexamethasone (49.3 % versus 36.7 %, $p < 0.001$), and tocilizumab (10.0 % versus 6.8 %, $p < 0.001$) than old patients. The mortality rate was comparable between the two age subgroups (14 % versus 15.2 %). Independent predictors of in-hospital mortality included disease severity and comorbidities such as end-stage renal disease (ESRD), cirrhosis, solid tumours, and haematologic malignancies. Ageing was not correlated with increased in-hospital mortality across all comorbidity subgroups.
Conclusions: In the later stages of the pandemic, with widespread vaccination and advancements in COVID-19 treatments, outcomes for hospitalized elderly and oldest-old patients with COVID-19 have improved. The influence of age on in-hospital mortality has diminished, while comorbidities such as ESRD, cirrhosis, solid tumours, and hematologic malignancies have been associated with mortality.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 767 million people, resulting in 6.9 million deaths worldwide as of June 2023.[1] In the context of the pandemic, the presence of comorbidities and aging have been reported as independent risk factors for disease severity and hospitalization,[2,3] with significant negative effects on prognosis.[4,5] Age is strongly linked to mortality, showing a significant increase after the age of 65, and the mortality rate for individuals over 80 years of age reaches nearly 60 %.[6] There have been reports on the treatment and outcomes of COVID-19 patients older than 80 years.[7,8] However, these reports mainly reflect the epidemiological features of the early pandemic phase.

With the advancement of COVID-19 management, including vaccination, the use of antiviral agents, corticosteroids, anti-inflammatory medication, and supportive care,[9—14] the prognosis of hospitalized patients has evolved. During the early stages of the 2020 pandemic, the Taiwan Central Epidemic Command Center was established with the aim of coordinating available resources, formulating effective policies, and implementing stringent interventions, such as early screening, efficient isolation/quarantine protocols, and widespread mask usage.[15] This approach effectively delayed virus transmission and further facilitated broader vaccination efforts.

Previous studies have highlighted the negative impact of ageing on medical decisions for more aggressive care, particularly in intensive care and cancer treatment, especially among the oldest-old patients.[16—18] During the late phase of the pandemic, limited studies have explored the risk factors associated with mortality among old and oldest-old COVID-19 patients during hospitalization. Therefore, this study aimed to address this research gap.

Materials and methods

Study design and patient selection

This single-centre observational study was conducted at China Medical University Hospital (CMUH) in central Taiwan from January to August 2022. CMUH serves as a tertiary referral hospital in the region and is a 2000-bed facility with a dedicated 50-bed adult medical intensive care unit (ICU). The prevalent viral strain during the study period was primarily the Omicron variant.[15]

Data were collected for all patients aged 65 years or older admitted with confirmed COVID-19, as determined by a positive result on real-time reverse-transcription polymerase chain reaction testing of a nasopharyngeal sample. Patients not admitted to the hospital or lacking sufficient data for analysis were excluded. This study received approval from the Institutional Review Board (IRB) of CMUH (CMUH111-REC1-194). It was conducted in accordance with the Declaration of Helsinki and followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. As the study design was retrospective and did not involve the collection of personally identifiable information, the requirement for informed consent was waived by the IRB of CMUH.

Data collection and definitions

Electronic medical records were reviewed retrospectively using the hospital information system. The recorded variables included patient characteristics, comorbidities, vaccination status, presenting symptoms, disease severity, results of laboratory tests, treatments, and outcomes. An 'old' patient is defined as an individual between 65 and 79 years of age, and an 'oldest-old' patient refers to an

individual who is 80 years or older.[19] Dyspnoea was recorded as an independent symptom, and other respiratory symptoms included cough, nasal obstruction, or sore throat. COVID-19 disease severity was defined according to the World Health Organization treatment guidelines.[20] Lymphopenia was defined as an absolute count of fewer than 1100 cells/μL.[21] The initial laboratory data were documented either on the date of COVID-19 symptom onset or during the visit to the Emergency Department (if the symptom onset date was not recorded). In cases where no data were accessible, laboratory results within a 3-day period were recorded. If there was still no data available, it was marked as missing. A thorough documentation of all COVID-19 treatments was performed, covering oral antiviral agents, remdesivir, and anti-inflammatory therapy. For patients undergoing a sequential treatment regimen involving oral antiviral agents followed by remdesivir, each treatment was documented separately. Regarding systemic steroid usage, our emphasis was on the administration of dexamethasone.

Outcomes

The outcome measures included all-cause in-hospital mortality and factors predicting in-hospital mortality.

Statistical analyses

All statistical analyses were performed using R software (version 4.0, http://cran.r-project.org/). Continuous data are presented as the medians and interquartile ranges (IQRs), and differences between groups were determined using the Mann—Whitney *U* test. Categorical variables are presented as percentages and counts, and they were analysed using the chi-square test. A multivariate regression model was employed to evaluate significant variables predicting in-hospital mortality. The strength of the association was expressed as the odds ratio (OR) along with its corresponding 95 % confidence interval (CI). Throughout this study, all tests were two-sided, with significance denoted by p-value <0.05. Missing laboratory data were imputed by using the R package mice with classification and regression tree methods.

Results

Patient characteristics

During the study period, a total of 1399 patients were admitted to the hospital with confirmed COVID-19, and 797 patients were older than 65 years. Among the 797 elderly patients, 428 were aged 65—79 years (old), and 369 were aged 80 years or more (oldest-old) (Fig. 1). The median age of the patients was 71.6 years (IQR 68.0—75.5 years) in the old subgroup and 85.8 years (IQR 82.8—90.1 years) in the oldest-old subgroup. The old subgroup had a significantly higher proportion of diabetes mellitus (44.2 % versus 36.6 %, $p = 0.036$), end-stage renal disease (ESRD) (11.0 % versus 5.7 %, $p = 0.011$), liver cirrhosis (7.7 % versus 1.1 %, $p < 0.001$), solid tumours (30.4 % versus. 17.9 %, $p < 0.001$),

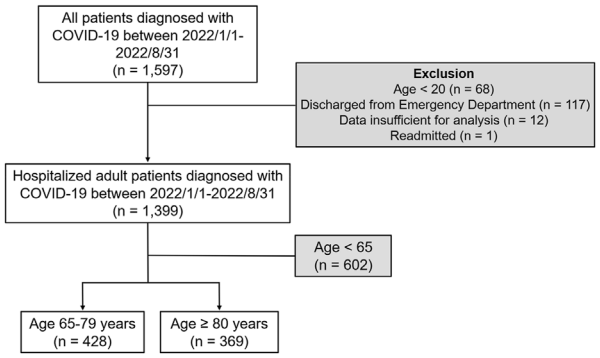

Figure 1. Study flow chart. COVID-19, coronavirus disease 2019.

and haematologic malignancies (3.5 % versus 0.5 %, $p = 0.008$) (Table 1). In the two subgroups, 66.6 % and 59.6 % of patients received at least one dose of the COVID-19 vaccine, with the majority receiving three doses. Among the patients who received at least one COVID-19 vaccine dose, 67.9 % (343/505) had a disease severity of moderate or higher, and 45.3 % (229/505) experienced a severe or higher disease severity (Fig. 2).

Clinical presentation and clinical measures

The most prevalent symptoms in the study population were fever (43.3 %) and respiratory symptoms (40.0 %). In the oldest-old subgroup, there was a higher incidence of dyspnoea (35.7 % versus 25.6 %, $p = 0.006$), respiratory symptoms (53.7 % versus 41.5 %, $p = 0.002$), flu-like symptoms (22.0 % versus 15.6 %, $p = 0.042$), and disturbance of consciousness (9.9 % versus 4.0 %, $p = 0.004$) (Table 1).

A total of 57.5 % of the oldest-old patients had severe or critical disease, which was significantly higher than the old subgroup's rate of 43.0 % (Table 2). Approximately 40 % of the patients received oral antiviral agents either before or upon hospital admission. A greater percentage of the oldest-old patients received remdesivir (53.4 % versus 39.7 %, $p < 0.001$), dexamethasone (49.3 % versus 36.7 %, $p < 0.001$), and tocilizumab (10.0 % versus 6.8 %, $p < 0.001$). More than 60 % of the patients required oxygen and respiratory support, with a notably higher proportion using non-rebreathing masks (7.3 % versus 3.0 %), high-flow nasal cannulas (6.0 % versus 2.1 %), and noninvasive positive-pressure ventilation (4.3 % versus 1.4 %) in the oldest-old subgroup (Table 2). In contrast, the oldest-old patients had lower utilization of IMV (11.7 % versus 17.8 %) and ICU transfer (14.1 % versus 20.1 %, $p = 0.032$).

Hospital outcomes and risk factors for in-hospital mortality

The overall in-hospital mortality rate was 14.6 %, with no significant difference between the two subgroups (14.0 % versus 15.2 %, $p = 0.718$). The hospital LOS was also similar between the two subgroups (16 days versus 15 days, $p = 0.537$). Among the 138 critically ill patients, the in-hospital mortality rate was 36.2 %, and there was no

Table 1 Demographic data and laboratory findings of hospitalized elderly patients with COVID-19 stratified by age group.

Variables	All (n = 797)	Age 65–79 years (n = 428)	Age ≥80 years (n = 369)	*P* value
Age (years)	79.1 (71.3–85.3)	71.6 (68.0–75.5)	85.8 (82.8–90.1)	<0.001
Female (%)	350 (43.9)	169 (39.5)	181 (49.1)	0.008
Body weight, kg	58.3 (50.0–66.7)	59.0 (50.9–68.2)	57.6 (50.0–65.0)	0.006
BMI, kg/m^2	22.9 (20.4–25.5)	23.1 (20.8–25.7)	22.6 (20.0–25.4)	0.025
Smoking (%)	93 (11.7)	64 (15.0)	29 (7.9)	0.003
Comorbidities, n (%)				
Hypertension	495 (62.1)	249 (58.2)	246 (66.7)	0.017
Diabetes mellitus	324 (40.7)	189 (44.2)	135 (36.6)	0.036
Cerebrovascular accident	149 (18.7)	72 (16.8)	77 (20.9)	0.171
Coronary artery disease	118 (14.8)	60 (14.0)	58 (15.7)	0.566
Congestive heart failure	78 (9.8)	31 (7.2)	47 (12.7)	0.013
End-stage renal disease	68 (8.5)	47 (11.0)	21 (5.7)	0.011
Liver cirrhosis	37 (4.6)	33 (7.7)	4 (1.1)	<0.001
Chronic obstructive pulmonary disease	47 (5.9)	19 (4.4)	28 (7.6)	0.083
Asthma	7 (0.9)	2 (0.5)	5 (1.4)	0.338
Solid tumours	196 (24.6)	130 (30.4)	66 (17.9)	<0.001
Haematologic malignancies	17 (2.1)	15 (3.5)	2 (0.5)	0.008
Autoimmune diseases	11 (1.4)	8 (1.9)	3 (0.8)	0.332
Organ transplantation	9 (1.1)	9 (2.1)	0	0.014
Charlson Comorbidity Index	5 (4–6)	4 (4–5)	5 (5–6)	<0.001
Vaccine history, n (%)				0.115
0 dose	292 (36.6)	143 (33.4)	149 (40.4)	
1 dose	66 (8.3)	33 (7.7)	33 (8.9)	
2 doses	95 (11.9)	55 (12.9)	40 (10.8)	
3 doses	309 (38.8)	173 (40.4)	136 (36.9)	
4 doses	35 (4.4)	24 (5.6)	11 (3.0)	
Symptoms, n (%)				
Fever	345 (43.3)	176 (50.0)	169 (52.5)	0.570
Dyspnoea	205 (25.7)	90 (25.6)	115 (35.7)	0.006
Respiratory symptoms[a]	319 (40.0)	146 (41.5)	173 (53.7)	0.002
Chest pain	21 (2.6)	14 (4.0)	7 (2.2)	0.261
Gastrointestinal symptoms	58 (7.3)	34 (9.7)	24 (7.5)	0.378
Flu-like symptoms	126 (15.8)	55 (15.6)	71 (22.0)	0.042
Disturbance of consciousness	46 (5.8)	14 (4.0)	32 (9.9)	0.004
Laboratory results[b]				
Routine Blood Tests				
White blood cell count, x10^3/ul (n = 795)[c]	7.9 (5.5–11.2)	7.90 (5.5–10.9)	7.9 (5.5–11.3)	0.785
Neutrophil count, x10^3/ul (n = 795)[c]	5.8 (3.8–9.0)	5.8 (3.7–9.0)	5.9 (3.9–9.0)	0.569
Lymphocyte count,/ul (n = 795)[c]	832.0 (533.4–1240.7)	831.6 (533.8–1220.5)	835.2 (530.0–1263.7)	0.669
Lymphopenia (%) (n = 795)[c]	537 (67.6)	293 (68.6)	244 (66.3)	0.536
Neutrophil-lymphocyte ratio (n = 791)[c]	7.1 (3.7–13.7)	7.1 (3.64–14.09)	7.1 (3.8–12.9)	0.874
Haemoglobin concentration, g/L (n = 795)[c]	11.2 (9.7–13.0)	11.1 (9.6–13.1)	11.3 (9.8–12.9)	0.895
Platelet count, x10^3/ul (n = 792)[c]	199.0 (144.0–263.3)	204.0 (145.0–271.0)	193.0 (143.0–256.0)	0.205
Blood Coagulation				
PT, sec (n = 658)[c]	12.3 (11.4–13.6)	12.4 (11.4–13.7)	12.2 (11.5–13.4)	0.573
APTT, sec (n = 655)[c]	31.2 (28.5–34.0)	31.4 (28.8–34.2)	31.0 (28.3–33.9)	0.074
D-dimer, mg/L (n = 383)[c]	1854.7 (1105.5–4397.6)	1697.8 (970.8–4566.7)	1938.5 (1182.2–4221.5)	0.171
Fibrinogen, mg/dL (n = 371)[c]	368.3 (289.3–440.9)	382.0 (304.2–457.3)	356.6 (278.5–424.8)	0.024
Blood Biochemistry				
Alanine aminotransferase, U/L (n = 775)[c]	16.0 (10.0–27.5)	17.0 (11.0–30.3)	15.0 (10.0–25.0)	0.003

Table 1 (*continued*)

Variables	All (n = 797)	Age 65–79 years (n = 428)	Age ≥80 years (n = 369)	*P* value
Total bilirubin, mg/dL (n = 606)[c]	0.6 (0.4–0.9)	0.62 (0.4–1.0)	0.6 (0.4–0.9)	0.092
Creatinine, mg/dL (n = 791)[c]	1.1 (0.8–1.9)	1.0 (0.7–2.1)	1.1 (0.8–1.7)	0.721
Albumin, g/dL (n = 549)[c]	3.2 (2.8–3.6)	3.2 (2.9–3.6)	3.2 (2.8–3.5)	0.110
Inflammatory Markers				
MDW, U (n = 769)[c]	22.5 (19.8–25.3)	21.7 (19.2–25.1)	23.0 (20.5–25.5)	0.004
CRP, mg/L (n = 719)[c]	3.4 (1.1–10.1)	3.4 (1.0–11.3)	3.3 (1.2–9.3)	0.828
Procalcitonin, mg/L (n = 384)[c]	0.3 (0.1–1.6)	0.4 (0.1–2.1)	0.2 (0.1–1.5)	0.057
ESR, mm/1 h (n = 233)[c]	36.0 (19.0–68.0)	41.0 (20.8–72.3)	34.0 (17.0–60.0)	0.183
Ferritin, ng/mL (n = 331)[c]	340.6 (160.2–655.7)	408.0 (195.7–784.9)	299.1 (139.9–594.2)	0.005

[a] Including cough, nasal obstruction, or sore throat.
[b] The initial laboratory data were documented either on the date of COVID-19 symptom onset or during the visit to the Emergency Department (if the symptom onset date was not recorded). In cases where no data were accessible, laboratory results within a 3-day period were recorded. If there was still no data available, it was marked as missing.
[c] Number of participants with available results.
Data are median (IQR) and n (%).
APTT, Activated partial thromboplastin time; BMI, Body mass index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; IQR, Interquartile range; MDW, Monocyte distribution width; PT, Prothrombin time.

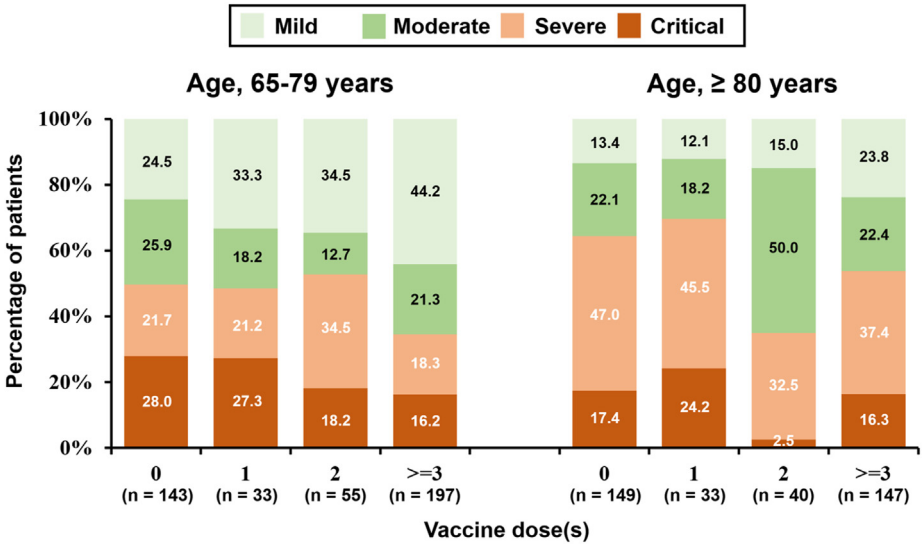

Figure 2. Distribution of COVID-19 vaccination status before hospitalization and disease severity among hospitalized elderly patients with COVID-19. COVID-19, coronavirus disease 2019.

significant difference between the two subgroups (37.2 % versus 34.6 %, $p = 0.901$). A significantly longer hospital LOS was observed in the old subgroup (50 days versus 26 days, $p = 0.026$).

The clinical characteristics differentiating survivors from nonsurvivors within the study population are presented in Table 3. Nonsurvivors exhibited a higher prevalence of ESRD, liver cirrhosis, solid tumours, and haematologic malignancies. Symptoms such as dyspnoea and disturbance of consciousness were significantly more prevalent among nonsurvivors. Additionally, nonsurvivors exhibited significantly lower absolute lymphocyte counts and higher neutrophil-lymphocyte ratios, D-dimer levels, monocyte distribution width, C-reactive protein (CRP) levels, procalcitonin levels, and ferritin levels (Table 3).

In the multivariate logistic regression analyses, comorbidities including ESRD (OR 4.7, 95 % CI 1.7–13.1, $p = 0.003$), liver cirrhosis (OR 3.0, 95 % CI 1.1–8.4, $p = 0.034$), solid tumours (OR 1.8, 95 % CI 1.0–3.1, $p = 0.048$), and haematologic malignancies (OR 4.2, 95 % CI 1.0–17.6, $p = 0.047$) were independently related to an increased risk of in-hospital mortality (Table 4).

Subgroup analyses were conducted to assess the impact of ageing and vaccination on patients with different comorbidities. The analysis revealed that older age did not result in a higher in-hospital mortality rate across all subgroups (Table S1). Furthermore, vaccination was not associated with improved 90-day survival in our cohort, irrespective of the vaccine dose received (Fig. S1). The subgroup analysis did not demonstrate a survival benefit on

Table 2 Disease severity and treatment outcomes of hospitalized elderly patients with COVID-19 stratified by age group.

Variables	All (n = 797)	Age 65–79 years (n = 428)	Age ≥80 years (n = 369)	*P* value
Disease severity, n (%)				<0.001
Mild	217 (27.2)	152 (35.5)	65 (17.6)	
Moderate	184 (23.1)	92 (21.5)	92 (24.9)	
Severe	246 (30.9)	93 (21.7)	153 (41.5)	
Critical	150 (18.8)	91 (21.3)	59 (16.0)	
Oral antiviral agents, n (%)				0.089
Nirmatrelvir-ritonavir	91 (11.4)	57 (13.3)	34 (9.2)	
Molnupiravir	220 (27.6)	108 (25.2)	112 (30.4)	
Remdesivir (%)	367 (46.0)	170 (39.7)	197 (53.4)	<0.001
Dexamethasone (%)	339 (42.5)	157 (36.7)	182 (49.3)	<0.001
Tocilizumab (%)	66 (8.3)	29 (6.8)	37 (10.0)	<0.001
Respiratory and oxygen support[a], n (%)				<0.001
No oxygen use	311 (39.0)	198 (46.3)	113 (30.6)	
Nasal cannula	231 (29.0)	107 (25.0)	124 (33.6)	
Venturi mask	43 (5.4)	19 (4.4)	24 (6.5)	
Non-rebreathing mask	40 (5.0)	13 (3.0)	27 (7.3)	
High-flow nasal cannula	31 (3.9)	9 (2.1)	22 (6.0)	
Noninvasive positive-pressure ventilation	22 (2.8)	6 (1.4)	16 (4.3)	
Invasive mechanical ventilation	119 (14.9)	76 (17.8)	43 (11.7)	
Intensive care unit admission (%)	138 (17.3)	86 (20.1)	52 (14.1)	0.032
Hospital outcomes				
Hospital LOS, days	16.0 (8.0–31.0)	16.0 (8.0–33.0)	15.0 (9.0–27.0)	0.537
Hospital LOS among survivors, days	15.0 (8.0–30.0)	15.0 (8.0–32.0	16.0 (9.0–27.0)	0.936
Hospital mortality (%)	116 (14.6)	60 (14.0)	56 (15.2)	0.718
Hospital outcomes among critically ill patients (n = 138)				
Hospital LOS, days	38.5 (18.0–66.0)	50.0 (20.0–73.5)	26.0 (17.0–56.0)	0.026
Hospital LOS among survivors, days	57.0 (23.0–76.0)	61.0 (39.0–85.0)	38.0 (19.0–60.8)	0.009
Hospital mortality (%)	50 (36.2)	32 (37.2)	18 (34.6)	0.901

[a] The most advanced and exclusive category ever used during hospitalization.
Data are median (IQR) and n (%).
LOS, Length of stay.

in-hospital mortality associated with vaccination, regardless of whether at least one or two COVID-19 vaccines were administered across all subgroups (Fig. S2).

Discussion

To our knowledge, this is the first real-world study to explore the hospital outcomes of old and oldest-old COVID-19 patients after widespread vaccination and a good understanding of the associated complications of COVID-19. Our study demonstrated that the outcomes of old and oldest-old patients have improved compared to previous studies conducted during the early phase of the pandemic. In-hospital mortality was found to be comparable between the old and oldest-old patients, while comorbidities continued to be an important factor for in-hospital mortality.

During the initial phase of the COVID-19 pandemic, a multicentre study revealed a mortality rate of 47 % among hospitalized patients aged 75 and above.[22] Similarly, two extensive studies conducted in 2020 involving a substantial number of patients admitted to hospitals due to COVID-19 reported mortality rates of 53.7 % and 37 % for individuals aged 80 and older.[23,24] Notably, there was a clear and strong association between older age and an increased risk of mortality.[25] In this study, the overall in-hospital mortality rate was 14.7 %, with no difference between the old and oldest-old patients. Although the crude mortality rate cannot be directly compared between studies due to differences in viral strains and differing medical resources, we still hypothesized that the impact of ageing has decreased due to widespread vaccination and improvements in the treatment of COVID-19. Furthermore, older age did not result in a higher in-hospital mortality rate across all comorbidity subgroups.

We found that the oldest-old patients experienced more severe illness during admission, resulting in a higher prevalence of corticosteroid, remdesivir, and tocilizumab utilization. Nevertheless, the ICU and IMV utilization was lower in comparison to the old subgroup. This observation aligns with that in a large international cohort study,[25] suggesting that the lower utilization may be linked to a higher prevalence of do-not-intubate decisions among oldest-old patients and a generally more conservative approach among aged people, as previously shown in intensive care and cancer management.[16–18] Although it is difficult to decide when to provide older patients, and even the oldest-old patients, with more aggressive treatment, based on the current data, an individualized approach should be offered

Table 3 Demographic data, disease severity and outcomes of hospitalized elderly patients with COVID-19 stratified by hospital outcome.

Variables	Survivors (n = 681)	Nonsurvivors (n = 116)	*P* value
Age (years)	78.8 (71.3–85.2)	79.3 (70.8–86.5)	0.644
Female (%)	295 (43.3)	55 (47.4)	0.471
Body weight, kg	58.3 (50.0–67.0)	59.6 (50.0–66.4)	0.981
BMI, kg/m^2	22.9 (20.4–25.5)	22.5 (20.1–25.8)	0.602
Smoking (%)	77 (11.3)	16 (13.8)	0.539
Comorbidities, n (%)			
Hypertension	424 (62.3)	71 (61.2)	0.910
Diabetes mellitus	270 (39.6)	54 (46.6)	0.195
Cerebrovascular accident	129 (18.9)	20 (17.2)	0.760
Coronary artery disease	104 (15.3)	14 (12.1)	0.449
Congestive heart failure	65 (9.5)	13 (11.2)	0.698
End-stage renal disease	48 (7.0)	20 (17.2)	0.001
Liver cirrhosis	26 (3.8)	11 (9.5)	0.015
Chronic obstructive pulmonary disease	42 (6.2)	5 (4.3)	0.568
Asthma	6 (0.9)	1 (0.9)	>0.999
Solid tumours	154 (22.6)	42 (36.2)	0.002
Haematologic malignancies	10 (1.5)	7 (6.0)	0.005
Autoimmune diseases	9 (1.3)	2 (1.7)	>0.999
Organ transplantation	7 (1.0)	2 (1.7)	0.857
Charlson Comorbidity Index	5 (4–6)	5 (5–7)	<0.001
Vaccine history, n (%)			0.741
0 dose	245 (36.0)	47 (40.5)	
1 dose	55 (8.1)	11 (9.5)	
2 doses	82 (12.0)	13 (11.2)	
3 doses	270 (39.7)	39 (33.6)	
4 doses	29 (4.3)	6 (5.2)	
Symptoms, n (%)			
Fever	298 (51.6)	47 (49.0)	0.718
Dyspnoea	158 (27.3)	47 (49.0)	<0.001
Respiratory symptoms[a]	268 (46.4)	51 (53.1)	0.264
Chest pain	18 (3.1)	3 (3.1)	>0.999
Gastrointestinal symptoms	49 (8.5)	9 (9.4)	0.925
Flu-like symptoms	111 (19.2)	15 (15.6)	0.489
Disturbance of consciousness	33 (5.7)	13 (13.5)	0.009
Laboratory results[b]			
Routine Blood Tests			
White blood cell count, x10^3/ul (n = 795)[c]	7.8 (5.5–10.8)	9.1 (5.6–13.2)	0.129
Neutrophil count, x10^3/ul (n = 795)[c]	5.8 (3.8–8.8)	6.7 (4.1–11.0)	0.131
Lymphocyte count,/ul (n = 795)[c]	848.0 (539.6–1255.0)	686.7 (494.1–1159.2)	0.036
Lymphopenia (%) (n = 795)[c]	452 (66.6)	85 (73.3)	0.187
Neutrophil-lymphocyte ratio (n = 791)[c]	6.9 (3.7–12.9)	8.9 (4.2–17.7)	0.032
Haemoglobin concentration, g/L (n = 795)[c]	11.5 (9.9–13.1)	10.2 (9.1–11.5)	<0.001
Platelet count, x10^3/ul (n = 792)[c]	202.5 (151.0–263.0)	174.0 (102.8–267.8)	0.005
Blood Coagulation			
PT, sec (n = 658)[c]	12.2 (11.4–13.4)	13.1 (12.0–15.4)	<0.001
APTT, sec (n = 655)[c]	31.3 (28.6–34.0)	31.1 (28.1–33.2)	0.521
D-dimer, mg/L (n = 383)[c]	1661.2 (997.2–3869.9)	3415.8 (1576.4–6681.7)	<0.001
Fibrinogen, mg/dL (n = 371)[c]	370.2 (295.1–449.4)	340.5 (257.1–424.0)	0.032
Blood Biochemistry			
Alanine aminotransferase, U/L (n = 775)[c]	16.0 (11.0–27.0)	16.5 (8.0–31.2)	0.512
Total bilirubin, mg/dL (n = 606)[c]	0.6 (0.4–0.9)	0.7 (0.5–1.0)	0.081
Creatinine, mg/dL (n = 791)[c]	1.0 (0.8–1.7)	1.2 (0.8–2.7)	0.016
Albumin, g/dL (n = 549)[c]	3.3 (2.9–3.6)	2.8 (2.4–3.2)	<0.001
Inflammatory Markers			
MDW, U (n = 769)[c]	22.0 (19.5–25.0)	24.6 (21.1–27.2)	<0.001
CRP, mg/L (n = 719)[c]	3.0 (1.0–9.3)	6.8 (2.5–14.2)	<0.001

(*continued on next page*)

Table 3 (*continued*)

Variables	Survivors (n = 681)	Nonsurvivors (n = 116)	*P* value
Procalcitonin, mg/L (n = 384)[c]	0.2 (0.1, 1.2)	1.4 (0.3, 3.6)	<0.001
ESR, mm/1 h (n = 233)[c]	35.0 (18.0–69.0)	38.5 (28.8–59.2)	0.494
Ferritin, ng/mL (n = 331)[c]	313.6 (152.3–565.8)	547.5 (292.2–1053.1)	<0.001
Disease severity, n (%)			<0.001
Mild	212 (31.1)	5 (4.3)	
Moderate	175 (25.7)	9 (7.8)	
Severe	201 (29.5)	45 (38.8)	
Critical	93 (13.7)	57 (49.1)	
Oral antiviral agents, n (%)			0.247
Nirmatrelvir-ritonavir	82 (12.0)	9 (7.8)	
Molnupiravir	191 (28.0)	29 (25.0)	
Remdesivir (%)	291 (42.7)	76 (65.5)	<0.001
Dexamethasone (%)	264 (38.8)	75 (64.7)	<0.001
Tocilizumab (%)	45 (6.6)	21 (18.1)	<0.001
Respiratory and oxygen support[d], n (%)			<0.001
No oxygen use	306 (44.9)	5 (4.3)	
Nasal cannula	220 (32.3)	11 (9.5)	
Venturi mask	33 (4.8)	10 (8.6)	
Non-rebreathing mask	18 (2.6)	22 (19.0)	
High-flow nasal cannula	15 (2.2)	16 (13.8)	
Noninvasive positive-pressure ventilation	16 (2.3)	6 (5.2)	
Invasive mechanical ventilation	73 (10.7)	46 (39.7)	
Intensive care unit admission (%)	88 (12.9)	50 (43.1)	<0.001
Hospital LOS, days	15.0 (8.0–30.0)	16.5 (8.8–31.0)	0.790
Hospital LOS among critically ill patients, days (n = 138)[c]	57.0 (23.0–76.0)	20.0 (10.0–39.0)	<0.001

[a] Including cough, nasal obstruction, or sore throat.
[b] The initial laboratory data were documented either on the date of COVID-19 symptom onset or during the visit to the Emergency Department (if the symptom onset date was not recorded). In cases where no data were accessible, laboratory results within a 3-day period were recorded. If there was still no data available, it was marked as missing.
[c] Number of participants with available results.
[d] The most advanced and exclusive category ever used during hospitalization.
Data are median (IQR) and n (%).
APTT, Activated partial thromboplastin time; BMI, Body mass index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; IQR, Interquartile range; LOS, Length of stay; MDW, Monocyte distribution width; PT, Prothrombin time.

to older adults targeting beneficial therapeutic decisions. This approach should consider the comorbidities, levels of baseline frailty and disability, along with an understanding of prognostic factors associated with ageing across various diseases.[26,27]

Although the oldest-old patients presented with more severe diseases, the hospital outcomes were similar between the two age subgroups. These results may be attributed to advancements in COVID-19 pharmacological treatments and supportive care, leading to improved COVID-19-related mortality. Nevertheless, patients in the old subgroup might have experienced prolonged hospitalization and eventual death due to their more severe comorbidities and related complications.

Early reports have shown that underlying diseases, such as cardiovascular disease, chronic lung disease, and diabetes mellitus, are associated with the development of critical disease or death.[28,29] In our study, only ESRD, liver cirrhosis, solid tumours, and haematologic malignancies were found to be independently related to in-hospital mortality. Similar to ageing, the negative impact of certain comorbidities on survival was also mitigated in our study. While more research is needed to examine these results, special attention and more proactive measures, such as vaccination, are continuously needed for patients with the most severe comorbidities.[30]

The presenting symptoms of dyspnoea and disturbance of consciousness were observed more frequently in non-survivors. While dyspnoea often indicates the severity of the respiratory system and is more prevalent among deceased COVID-19 patients,[29] the correlation between disturbance of consciousness and disease severity, as well as poor outcomes, may be underestimated. Older individuals tend to exhibit atypical presentations of illnesses, including infectious diseases, which can contribute to adverse clinical outcomes.[31] The literature reports varying rates of disturbance of consciousness in the general population with COVID-19, ranging from 9 % to 29.7 %,[32,33] with the rate increasing with age.[25] Recognizing atypical presentations of COVID-19 in elderly individuals, such as disturbance of consciousness, is crucial for providing appropriate care.[34]

Several biomarkers have shown significant associations with COVID-19-related mortality, including lymphopenia,[21] higher levels of CRP, procalcitonin, ferritin, and the neutrophil-to-lymphocyte ratio (NLR).[35–38] In our study, we

Table 4 Logistic regression analyses of clinical variables associated with hospital mortality.

Variables	Univariate model		Multivariate model	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age (each additional year)	1.0 (1.0—1.0)	0.668	1.0 (1.0—1.1)	0.161
Gender (female vs. Male)	1.2 (0.8—1.8)	0.412		
Body weight (per kg higher)	1.0 (1.0—1.0)	0.726		
BMI (per kg/m^2 higher)	1.0 (0.9—1.0)	0.361		
Smoking	1.3 (0.7—2.2)	0.442		
Comorbidities				
Hypertension	1.0 (0.6—1.4)	0.829		
Diabetes mellitus	1.3 (0.9—2.0)	0.163		
Cerebrovascular accident	0.9 (0.5—1.5)	0.664		
Coronary artery disease	0.8 (0.4—1.4)	0.371		
Congestive heart failure	1.2 (0.6—2.2)	0.578		
End-stage renal disease	2.7 (1.6—4.8)	<0.001	4.7 (1.7—13.1)	0.003
Liver cirrhosis	2.6 (1.3—5.5)	0.010	3.0 (1.1—8.4)	0.034
Chronic obstructive pulmonary disease	0.7 (0.3—1.8)	0.435		
Asthma	1.0 (0.1—8.2)	0.984		
Solid tumours	1.9 (1.3—3.0)	0.002	1.8 (1.0—3.1)	0.048
Haematologic malignancies	4.3 (1.6—11.6)	0.004	4.2 (1.0—17.6)	0.047
Autoimmune diseases	1.3 (0.3—6.1)	0.732		
Organ transplantation	1.7 (0.3—8.2)	0.517		
Charlson Comorbidity Index	1.4 (1.2—1.5)	<0.001		
Vaccine history				
0 dose	reference			
1 dose	1.0 (0.5—2.1)	0.910		
2 doses	0.8 (0.4—1.6)	0.573		
3 doses	0.8 (0.5—1.2)	0.225		
4 doses	1.1 (0.4—2.7)	0.874		
Laboratory results				
Routine Blood Tests				
White blood cell count (x10^3/ul)	1.2 (1.0—1.3)	0.073	0.7 (0.3—1.4)	0.292
Neutrophil count (x10^3/ul)	1.2 (1.0—1.4)	0.056	1.7 (0.8—3.5)	0.154
Lymphocyte count (/ul)	0.8 (0.6—1.2)	0.346		
Haemoglobin concentration (g/L)	0.6 (0.5—0.8)	<0.001	0.8 (0.6—1.0)	0.096
Platelet count (x10^3/ul)	0.8 (0.6—1.0)	0.032	1.0 (0.8—1.2)	0.796
Lymphopenia	0.9 (0.8—1.2)	0.604		
Neutrophil-lymphocyte ratio	1.4 (1.1—1.8)	0.008	1.1 (0.9—1.3)	0.208
Blood Coagulation				
PT (sec)	1.1 (1.0—1.3)	0.095	1.2 (1.0—1.5)	0.059
APTT (sec)	0.8 (0.5—1.3)	0.406		
D-dimer (mg/L)	1.3 (1.1—1.5)	0.002	1.0 (0.9—1.3)	0.68
Fibrinogen (mg/dL)	0.9 (0.7—1.0)	0.121		
Blood Biochemistry				
Alanine aminotransferase (U/L)	1.1 (1.0—1.3)	0.116		
Total bilirubin (mg/dL)	1.1 (0.9—1.3)	0.300		
Creatinine (mg/dL)	1.2 (1.0—1.4)	0.031	0.9 (0.6—1.2)	0.467
Albumin (g/dL)	0.5 (0.4—0.7)	<0.001	0.8 (0.6—1.1)	0.149
Inflammatory Markers				
MDW (U)	1.6 (1.3—1.9)	<0.001	1.2 (0.9—1.5)	0.188
C-reactive protein (mg/L)	1.4 (1.2—1.7)	<0.001	1.1 (0.8—1.4)	0.673
Procalcitonin (mg/L)	1.4 (1.1—1.8)	0.011	1.0 (0.8—1.2)	0.696
ESR (mm/hr)	1.3 (1.1—1.6)	0.003	0.9 (0.7—1.2)	0.618
Ferritin (ng/mL)	1.5 (1.2—1.8)	<0.001	1.1 (0.9—1.4)	0.488
Oral antiviral agents	0.7 (0.5—1.1)	0.136		
Remdesivir	2.5 (1.7—3.8)	<0.001	0.8 (0.4—1.6)	0.526
Dexamethasone	2.9 (1.9—4.4)	<0.001	1.5 (0.7—3.1)	0.268
Tocilizumab	3.1 (1.8—5.5)	<0.001	1.2 (0.6—2.5)	0.56
Disease severity				

(*continued on next page*)

Table 4 (*continued*)

Variables	Univariate model		Multivariate model	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Mild	reference		reference	
Moderate	2.2 (0.7—6.6)	0.169	2.0 (0.6—7.0)	0.255
Severe	9.5 (3.7—24.4)	<0.001	8.5 (2.9—25.1)	<0.001
Critical	26.0 (10.1—66.9)	<0.001	21.7 (7.1—66.1)	<0.001

APTT, Activated partial thromboplastin time; BMI, Body mass index; CI, Confidence interval; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; IQR, Interquartile range; MDW, Monocyte distribution width; OR, Odds ratio; PT, Prothrombin time.

observed that nonsurvivors exhibited a decrease in absolute lymphocyte count, an elevation in the NLR, and heightened levels of various inflammatory markers. In regression analysis, after adjusting for disease severity, laboratory findings did not predict in-hospital mortality, which differs from previous studies. However, patients sought medical care at different disease stages, potentially leading to variations in disease severity and, consequently, variations in laboratory test results. Inflammatory markers increased as disease severity increased (Table S2).

In this study, we did not find a significant association between vaccination and outcomes, contrasting with a recent, larger cohort study that demonstrated a link between COVID-19 vaccination and reduced mortality.[39] This discrepancy could be attributed to the exclusion of nonhospitalized COVID-19-infected patients from our research, as this group might have benefited from vaccination, avoiding disease progression or hospitalization. In the multivariate regression analysis, disease severity strongly correlated with in-hospital mortality in this study. Among the 505 hospitalized patients vaccinated against COVID-19 in this study, 67.9 % exhibited moderate or more severe disease severity, while 45.3 % had severe disease or higher. The correlation of oral antiviral agents and hospital outcomes may be similarly explained, as most patients with mild disease who received these agents were not admitted to the hospital. Therefore, our results should not be interpreted as indicating no benefit of vaccination or oral antiviral agents, given the possible selection bias in this retrospective study.

This study had several limitations. First, it was conducted at a single centre in Taiwan, and the prevalent viral strain during the study period was mainly the Omicron variant. Thus, the results may not be generalizable to other areas. Second, we could not analyse the impact of different SARS-CoV-2 variants because the identification of SARS-CoV-2 variants was not routinely performed at the height of the pandemic. Third, we documented mortality from all causes instead of focusing solely on COVID-19-related mortality. It is important to note that in some instances, SARS-CoV-2 infection might not directly lead to death, especially in patients with advanced metastatic cancer or terminal organ failure.

Conclusion

In conclusion, during the late phase of the pandemic, with widespread vaccination and advancements in COVID-19 treatments, outcomes for hospitalized old and oldest-old patients with COVID-19 improved. In-hospital mortality was 14.6 % among COVID-19 patients aged 65 or older in this study, showing no significant difference between the old and oldest-old subgroups. Additionally, the prognostic factors for mortality have changed. The impact of age on in-hospital mortality has diminished, while comorbidities such as ESRD, liver cirrhosis, solid tumours, and haematologic malignancies are significantly related to poor hospital outcomes.

Ethics statement

This study received approval from the Institutional Review Board (IRB) of China Medical University Hospital (CMUH) (CMUH111-REC1-194). The IRB of CMUH waived the requirement for written informed consent because the study involved only minimal risk to the patients.

Authors' contributions

CLC, CKT, YCL and PRH contributed to study conception and design. CLC, CKT, WCC, SJL, HMS, and WJC contributed to the acquisition of data. CLC, CKT, WCC, SJL, CYT, YCL and PRH contributed to data analysis and interpretation. CLC, CKT, YCL, and PRH drafted the manuscript, with all authors revising it critically for intellectual content. All authors have read and approved the final version of the manuscript.

Funding

This work was supported by China Medical University Hospital, Taichung, Taiwan (grant number C1110831002-08). The funder had no involvement in the design of the study, data collection, data analysis or interpretation, report writing, or the decision to submit the article for publication.

Data availability statement

The data of this study are available on request from the corresponding author.

Declaration of competing interest

The authors have no competing interests to declare.

Acknowledgements

None.

References

1. World Health Organization. https://covid19.who.int. [Accessed 13 June 2023].
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in wuhan, China. *Lancet* 2020;**395**:497—506.
3. Liu Y, Mao B, Liang S, Yang JW, Lu HW, Chai YH, et al. Association between age and clinical characteristics and outcomes of COVID-19. *Eur Respir J* 2020;**55**:2001112.
4. Maltese G, Corsonello A, Di Rosa M, Soraci L, Vitale C, Corica F, et al. Frailty and COVID-19: a systematic scoping review. *J Clin Med* 2020;**9**:2106.
5. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020;**55**:2000524.
6. Sornette D, Mearns E, Schatz M, Wu K, Darcet D. Interpreting, analysing and modelling COVID-19 mortality data. *Nonlinear Dynam* 2020;**101**:1751—76.
7. Nabors C, Sridhar A, Hooda U, Lobo SA, Levine A, Frishman WH, et al. Characteristics and outcomes of patients 80 years and older hospitalized with coronavirus disease 2019 (COVID-19). *Cardiol Rev* 2021;**29**:39—42.
8. Nguyen NT, Chinn J, Nahmias J, Yuen S, Kirby KA, Hohmann S, et al. Outcomes and mortality among adults hospitalized with COVID-19 at US medical centers. *JAMA Netw Open* 2021;**4**:e210417.
9. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021;**384**:693—704.
10. Consortium WHOST. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the who solidarity randomised trial and updated meta-analyses. *Lancet* 2022;**399**:1941—53.
11. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet* 2022;**400**:1213—22.
12. Wu HY, Chang PH, Huang YS, Tsai CS, Chen KY, Lin IF, et al. Recommendations and guidelines for the diagnosis and management of coronavirus disease-19 (COVID-19) associated bacterial and fungal infections in Taiwan. *J Microbiol Immunol Infect* 2023;**56**:207—35.
13. Investigators R-C, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med* 2021;**384**:1491—502.
14. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by COVID-19 vaccines. *N Engl J Med* 2022;**386**:340—50.
15. Lai CC, Lee PI, Hsueh PR. How Taiwan has responded to COVID-19 and how COVID-19 has affected Taiwan, 2020-2022. *J Microbiol Immunol Infect* 2023;**56**:433—41.
16. Garrouste-Orgeas M, Boumendil A, Pateron D, Aergerter P, Somme D, Simon T, et al. Selection of intensive care unit admission criteria for patients aged 80 years and over and compliance of emergency and intensive care unit physicians with the selected criteria: an observational, multicenter, prospective study. *Crit Care Med* 2009;**37**:2919—28.
17. Tranvag EJ, Norheim OF, Ottersen T. Clinical decision making in cancer care: a review of current and future roles of patient age. *BMC Cancer* 2018;**18**:546.
18. Guidet B, Vallet H, Boddaert J, de Lange DW, Morandi A, Leblanc G, et al. Caring for the critically ill patients over 80: a narrative review. *Ann Intensive Care* 2018;**8**:114.
19. Galvez-Barron C, Arroyo-Huidobro M, Minarro A, Ananos G, Chamero A, Martin M, et al. COVID-19: clinical presentation and prognostic factors of severe disease and mortality in the oldest-old population: a cohort study. *Gerontology* 2022;**68**:30—43.
20. COVID-19 Treatment Guidelines Panel. *Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health*. https://www.covid19treatmentguidelines.nih.gov. [Accessed 13 June 2023].
21. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *J Intensive Care* 2020;**8**:36.
22. Szklarzewska S, Vande Walle J, De Breucker S, Schoevaerdts D. A comparison of clinical characteristics between old and oldest-old patients hospitalised for SARS-CoV2. *Acta Clin Belg* 2023;**78**:192—9.
23. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA* 2020;**323**:2052—9.
24. Lewnard JA, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. *BMJ* 2020;**369**:m1923.
25. Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, et al. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19. *Int J Epidemiol* 2023;**52**:355—76.
26. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res* 2020;**32**:1599—608.
27. Foley C, Bloomer M, Hutchinson AM. Factors that influence intensive care admission decisions for older people: a systematic review. *Aust Crit Care* 2023;**36**:274—84.
28. Ge E, Li Y, Wu S, Candido E, Wei X. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: a population-based cohort study. *PLoS One* 2021;**16**:e0258154.
29. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020;**80**:639—45.
30. Chen TH, Ho Y, Tai HL, Chu YC, Lin YP, Yang CY, et al. Survival benefit of a third dose of the COVID-19 vaccine among hemodialysis patients: a prospective cohort study. *J Microbiol Immunol Infect* 2023;**56**:1198—206.
31. Hofman MR, van den Hanenberg F, Sierevelt IN, Tulner CR. Elderly patients with an atypical presentation of illness in the emergency department. *Neth J Med* 2017;**75**:241—6.
32. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;**395**:507—13.
33. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatr* 2020;**7**:611—27.
34. Zhao TS, Zeng HL, Zhang X, Chen X, Jiang WL, Du J, et al. Neurological manifestations in COVID-19 patients and their

application in predicting fatal disease: a retrospective cohort study. *J Microbiol Immunol Infect* 2022;**55**:445—53.
35. Loomba RS, Villarreal EG, Farias JS, Aggarwal G, Aggarwal S, Flores S. Serum biomarkers for prediction of mortality in patients with COVID-19. *Ann Clin Biochem* 2022;**59**:15—22.
36. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol* 2020;**92**:2152—8.
37. Milenkovic M, Hadzibegovic A, Kovac M, Jovanovic B, Stanisavljevic J, Djikic M, et al. D-dimer, CRP, PCT, and IL-6 levels at admission to ICU can predict in-hospital mortality in patients with COVID-19 pneumonia. *Oxid Med Cell Longev* 2022;**2022**:8997709.
38. Prozan L, Shusterman E, Ablin J, Mitelpunkt A, Weiss-Meilik A, Adler A, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with influenza and respiratory syncytial virus infection. *Sci Rep* 2021;**11**:21519.
39. Baker TB, Bolt DM, Smith SS, Piasecki TM, Conner KL, Bernstein SL, et al. The relationship of COVID-19 vaccination with mortality among 86,732 hospitalized patients: subpopulations, patient factors, and changes over time. *J Gen Intern Med* 2023;**38**:1248—55.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.01.006.