Preventive Medicine Reports 39 (2024) 102632

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Vaccines reduced hospital length of stay and fraction of inspired oxygen of COVID-19 patients: A retrospective cohort study

Xiaomei Fang [a,*], Guofang Tao [a], Hua Zhou [b], Yuxia Zhou [b]

[a] Department of Nursing, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, P. R. China
[b] Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, P. R. China

ARTICLE INFO

Keywords:
COVID-19
Vaccine
Hospitalization
Length of stay
Endotracheal intubation
Mortality

ABSTRACT

Few studies have focused on the evaluation of vaccine effectiveness (VE) in mainland China. This study was to characterize the VE including the frequent symptoms, laboratory indices, along with endotracheal intubation, hospital length of stay (LoS), and survival status. This retrospective cohort study included patients with COVID-19 admitted to our hospital. Statistical comparisons of continuous variables were carried out with an independent Student's *t*-test or Mann-Whitney *U* test. For categorical variables, the Chi-square test and Fisher exact test were used. Multivariable regression analysis was performed to adjust the confounding factors such as age, gender, body mass index (BMI), residential area, smoking status, the Charlson comorbidity index (CCI) score, followed by investigating the effects of vaccination on critical ill prevention, reduced mortality and endotracheal intubation, LoS and inspired oxygen. This study included 549 hospitalized patients with COVID-19, including 222 (40.43 %) vaccinated participants and 327 (59.57 %) unvaccinated counterparts. There was no obvious difference between the two groups in typical clinical symptoms of COVID-19, clinical laboratory results and mortality. Multivariable analysis showed that COVID-19 vaccine obviously reduced LoS by 1.2 days (lnLoS = -0.14, 95 %CI[-0.24,-0.04]; P = 0.005) and decreased fraction of inspired oxygen by 40 % (OR: 0.60; 95 %CI [0.40,0.90]; P = 0.013) after adjusting age, gender, BMI, residential area, smoking status and CCI score. In contrast, vaccination induced reduction in the critically ill, mortality, and endotracheal intubation compared with the unvaccinated counterparts, but with no statistical differences. Vaccinated patients hospitalized with COVID-19 have a reduced LoS and fraction of inspired oxygen compared to unvaccinated cases in China.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to crisis to global public health (Tabari et al., 2020). Nowadays, multiple COVID-19 vaccines have received emergency use authorizations (EUA) in order to prevent severe COVID-19 illness, which may stimulate an immune response and provide active acquired immunity to infection (Chen et al., 2022). To date, four primary categories of COVID-19 vaccines have been developed, including inactivated or attenuated, protein subunit-based, viral vector, and nucleic acid vaccines (Ndwandwe and Wiysonge, 2021a). Phase III trials have confirmed high COVID-19 vaccines effectiveness (VE) against SARS-CoV-2 infection, such as 50.7 % effectiveness of absorbed COVID-19 vaccine, 70.4 % effectiveness of ChAdOx1 nCoV-19 vaccine, 95 % effectiveness of BNT162b2 mRNA vaccine, as well as 94.1 % effectiveness of mRNA-1273 vaccine (Baden et al., 2021; Palacios et al., 2020; Polack et al., 2020; Voysey et al., 2021; Zheng et al., 2022).

Among the 9 COVID-19 vaccines approved by WHO for emergency use, two vaccines named BBIBP-CorV and CoronaVac inactivated whole-virus vaccines are commonly utilized in mainland China. WHO has proposed an urgent need to investigate the COVID-19 VE against several

Abbreviations: VE, vaccine effectiveness; LoS, length of stay; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; EUA, emergency use authorizations; BMI, body mass index; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBL, peripheral blood lymphocyte; Cr, creatinine; CRP, C-reactive protein; AIDS, acquired immunodeficiency syndrome; CCI, Charlson comorbidity index.

* Corresponding author at: Department of Nursing, The First Affiliated Hospital, Zhejiang University School of Medicine, # 79 Qingchun Road, Shangcheng District, Hangzhou 310003, Zhejiang Province, P. R. China.
E-mail address: fangxm77@126.com (X. Fang).

https://doi.org/10.1016/j.pmedr.2024.102632
Received 4 September 2023; Received in revised form 23 January 2024; Accepted 25 January 2024
Available online 1 February 2024

major outcomes, such as symptomatic COVID-19, critical conditions, and COVID-19 related mortality (Patel et al., 2021). Current data indicated that authorized COVID-19 vaccines have been shown to be highly effective against COVID-19-associated hospitalizations among adults (Bajema et al., 2021; Rosenberg et al., 2021; Seiffert et al., 2020). Besides hospitalization, the COVID-19 vaccines have been shown to reduce infection rate, disease severity, and mortality (Mohammed et al., 2022). In mainland China, the dynamic COVID-zero policy proposed by the Chinese government severely limits outbreak size, which greatly protect the civilians from infection (Tang et al., 2022). In addition, the primary vaccination coverage of COVID-19 is very high, which makes unvaccinated comparison groups too small and too different for conducting absolute VE studies.

For the SARS-CoV-2 infected patients, real-world effectiveness data have shown that the poor prognosis or the need of mechanical ventilation is correlated to comorbidities, complications and demographical characteristics of hospitalized COVID-19 patients (Telle et al., 2021; L. Zhang et al., 2020a; Zhang et al., 2020b). Some studies reported that the majority of hospitalized COVID-19 cases requiring mechanical ventilation were under comorbid condition like hypertension, diabetes, and cardiovascular and cerebrovascular diseases (Wats et al., 2021; Zhang et al., 2020a; Zhang et al., 2020b). Little is known on the efficacy and safety of COVID-19-related vaccines in the patients against Omicron COVID-19. In this study, we categorized the hospitalized COVID-19 patients into unvaccinated and vaccinated groups, with an aim to compare the VE including the frequent symptoms, clinical laboratory indices, and prognostic outcomes. In addition, we assessed whether vaccination could affect the utilization of endotracheal intubation, survival status and length of hospital stay, as well as critically ill.

2. Methods

2.1. Study population

This retrospective cohort study enrolled patients with confirmed COVID-19 admitted to our hospital between January 2023 and February 2023. COVID-19 was diagnosed based on the WHO guidance and guidance for COVID-19 issued by National Health Commission of China, according to the previous description (Yu & Li, 2021). The severity of the symptoms (i.e. mild, moderate, severe and critical) was divided according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (version 10, Chinese Medical Association). The included patients were those aged 18 yrs or more that were firstly infected with COVID-19. Those with primary infection by other pathogens (e.g. bacteria, fungi, other respiratory virus, mycoplasma, or chlamydia) and incomplete medical files were excluded from this study. The study protocols were approved by the Ethics Committees of the First Affiliated Hospital, Zhejiang University School of Medicine (Approval No.: 2023–0079). Because the study was a retrospective study based on real-world situations, the need to obtain informed consent from eligible patients was waived.

2.2. Grouping

The patients were divided into vaccinated and unvaccinated groups according to the status of vaccination. The patients received fully vaccination (4 doses, n = 3) or those with vaccination of at least one dose (3 doses, n = 130; 2 doses, n = 53; 1 dose, n = 36) were all classified into the vaccinated group (n = 222). There were 327 unvaccinated patients enrolled in this study.

2.3. Data collection

After admission, the sociodemographic characteristics, symptoms, laboratory results, complications, comorbidity status, treatment and outcome were collected from each subject. The sociodemographic characteristics included age, sex, body mass index (BMI), marital status, residential area, education, occupation, history of smoking. The laboratory parameters were examined including ferritin, D-dimer, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), peripheral blood lymphocyte (PBL), creatinine (Cr) as well as C-reactive protein (CRP). The symptoms of COVID-19 included fever, fatigue, myalgia, cough, chest tightness and dyspnea, score throat, rhinorrhea, nasal obstruction, headache, vertigo, ageusia, sleeping disorders, nausea and vomiting and diarrhea. The major complications collected from each subject included hypoxemia, silent hypoxemia, and respiratory failure.

Comorbidity was defined as having at least one of the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes mellitus, hemiplegia, moderate/severe renal disease, diabetes with end-stage organ damage, any type of malignancy, leukemia, lymphoma, moderate/severe liver disease, metastatic solid tumor and acquired immunodeficiency syndrome (AIDS) for at least 6 months. To grade the comorbid condition of COVID-19 patients, the Charlson comorbidity index (CCI) score was calculated. The necessary information to calculate the CCI was obtained through the diagnostic codes obtained during the premeasurement period. Then the CCI was calculated by the summation of the scores of each comorbidity multiplied by their weight score, which has been listed in Supplementary Table 1.

The parameters for treatment included the utilization of antibiotics, hormone therapy, antiviral therapy, and oxygen inspiration, endotracheal intubation. The outcome included hospital LoS, survival and disease severity.

2.4. Statistical analysis

Statistical analysis was carried out using SPSS 20 Software (IBM, Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation or median (interquartile range). Categorical variables were described as counting (proportion). Statistical comparisons of continuous variables were carried out with an independent Student's *t*-test when the data were normally distributed. Otherwise, the Mann-Whitney *U* test was applied. Chi-square test and Fisher exact test were used for the statistical comparison of categorical variables. The variables with a P value of less than 0.15 between the vaccinated and unvaccinated groups were used as covariates. Then the binary logistic regression analysis was performed to analyze the effects of vaccination on the severe and critically ill, mortality and endotracheal intubation. Ordinal logistic regression analysis was utilized to analyze the effects of vaccination on inspired oxygen fraction. A P value of less than 0.05 was considered to be statistical difference.

3. Results

3.1. Participants

Table 1 summarized the sociodemographic features of 549 COVID-19 patients (male: 372; female: 177). The average age of the whole cohort was 71.16 ± 15.63 yrs, with the majority (80.14 %) were aged 60 yrs or more. In the whole cohort, 222 participants (40.43 %) received at least one dose of COVID-19 vaccine. There were no significant differences in the sociodemographic features between the unvaccinated patients and vaccinated patients except the gender ($P < 0.001$), residential area ($P = 0.025$), smoking status ($P < 0.001$), and CCI score ($P = 0.005$).

3.2. Vaccination significantly reduced the chest tightness and dyspnea

Then we compared the symptom of COVID-19 patients between the vaccinated and unvaccinated groups. There were no statistical differences between the two groups in typical clinical symptoms including

Table 1
Sociodemographic characteristics of in unvaccinated (n = 327) or vaccinated (n = 222) COVID-19 patients admitted to our hospital between January 2023 and February 2023.

Variables	All sets (n = 549)	Unvaccinated (n = 327)	Vaccinated (n = 222)	P value
Age, n (%)				0.085
<60	109 (19.85)	64(19.57)	45(20.27)	
60–80	261 (47.54)	144(44.04)	117(52.70)	
≥80	179 (32.60)	119(36.39)	60(27.03)	
Sex, n (%)				<0.001
Male	372 (67.76)	202(61.77)	170(76.58)	
Female	177 (32.24)	125(38.23)	52(23.42)	
BMI, n (%)				0.117
Underweight [BMI < 18.5]	66(12.0)	46(14.1)	20(9.0)	
Normal [18.5–23.9]	261 (47.5)	155(47.4)	106(47.7)	
Overweight [BMI ≥ 24]	222 (40.4)	126(38.5)	96(43.2)	
Marital status, n (%)				0.825
Married	504 (91.80)	299(91.44)	205(92.34)	
Single/Widowed	45(8.20)	28(8.56)	17(7.66)	
Residential area, n (%)				0.025
Urban	426 (77.60)	265(81.04)	161(72.52)	
Rural	123 (22.40)	62(18.96)	61(27.48)	
Highest educational qualification, n (%)				0.258
High education	140 (25.50)	88(26.91)	52(23.42)	
Lower and upper secondary	238 (43.35)	143(43.73)	95(42.79)	
Elementary education	138 (25.14)	76(23.24)	62(27.93)	
Less than elementary education	33(6.01)	20(6.12)	13(5.86)	
Occupation, n (%)				0.787
Unemployed	49(8.93)	27(8.26)	22(9.91)	
Manual worker	305 (55.56)	184(56.27)	121(54.50)	
Brain worker	195 (35.52)	116(35.47)	79(35.59)	
Smoking status, n (%)				<0.001
Never-smoker	337 (61.4)	223(68.2)	114(51.4)	
Smoker	212 (38.6)	104(31.8)	108(48.6)	
CCI score	2.61 ± 1.43	2.75 ± 1.37	2.40 ± 1.49	0.005

BMI, body mass index; CCI, charlson comorbidity index.

fever, fatigue, myalgia, cough, score throat, rhinorrhea, nasal obstruction, headache, vertigo, ageusia, sleep disorders, nausea and vomiting, and diarrhea (all P > 0.05) (Table 2). In contrast, the chest tightness and dyspnea in the vaccinated group was significantly lower than that of the unvaccinated group (P = 0.003). Moreover, there were no statistical differences in the number of symptoms between the two groups (P = 0.876).

3.3. Vaccines slightly reduced the complications

In this section, we evaluated the emergent endotracheal intubation complications between the two groups. Most of COVID-19 patients developed hypoxemia in unvaccinated group (74.31 %) and vaccinated group (72.97 %). There were no statistical differences in the incidence of silent hypoxemia between the unvaccinated group and vaccinated group (13.15 % vs. 12.61 %, P = 0.957). Similarly, the ratio of patients with respiratory failure in the unvaccinated group and vaccinated group was also not high, with no statistical differences (29.97 % vs. 22.97 %, P = 0.087, Table 3).

Table 2
Symptom comparison between unvaccinated (n = 327) and vaccinated (n = 222) patients admitted to our hospital between January 2023 and February 2023.

Variables	All sets (n = 549)	Unvaccinated (n = 327)	Vaccinated (n = 222)	P value
Fever, n (%)	491 (89.44)	291(88.99)	200(90.09)	0.787
Fatigue, n (%)	415 (75.59)	256(78.29)	159(71.62)	0.092
Myalgia, n (%)	213 (38.80)	126(38.53)	87(39.19)	0.948
Cough, n (%)	458 (83.42)	273(83.49)	185(83.33)	1.000
Chest tightness and dyspnea, n (%)	278 (50.64)	183(55.96)	95(42.79)	0.003
Score throat, n (%)	159 (28.96)	89(27.22)	70(31.53)	0.318
Rhinorrhea, n (%)	121 (22.04)	65(19.88)	56(25.23)	0.168
Nasal obstruction, n (%)	84 (15.30)	45(13.76)	39(17.57)	0.274
Headache, n (%)	73 (13.30)	43(13.15)	30(13.51)	1.000
Vertigo, n (%)	41(7.47)	26(7.95)	15(6.76)	0.721
Ageusia, n (%)	249 (45.36)	145(44.34)	104(46.85)	0.623
Sleep disorders, n (%)	124 (22.59)	74(22.63)	50(22.52)	1.000
Nausea and vomiting, n (%)	123 (22.40)	76(23.24)	47(21.17)	0.641
Diarrhea, n (%)	137 (24.95)	78(23.85)	59(26.58)	0.533
Number of symptoms	5.47 ± 2.41	5.48 ± 2.34	5.45 ± 2.52	0.876

3.4. Vaccines induced significant increase of ALT and decrease of Cr

Compared with unvaccinated individuals, vaccinated cases had a higher level of ALT (P = 0.003) and decreased level of creatinine (P = 0.009, Table 4). Compared to unvaccinated patients, vaccinated patients displayed no differences in other clinical laboratory indices including ferritin, D-dimer, LDH, CRP, PBL, interleukin-6 (IL-6), ALT, AST, and albumin/total bilirubin (all P > 0.05).

3.5. Vaccinated subjects showed a shorter hospital LoS and reduced mortality and fraction of inspired oxygen

Table 5 showed that there were statistical differences in the inspiratory oxygen fraction between the vaccinated and unvaccinated patients (P = 0.008). It was suggested that vaccinated patients had a shorter hospital LoS compared to unvaccinated cases (11.91 ± 6.99 vs.

Table 3
Comparison of complications between unvaccinated (n = 327) and vaccinated (n = 222) patients in our hospital between January 2023 and February 2023.

Variables	All sets (n = 549)	Unvaccinated (n = 327)	Vaccinated (n = 222)	P value
Hypoxemia, n (%)	405 (73.77)	243(74.31)	162(72.97)	0.802
Silent hypoxemia, n (%)	71(12.93)	43(13.15)	28(12.61)	0.957
Respiratory failure, n (%)	149 (27.14)	98(29.97)	51(22.97)	0.087

Table 4
Comparison of clinical laboratory results between unvaccinated (n = 327) and vaccinated (n = 222) patients admitted to our hospital between January 2023 and February 2023.

Variables	All sets (n = 549)	Unvaccinated (n = 327)	Vaccinated (n = 222)	P value
Ferritin, median (IQR)	604.40[352.35,1258.40]	650.70[372.90,1303.40]	560.80[327.10,1095.40]	0.104
D-dimer (μg/L), median (IQR)	1485.00[624.00,3566.00]	1524.00[646.00,3746.00]	1411.50[572.50,3201.50]	0.355
LDH (mmol/L), median (IQR)	1.95[1.40,2.70]	1.80[1.30,2.70]	2.10[1.50,2.80]	0.175
CRP (mg/L), median (IQR)	24.21[6.83,63.10]	24.76[6.83,62.40]	24.08[6.96,65.60]	0.662
PBL (10^9/L), median (IQR)	0.55[0.33,0.92]	0.53[0.32,0.88]	0.59[0.36,0.98]	0.211
Interleukin-6	6.81[4.54,15.06]	6.91[4.54,14.68]	6.75[4.53,16.10]	0.963
ALT (U/L), median (IQR)	25.00[15.00,46.00]	23.00[14.00,42.00]	27.00[16.00,51.00]	0.003
AST (U/L), median (IQR)	21.00[15.00,33.00]	21.00[15.00,31.00]	22.00[15.00,36.00]	0.229
Albumin/Total bilirubin, median (IQR)	4.33[2.95,6.38]	4.44[2.96,6.42]	4.07[2.95,6.14]	0.420
Creatinine (mg/dL), median (IQR)	79.00[62.00,104.00]	82.00[64.00,110.00]	76.00[60.00,100.00]	0.009

Note. IQR, inter quartile range; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBL, peripheral blood lymphocyte; CRP, C-reactive protein.

Table 5
Analysis of differences in treatment and clinical outcome between unvaccinated (n = 327) and vaccinated (n = 222) patients enrolled from our hospital between January 2023 and February 2023.

Variables	All sets (n = 549)	Unvaccinated (n = 327)	Vaccinated (n = 222)	P value
Fever duration (days), median (IQR)	5.0 [2.0,9.0]	5.0[2.00,9.0]	4.00 [2.0,8.0]	0.266
Antibiotic drugs	533 (97.09)	316(96.64)	217(97.75)	0.616
Hormone drugs	527 (95.99)	318(97.25)	209(94.14)	0.110
Antiviral drugs	259 (47.18)	165(50.46)	94(42.34)	0.075
Inspired oxygen fraction				0.008
<40	396 (72.13)	224(68.50)	172(77.48)	
40–60	81(14.75)	47(14.37)	34(15.32)	
≥60	72(13.11)	56(17.13)	16(7.21)	
Endotracheal intubation	51(9.29)	33(10.09)	18(8.11)	0.525
Hospital LoS (days)	13.31 ± 7.45	14.26 ± 7.61	11.91 ± 6.99	<0.001
Survival status (dead), n (%)	49(8.93)	36(11.01)	13(5.86)	0.038
Disease classification				0.159
Moderate	291 (53.01)	167(51.07)	124(55.86)	
Severe	183 (33.33)	109(33.33)	74(33.33)	
Critically ill	75(13.66)	51(15.60)	24(10.81)	

Note. P/F, PaO2/FiO2; LoS, length of stay.

14.26 ± 7.61, P < 0.001). Additionally, we observed that the mortality rate was significantly decreased in the vaccinated group compared to the unvaccinated group (P = 0.038).

3.6. Effects of vaccines on LoS, severe and critically ill, endotracheal intubation, mortality and inspired oxygen ratio after adjusting age, gender, residential area, smoking and CCI

After correction for age, gender, BMI, residential area, smoking status and CCI score, patients received COVID-19 vaccination showed a decreased LoS by 1.2 days (lnLoS = -0.14, 95 %CI[-0.24,-0.04]; P = 0.005, Table 6) and decreased fraction of inspired oxygen by 40 % (OR: 0.60; 95 %CI[0.40,0.90]; P = 0.013) compared to the unvaccinated cases. Although vaccines seemed to reduce the critically ill, mortality (OR = 0.87; 95 %CI[0.60,1.25]; P = 0.439), mortality (OR = 0.60; 95 % CI[0.30,1.19]; P = 0.141), and endotracheal intubation (OR = 0.96; 95 %CI[0.51,1.82]; P = 0.905), the statistical differences were not significant. See (Table 7).

4. Discussion

There is still a lack of large cohort studies on the changing demographics of hospitalized COVID-19 patients and the evolving risk factors for poor outcomes after vaccination. In this cohort involving 549 hospitalized patients with COVID-19 admitted to our hospital, we evaluated the VE of the vaccines used in mainland China to protect against symptomatic infection. Our data showed that vaccinated patients had a shorter hospital LoS and decreased fraction of inspired oxygen compared to unvaccinated counterparts. Besides, the vaccinated subjects showed decrease in the severe and critically ill, mortality, and endotracheal intubation compared with the unvaccinated counterparts, but the statistical differences were not significant. These proved the efficiency of vaccines used in mainland China.

Vaccine development has been accelerated in order to enhance host immunity to the virus. According to the World Health Organization (WHO) data, by December 2022, 50 vaccines have been approved by at least one country worldwide (Chakraborty et al., 2023), which include whole virus live attenuated or inactivated, protein-based, viral vector, and nucleic acid vaccines (Ndwandwe and Wiysonge, 2021b). As of 1 December 2022, over 13 billion COVID-19 vaccine doses have been administered (Tang et al., 2023). In China, as of 31 December 2022, China has reported more than 3.4 billion cumulative doses of the COVID-19 vaccines (Ma et al., 2023; Sun et al., 2023). In the whole cohort of this study, 222 participants (40.43 %) received at least one dose of COVID-19 vaccine. This may be related to the fact that a large number of aged individuals are excluded from vaccination considering co-morbidities and frailty.

COVID-19 vaccines provide strong protection against hospitalization after being infected with alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529) variants (Firouzabadi et al., 2023). Several post-marketing observational studies have also reported a clear correlation between vaccination and decreased risks of COVID-19 hospitalization (Haas et al., 2021; Sheikh et al., 2021). Tenforde et al. reported an estimated overall vaccine effectiveness of 85 % for mRNA vaccines to prevent COVID-19 hospitalizations (Tenforde et al., 2021a). The effectiveness of COVID-19 vaccines in shortening the hospital LoS has been confirmed in COVID-19 patients aged 18–64 years in Norway (Tenforde et al., 2021b; Whittaker et al., 2022). Older patients underwent vaccination with a mean age of 58.16 ± 17.39 years exhibited a decreased LoS (-2.13 days, CI: 2.73–1.55 days) in the United States (Lee et al., 2023). In our study, multiple linear regression analysis revealed that vaccination significantly shortened the hospital LoS for COVID-19 patients especially for elderly hospitalized patients with COVID-19 (60–80 yrs: OR = 0.18; 95 %CI: [0.06,0.31]; P = 0.005; >80 yrs: OR = 0.31; 95 %CI: [0.17,0.44]; P < 0.001). After correction for age, gender, BMI, residential area, smoking status and CCI score, the hospital LoS decreased by 1.2 days in patients received COVID-19 vaccination when comparing with the unvaccinated subjects. These implied that

Table 6
Multivariable logistic regression analysis of risk factors related to severe/critically ill, mortality, requirement of endotracheal intubation, length of hospital stay, and fraction of inspired oxygen for COVID-19 patients admitted to our hospital between January 2023 and February 2023.

Variables	Severe/ critically ill		Mortality		Endotracheal intubation	
	Binary logistic regression OR[95 %CI; P]	Multiple binary logistic regression OR[95 %CI; P]	Binary logistic regression OR[95 %CI; P]	Multiple binary logistic regression OR[95 %CI; P]	Binary logistic regression OR[95 %CI; P]	Multiple binary logistic regression OR[95 %CI; P]
Age						
<60	–	–	–	–	–	–
60–80	1.80 [1.13,2.88;0.014]	1.76[1.09,2.85;0.022]	1.02[0.41,2.52; 0.974]	0.93[0.35,2.42;0.875]	2.11 (0.78,5.67;0.141)	2.43[0.87,6.81;0.090]
≥80	2.87 [1.74,4.72;<0.001]	2.81 [1.68,4.72;<0.001]	2.37[0.99,5.67; 0.054]	2.42[0.95,6.16;0.065]	2.91 [1.07,7.94;0.036]	3.55 [1.23,10.23;0.019]
Sex: Female	0.89 [0.55,1.13;0.189]	0.70[0.45,1.08;0.105]	0.66[0.33,1.30; 0.227]	0.45[0.20,0.98;0.044]	0.86 [0.46,1.62;0.650]	0.56[0.27,1.16;0.117]
BMI						
Normal	–	–	–	–	–	–
Underweight	0.99 [0.58,1.71;0.982]	1.08[0.62,1.90;0.779]	2.19 [1.03,4.66;0.041]	2.32[1.05,5.12;0.037]	1.81 [0.84,3.88;0.129]	1.95[0.88,4.33;0.100]
Overweight	0.99 [0.69,1.42;0.951]	1.01[0.70,1.46;0.942]	0.61 [0.30,1.24;0.172]	0.62[0.30,1.26;0.184]	0.61 [0.31,1.20;0.150]	0.61[0.31,1.21;0.160]
Resident: Rural	0.75 [0.50,1.13;0.164]	0.94[0.61,1.44;0.777]	0.55 [0.24,1.26;0.158]	0.73[0.30,1.77;0.486]	0.83 [0.40,1.71;0.616]	1.14[0.53,2.47;0.732]
Smoker: YES	0.95 [0.67,1.34;0.775]	0.81[0.54,1.22;0.315]	0.92 [0.50,1.68;0.777]	0.73[0.36,1.48;0.387]	0.57 [0.30,1.09;0.089]	0.40[0.19,0.83;0.013]
CCI score	1.05 [0.93,1.18;0.454]	1.05[0.93,1.19;0.410]	1.29 [1.05,1.58;0.016]	1.29[1.04,1.61;0.023]	1.25 [1.02,1.52;0.031]	1.27[1.02,1.57;0.030]
COVID vaccine: YES	0.83 [0.59,1.16;0.270]	0.87[0.60,1.25;0.439]	0.50 [0.26,0.97;0.041]	0.60[0.30,1.19;0.141]	0.79 [0.43,1.43;0.433]	0.96[0.51,1.82;0.905]

Note. BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; OR, odd ratio; LoS, length of hospital stay.

Table 7
Multivariable logistic regression analysis of risk factors related to severe/critically ill, mortality, requirement of endotracheal intubation, length of hospital stay, and fraction of inspired oxygen for COVID-19 patients admitted to our hospital between January 2023 and February 2023.

Variables	Ln. LoS		Fraction of inspired oxygen	
	Linear regression β [95 %CI; P]	Multiple linear regression β[95 %CI; P]	Ordinal logistic regression OR[95 %CI; P]	Multiple ordinal logistic regression OR[95 %CI; P]
Age				
<60	–	–	–	–
60–80	0.17[0.05,0.30;0.007]	0.18[0.06,0.31;0.005]	1.93[1.09,3.41;0.024]	2.02[1.12,2.64;0.020]
≥80	0.31[0.18,0.45;<0.001]	0.31[0.17,0.44;<0.001]	2.63[1.46,4.74;0.001]	2.73[1.47;5.05;0.001]
Sex: Female	0.02[-0.09,0.12;0.768]	−0.06[-0.17,0.06;0.339]	0.70[0.46,1.06;0.089]	0.54[0.33,0.87;0.011]
BMI				
Normal	–	–	–	–
Underweight	0.15[-0.01,0.30;0.063]	0.15[-0.00,0.30;0.053]	1.54[0.87,2.71;0.136]	1.66[0.92,2.98;0.092]
Overweight	−0.02[-0.13,0.08;0.639]	−0.01[-0.11,0.09;0.792]	0.92[0.62,1.38;0.695]	0.94[0.62,1.41;0.748]
Resident: Rural	−0.12[-0.24,-0.01;0.032]	−0.04[-0.15,0.08;0.505]	0.92[0.59,1.43;0.702]	1.24[0.77,1.99;0.375]
Smoker: YES	−0.09[-0.19,0.01.0.071]	−0.10[-0.21,0.01;0.086]	0.90[0.62,1.31;0.586]	0.72[0.46,1.11;0.139]
CCI score	0.03[-0.01,0.06;0.124]	0.02[-0.01,0.06;0.183]	6.36[4.77,8.47;<0.001]	1.04[0.91,1.20;0.536]
COVID vaccine: YES	−0.18[-0.27,-0.08;<0.001]	−0.14[-0.24,-0.04;0.005]	0.59[0.40,0.87;0.008]	0.60[0.40,0.90;0.013]

Note. BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; OR, odd ratio; LoS, length of hospital stay.

vaccination contributed to the reduced hospital LoS in mainland China. All these Real-World data from the large health system indicated the efficiency of vaccines on attenuating the overall diseases severity.

Vaccines may attenuate disease severity and mortality among COVID-19 patients (Corey et al., 2020; Lipsitch & Dean, 2020; McIntyre et al., 2022; Mark W Tenforde et al., 2021). A study enrolling 1,983 hospitalized COVID-19 patients reported that progression to death after COVID-19 hospitalization was related to a decreased likelihood of vaccination (OR, 0.41; 95 % CI, 0.19–0.88) (Mark W Tenforde et al., 2021). Indeed, COVID-19 related mortality in the elder population is higher as they have higher rates of comorbidities and may experience more severe inflammatory responses (Dadras et al., 2022). Besides, failure of COVID-19 vaccine due to presence of severe diseases was particularly likely to occur in elderly patients with high prevalence of medical comorbidities and multimorbidity who were relatively over-represented in the inpatient settings compared to the general population (Wang et al., 2020). Our findings suggested that the risk of mortality in the vaccinated group reduced by 40 % compared with that of the unvaccinated group, but there were no statistical differences (OR = 0. 3; 95 %CI: [0.30,1.19]; P = 0.141). Consistent with the previous studies (Baden et al., 2021; Polack et al., 2020), our data suggested that COVID-19 vaccines could improve the chest tightness and dyspnea, which were closely related to the reduced risk of mortality. In the future, more studies of a large sample size would prove the efficiency of vaccination in reducing the mortality.

Invasive mechanical ventilation has been reported to be associated with a lower likelihood of vaccination (Mark W Tenforde et al., 2021; Whittaker et al., 2022). In a US-21-site case-control study including 142 patients fully vaccinated with an mRNA vaccine, vaccination was related to mechanical ventilation (M. W. Tenforde et al., 2021). In contrast, in a multicenter cohort study, the 129 fully vaccinated patients (vaccinated with Comirnaty, Spikevax, or Janssen) did not show a lower risk of mechanical ventilation to unvaccinated patients (Bahl et al., 2021). In our study, there was a decreased risk of endotracheal intubation after vaccination when comparing 327 unvaccinated cases to 222 vaccinated patients with COVID-19, but there were no statistical differences. Interestingly, vaccinated patients showed a significant decrease (by 40 %) in the fraction of inspired oxygen compared to the unvaccinated cases. This indicated that vaccines improved the respiratory function. Although our data showed that the vaccination showed a trendy of decrease with no statistical difference, this would be proved by the subsequent studies involving a large sample size.

COVID-19 vaccine doses affect the effectiveness against symptomatic disease caused by the omicron variant or other variants (Polack et al., 2020; Thomas et al., 2021). In a previous study, mRNA vaccines showed a high VE against COVID-19 hospitalization after the third dose (Thompson et al., 2022). Specifically, after two doses, there was a higher protection against COVID-19 related hospitalization after being infected with the Alpha and Delta variants, and the third dose led to greater protection against hospitalization after infection of Omicron variant (Gram et al., 2022). Other studies also published that timely vaccination with the booster dose provided effective protection against COVID-19 outcomes (Huang et al., 2022; Huang et al., 2023; McMenamin et al., 2022). In our study, a total 222 patients received at least one dose (4 doses, n = 3; 3 doses, n = 130; 2 doses, n = 53; 1 dose, n = 36), showing consistent results with these reports. The SARS-CoV-2 omicron is the main variant causing the epidemic wave of COVID-19 between November 2021 and February 2023 in 189 countries (Niu et al., 2023). The eventual cancellation of zero COVID-19 policy in China on December 7, 2022 contributed to an unprecedented large-scale omicron wave in December 2022 together with a sharp rise in influenza incidence in February 2023 (Zeng et al., 2023). This was consistent with the variant type identified in our patients.

For healthcare systems to cope better during a disease X event than during COVID-19, multiple highly specific artificial intelligence (AI) algorithms should be proposed and targeted for solving specific problems (Radanliev & De Roure, 2023). Indeed, AI algorithms have already been used to help mitigate the impact of COVID-19 outbreak (Khan et al., 2021). A healthcare system supported by autonomous AI may use the real-time data on COVID-19 vaccination risk factors for older people to assess adverse events, besides to tackle to the logistical challenges and disruption of complex production and supply chains for vaccine distribution (Radanliev & De Roure, 2022, 2023).

There are some unresolved questions showing the limitations of this study. First, the small sample size in this study limits further assessment of the effect of vaccine type, vaccination dose, time interval between the two vaccine doses, and viral variants on disease progression. Although the vaccination showed efficiency in reducing the mortality and severe and critically ill, the statistical differences were not significant due to a relatively small sample size in this study. Second, immunologic studies have different vaccine types may contribute to product-specific antibody responses after vaccination; however, the association between types of COVID-19 vaccine and risk of COVID-19 hospitalization was not analyzed in this study. Third, this analysis cannot inform whether declining immunity or evasion of immunity by the variants contributes to the low likelihood association between COVID-19 vaccine and disease severity. Fourthly, the current study did not compare the LoS and fraction of inspired oxygen for different doses of vaccination because of the sample size, and we will increase the sample size to investigate the effects in the future.

5. Conclusions

Vaccination with COVID-19 vaccine led to decreased hospital LoS and fraction of inspired oxygen after adjusting age, gender, BMI, residential area, smoking status and CCI score. The vaccination triggered decrease in the severe and critically ill, mortality, and endotracheal intubation compared with the unvaccinated counterparts although there were no statistical differences. The statistical differences would be significant with the increase of the sample size. Finally, it is remarkable that digital healthcare systems should be adequately applied to evaluate the vaccination risk or adverse events for older patients.

6. Ethics approval and consent to participate

The study protocols were approved by the Ethics Committees of the First Affiliated Hospital, Zhejiang University School of Medicine (Approval No.: 2023–0079). Because the study was a retrospective study based on real-world situations, the need to obtain informed consent from eligible patients was waived.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Xiaomei Fang: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Guofang Tao:** Writing – review & editing, Investigation, Data curation. **Hua Zhou:** Writing – review & editing, Investigation, Data curation. **Yuxia Zhou:** Writing – review & editing, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary file.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102632.

References

Baden, L.R., El Sahly, H.M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S.A., Rouphael, N., Creech, C.B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., Janes, H., Follmann, D., Marovich, M., Mascola, J., Polakowski, L., Ledgerwood, J., Graham, B.S., Bennett, H., Pajon, R., Knightly, C., Leav, B., Deng, W., Zhou, H., Han, S., Ivarsson, M., Miller, J., Zaks, T., 2021. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N. Engl. J. Med. 384 (5), 403–416. https://doi.org/10.1056/NEJMoa2035389.

Bahl, A., Johnson, S., Maine, G., Garcia, M.H., Nimmagadda, S., Qu, L., Chen, N.-W., 2021. Vaccination reduces need for emergency care in breakthrough COVID-19 infections: a multicenter cohort study. The Lancet Regional Health-Americas 4, 100065.

Bajema, K.L., Dahl, R.M., Prill, M.M., Meites, E., Rodriguez-Barradas, M.C., Marconi, V. C., Beenhouwer, D.O., Brown, S.T., Holodniy, M., Lucero-Obusan, C., Rivera-Dominguez, G., Morones, R.G., Whitmire, A., Goldin, E.B., Evener, S.L., Tremarelli, M., Tong, S., Hall, A.J., Schrag, S.J., McMorrow, M., Kobayashi, M., Verani, J.R., Surie, D., 2021. Effectiveness of COVID-19 mRNA vaccines against COVID-19-associated hospitalization - five veterans affairs medical centers, united states, february 1-august 6, 2021. MMWR Morb. Mortal. Wkly Rep. 70 (37), 1294–1299. https://doi.org/10.15585/mmwr.mm7037e3.

Chakraborty, C., Bhattacharya, M., Dhama, K., 2023. SARS-CoV-2 vaccines, vaccine development technologies, and significant efforts in vaccine development during the pandemic: the lessons learned might help to fight against the next pandemic. Vaccines (basel) 11 (3). https://doi.org/10.3390/vaccines11030682.

Chen, G.L., Li, X.F., Dai, X.H., Li, N., Cheng, M.L., Huang, Z., Shen, J., Ge, Y.H., Shen, Z. W., Deng, Y.Q., Yang, S.Y., Zhao, H., Zhang, N.N., Zhang, Y.F., Wei, L., Wu, K.Q., Zhu, M.F., Peng, C.G., Jiang, Q., Cao, S.C., Li, Y.H., Zhao, D.H., Wu, X.H., Ni, L., Shen, H.H., Dong, C., Ying, B., Sheng, G.P., Qin, C.F., Gao, H.N., Li, L.J., 2022. Safety and immunogenicity of the SARS-CoV-2 ARCoV mRNA vaccine in Chinese adults: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Microbe 3 (3), e193–e202. https://doi.org/10.1016/s2666-5247(21)00280-9.

Corey, L., Mascola, J.R., Fauci, A.S., Collins, F.S., 2020. A strategic approach to COVID-19 vaccine R&D. Science 368 (6494), 948–950.
Dadras, O., SeyedAlinaghi, S., Karimi, A., Shamsabadi, A., Qaderi, K., Ramezani, M., Mirghaderi, S.P., Mahdiabadi, S., Vahedi, F., Saeidi, S., Shojaei, A., Mehrtak, M., Azar, S.A., Mehraeen, E., Voltarelli, F.A., 2022. COVID-19 mortality and its predictors in the elderly: a systematic review. Health Sci. Rep. 5 (3), e657.
Firouzabadi, N., Ghasemiyeh, P., Moradishooli, F., Mohammadi-Samani, S., 2023. Update on the effectiveness of COVID-19 vaccines on different variants of SARS-CoV-2. Int. Immunopharmacol. 117, 109968 https://doi.org/10.1016/j.intimp.2023.109968.
Gram, M.A., Emborg, H.D., Schelde, A.B., Friis, N.U., Nielsen, K.F., Moustsen-Helms, I.R., Legarth, R., Lam, J.U.H., Chaine, M., Malik, A.Z., Rasmussen, M., Fonager, J., Sieber, R.N., Stegger, M., Ethelberg, S., Valentiner-Branth, P., Hansen, C.H., 2022. Vaccine effectiveness against SARS-CoV-2 infection or COVID-19 hospitalization with the alpha, delta, or omicron SARS-CoV-2 variant: a nationwide Danish cohort study. PLoS Med. 19 (9), e1003992.
Haas, E.J., Angulo, F.J., McLaughlin, J.M., Anis, E., Singer, S.R., Khan, F., Brooks, N., Smaja, M., Mircus, G., Pan, K., Southern, J., Swerdlow, D.L., Jodar, L., Levy, Y., Alroy-Preis, S., 2021. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 397 (10287), 1819–1829. https://doi.org/10.1016/s0140-6736(21)00947-8.
Huang, Z., Xu, S., Liu, J., Wu, L., Qiu, J., Wang, N., Ren, J., Li, Z., Guo, X., Tao, F., Chen, J., Lu, D., Sun, X., Wang, W., 2022. Effectiveness of inactivated and Ad5-nCoV COVID-19 vaccines against SARS-CoV-2 Omicron BA. 2 variant infection, severe illness, and death. BMC Med. 20 (1), 400. https://doi.org/10.1186/s12916-022-02606-8.
Huang, Z., Xu, S., Liu, J., Wu, L., Qiu, J., Wang, N., Ren, J., Li, Z., Guo, X., Tao, F., Chen, J., Lu, D., Wang, Y., Li, J., Sun, X., Wang, W., 2023. Effectiveness of inactivated COVID-19 vaccines among older adults in Shanghai: retrospective cohort study. Nat. Commun. 14 (1), 2009. https://doi.org/10.1038/s41467-023-37673-9.
Khan, M., Mehran, M.T., Haq, Z.U., Ullah, Z., Naqvi, S.R., Ihsan, M., Abbass, H., 2021. Applications of artificial intelligence in COVID-19 pandemic: a comprehensive review. Expert Syst. Appl. 185, 115695 https://doi.org/10.1016/j.eswa.2021.115695.
Lee, S.W., Ma, D., Davoodian, A., Ayutyanont, N., Werner, B., 2023. COVID-19 vaccination decreased COVID-19 hospital length of stay, in-hospital death, and increased home discharge. Prev. Med. Rep. 32, 102152 https://doi.org/10.1016/j.pmedr.2023.102152.
Lipsitch, M., Dean, N.E., 2020. Understanding COVID-19 vaccine efficacy. Science 370 (6518), 763–765.
Ma, C., Huang, C., Wang, W., Song, Y., Jiang, X., Tian, X., Liu, B., Chi, F., Lang, S., Liu, D., Sun, W., Tang, L., Wu, D., Song, Y., Li, J., Rodewald, L., Yin, Z., An, Z., 2023. Effectiveness of inactivated COVID-19 vaccines against delta-variant COVID-19: evidence from an outbreak in inner mongolia autonomous region, China. Vaccines (basel) 11 (2). https://doi.org/10.3390/vaccines11020292.
McIntyre, P.B., Aggarwal, R., Jani, I., Jawad, J., Kochhar, S., MacDonald, N., Madhi, S.A., Mohsni, E., Mulholland, K., Neuzil, K.M., 2022. COVID-19 vaccine strategies must focus on severe disease and global equity. Lancet 399 (10322), 406–410.
McMenamin, M.E., Nealon, J., Lin, Y., Wong, J.Y., Cheung, J.K., Lau, E.H.Y., Wu, P., Leung, G.M., Cowling, B.J., 2022. Vaccine effectiveness of one, two, and three doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong: a population-based observational study. Lancet Infect. Dis. 22 (10), 1435–1443. https://doi.org/10.1016/s1473-3099(22)00345-0.
Mohammed, I., Nauman, A., Paul, P., Ganesan, S., Chen, K.-H., Jalil, S.M.S., Jaouni, S.H., Kawas, H., Khan, W.A., Vattoth, A.L., 2022. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. Hum. Vaccin. Immunother. 18 (1), 2027160.
Ndwandwe, D., Wiysonge, C.S., 2021. COVID-19 vaccines. Curr. Opin. Immunol. 71, 111–116. https://doi.org/10.1016/j.coi.2021.07.003.
Niu, B., Ji, S., Zhao, S., Lei, H., 2023. Timing and magnitude of the second wave of the COVID-19 omicron variant - 189 Countries and territories, november 2021 to february 2023. China CDC Wkly 5 (18), 397–401. https://doi.org/10.46234/ccdcw2023.076.
Palacios, R., Patiño, E.G., de Oliveira Piorelli, R., Conde, M., Batista, A.P., Zeng, G., Xin, Q., Kallas, E.G., Flores, J., Ockenhouse, C.F., Gast, C., 2020. Double-blind, randomized, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of treating healthcare professionals with the adsorbed COVID-19 (inactivated) vaccine manufactured by sinovac - PROFISCOV: a structured summary of a study protocol for a randomised controlled trial. Trials 21 (1), 853. https://doi.org/10.1186/s13063-020-04775-4.
Patel, M.K., Bergeri, I., Bresee, J.S., Cowling, B.J., Crowcroft, N.S., Fahmy, K., Hirve, S., Kang, G., Katz, M.A., Lanata, C.F., L'Azou Jackson, M., Joshi, S., Lipsitch, M., Mwenda, J.M., Nogareda, F., Orenstein, W.A., Ortiz, J.R., Pebody, R., Schrag, S.J., Smith, P.G., Srikantiah, P., Subissi, L., Valenciano, M., Vaughn, D.W., Verani, J.R., Wilder-Smith, A., Feikin, D.R., 2021. Evaluation of post-introduction COVID-19 vaccine effectiveness: summary of interim guidance of the World Health Organization. Vaccine 39 (30), 4013–4024. https://doi.org/10.1016/j.vaccine.2021.05.099.
Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Moreira, E.D., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck Jr., R.W., Hammitt, L.L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Şahin, U., Jansen, K.U., Gruber, W.C., 2020. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N. Engl. J. Med. 383 (27), 2603–2615. https://doi.org/10.1056/NEJMoa2034577.
Radanliev, P., De Roure, D., 2022. Advancing the cybersecurity of the healthcare system with self-optimising and self-adaptative artificial intelligence (part 2). Health Technol (berl) 12 (5), 923–929. https://doi.org/10.1007/s12553-022-00691-6.
Radanliev, P., De Roure, D., 2023. Disease X vaccine production and supply chains: risk assessing healthcare systems operating with artificial intelligence and industry 4.0. Health Technol (berl) 13 (1), 11–15. https://doi.org/10.1007/s12553-022-00722-2.
Rosenberg, E.S., Holtgrave, D.R., Dorabawila, V., Conroy, M., Greene, D., Lutterloh, E., Backenson, B., Hoefer, D., Morne, J., Bauer, U., 2021. New COVID-19 cases and hospitalizations among adults, by vaccination status—New York, May 3–July 25, 2021. Morb. Mortal. Wkly Rep. 70 (34), 1150.
Seiffert, M., Brunner, F.J., Remmel, M., Thomalla, G., Marschall, U., L'Hoest, H., Acar, L., Debus, E.S., Blankenberg, S., Gerloff, C., 2020. Temporal trends in the presentation of cardiovascular and cerebrovascular emergencies during the COVID-19 pandemic in Germany: an analysis of health insurance claims. Clin. Res. Cardiol. 109, 1540–1548.
Sheikh, A., McMenamin, J., Taylor, B., Robertson, C., 2021. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet 397 (10293), 2461–2462. https://doi.org/10.1016/s0140-6736(21)01358-1.
Sun, Y., Li, X., Guo, D., 2023. COVID-19 vaccine hesitancy in China: an analysis of reasons through mixed methods. Vaccines (basel) 11 (3). https://doi.org/10.3390/vaccines11030712.
Tabari, P., Amini, M., Moghadami, M., Moosavi, M., 2020. International public health responses to COVID-19 outbreak: a rapid review. Iran. J. Med. Sci. 45 (3), 157.
Tang, L., Zhang, Y., Wang, F., Wu, D., Qian, Z.H., Zhang, R., Wang, A.B., Huang, C., Wang, H., Ye, Y., Lu, M., Wang, C., Ma, Y.T., Pan, J., Li, Y.F., Lv, X.Y., An, Z., Rodewald, L., Wang, X.Y., Shao, Y.M., Wu, Z.Y., Yin, Z., 2022. Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study. BMJ Open 12 (11), e063919.
Tang, L., Wang, F.Z., Rodewald, L.E., Wang, X.Y., Liu, S.Y., Liu, Q.Q., Wang, X.Q., Wu, D., Li, M.S., Zhang, Q., Shao, Y.M., Huang, L.F., Song, Y.D., Huang, Y., Zeng, X., Liu, L.J., Yang, H., Huang, A.D., Bao, L.M., Zheng, H., Ma, C., Lv, X.Y., Song, L., Ma, Z., Wang, S.G., Ma, H., Guan, W.J., Wu, Z.Y., Zhong, N.S., Yin, Z.D., 2023. Real-world effectiveness of primary series and booster doses of inactivated coronavirus disease 2019 vaccine against omicron BA.2 variant infection in China: a retrospective cohort study. J Infect Dis 228 (3), 261–269. https://doi.org/10.1093/infdis/jiad090.
Telle, K.E., Grøsland, M., Helgeland, J., Håberg, S.E., 2021. Factors associated with hospitalization, invasive mechanical ventilation treatment and death among all confirmed COVID-19 cases in Norway: Prospective cohort study. Scand. J. Public Health 49 (1), 41–47.
Tenforde, M.W., Self, W.H., Adams, K., Gaglani, M., Ginde, A.A., McNeal, T., Ghamande, S., Douin, D.J., Talbot, H.K., Casey, J.D., 2021a. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. J. Am. Med. Assoc. 326 (20), 2043–2054.
Tenforde, M.W., Self, W.H., Adams, K., Gaglani, M., Ginde, A.A., McNeal, T., Ghamande, S., Douin, D.J., Talbot, H.K., Casey, J.D., Mohr, N.M., Zepeski, A., Shapiro, N.I., Gibbs, K.W., Files, D.C., Hager, D.N., Shehu, A., Prekker, M.E., Erickson, H.L., Exline, M.C., Gong, M.N., Mohamed, A., Henning, D.J., Steingrub, J. S., Peltan, I.D., Brown, S.M., Martin, E.T., Monto, A.S., Khan, A., Hough, C.L., Busse, L.W., Ten Lohuis, C.C., Duggal, A., Wilson, J.G., Gordon, A.J., Qadir, N., Chang, S.Y., Mallow, C., Rivas, C., Babcock, H.M., Kwon, J.H., Halasa, N., Chappell, J.D., Lauring, A.S., Grijalva, C.G., Rice, T.W., Jones, I.D., Stubblefield, W. B., Baughman, A., Womack, K.N., Rhoads, J.P., Lindsell, C.J., Hart, K.W., Zhu, Y., Olson, S.M., Kobayashi, M., Verani, J.R., Patel, M.M., 2021b. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. J. Am. Med. Assoc. 326 (20), 2043–2054. https://doi.org/10.1001/jama.2021.19499.
Thomas, S.J., Moreira Jr., E.D., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Polack, F.P., Zerbini, C., Bailey, R., Swanson, K.A., Xu, X., Roychoudhury, S., Koury, K., Bouguermouh, S., Kalina, W.V., Cooper, D., Frenck Jr., R.W., Hammitt, L.L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Yang, Q., Liberator, P., Tresnan, D.B., Mather, S., Dormitzer, P.R., Şahin, U., Gruber, W.C., Jansen, K.U., 2021. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N. Engl. J. Med. 385 (19), 1761–1773. https://doi.org/10.1056/NEJMoa2110345.
Thompson, M.G., Natarajan, K., Irving, S.A., Rowley, E.A., Griggs, E.P., Gaglani, M., Klein, N.P., Grannis, S.J., DeSilva, M.B., Stenehjem, E., Reese, S.E., Dickerson, M., Naleway, A.L., Han, J., Konatham, D., McEvoy, C., Rao, S., Dixon, B.E., Dascomb, K., Lewis, N., Levy, M.E., Patel, P., Liao, I.C., Kharbanda, A.B., Barron, M.A., Fadel, W. F., Grisel, N., Goddard, K., Yang, D.H., Wondimu, M.H., Murthy, K., Valvi, N.R., Arndorfer, J., Fireman, B., Dunne, M.M., Embi, P., Azziz-Baumgartner, E., Zerbo, O., Bozio, C.H., Reynolds, S., Ferdinands, J., Williams, J., Link-Gelles, R., Schrag, S.J., Verani, J.R., Ball, S., Ong, T.C., 2022. Effectiveness of a third dose of mrna vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance - VISION network, 10 states, august 2021-january 2022. MMWR Morb. Mortal. Wkly Rep. 71 (4), 139–145. https://doi.org/10.15585/mmwr.mm7104e3.
Voysey, M., Clemens, S.A.C., Madhi, S.A., Weckx, L.Y., Folegatti, P.M., Aley, P.K., Angus, B., Baillie, V.L., Barnabas, S.L., Bhorat, Q.E., Bibi, S., Briner, C., Cicconi, P., Collins, A.M., Colin-Jones, R., Cutland, C.L., Darton, T.C., Dheda, K., Duncan, C.J.A., Emary, K.R.W., Ewer, K.J., Fairlie, L., Faust, S.N., Feng, S., Ferreira, D.M., Finn, A., Goodman, A.L., Green, C.M., Green, C.A., Heath, P.T., Hill, C., Hill, H., Hirsch, I., Hodgson, S.H.C., Izu, A., Jackson, S., Jenkin, D., Joe, C.C.D., Kerridge, S., Koen, A., Kwatra, G., Lazarus, R., Lawrie, A.M., Lelliott, A., Libri, V., Lillie, P.J., Mallory, R.,

Mendes, A.V.A., Milan, E.P., Minassian, A.M., McGregor, A., Morrison, H., Mujadidi, Y.F., Nana, A., O'Reilly, P.J., Padayachee, S.D., Pittella, A., Plested, E., Pollock, K.M., Ramasamy, M.N., Rhead, S., Schwarzbold, A.V., Singh, N., Smith, A., Song, R., Snape, M.D., Sprinz, E., Sutherland, R.K., Tarrant, R., Thomson, E.C., Török, M.E., Toshner, M., Turner, D.P.J., Vekemans, J., Villafana, T.L., Watson, M.E.E., Williams, C.J., Douglas, A.D., Hill, A.V.S., Lambe, T., Gilbert, S.C., Pollard, A.J., 2021. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397 (10269), 99–111. https://doi.org/10.1016/s0140-6736(20)32661-1.

Wang, L., Lv, Q., Zhang, X., Jiang, B., Liu, E., Xiao, C., Yu, X., Yang, C., Chen, L., 2020. The utility of MEWS for predicting the mortality in the elderly adults with COVID-19: a retrospective cohort study with comparison to other predictive clinical scores. PeerJ 8, e10018.

Wats, K., Rodriguez, D., Prins, K.W., Sadiq, A., Fogel, J., Goldberger, M., Moskovits, M., Tootkaboni, M.P., Shani, J., Jacob, J., 2021. Association of right ventricular dysfunction and pulmonary hypertension with adverse 30-day outcomes in COVID-19 patients. Pulmonary Circulation 11 (2), 20458940211007040.

Whittaker, R., Kristofferson, A.B., Salamanca, B.V., Seppälä, E., Golestani, K., Kvåle, R., Watle, S.V., Buanes, E.A., 2022. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. Clin. Microbiol. Infect. 28 (6), 871–878.

Yu, X., Li, N., 2021. Understanding the beginning of a pandemic: China's response to the emergence of COVID-19. J. Infect. Public Health 14 (3), 347–352. https://doi.org/10.1016/j.jiph.2020.12.024.

Zeng, X., Xie, Y., Yang, X., Peng, Z., Tang, J., Yang, L., Lin, S., Han, J., Zhang, Y., Wang, D., 2023. SARS-CoV-2 surveillance through china influenza surveillance information system - China, december 1, 2022 to february 12, 2023. China CDC Wkly 5 (7), 152–158. https://doi.org/10.46234/ccdcw2023.027.

Zhang, Y., Cui, Y., Shen, M., Zhang, J., Liu, B., Dai, M., et al., (2020). Comorbid diabetes mellitus was associated with poorer prognosis in patients with COVID-19: a retrospective cohort study. MedRxiv, 2020.2003. 2024.20042358.

Zhang, L., Zhu, F., Xie, L., Wang, C., Wang, J., Chen, R., Jia, P., Guan, H., Peng, L., Chen, Y., 2020a. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan China. Annals of Oncology 31 (7), 894–901.

Zheng, C., Shao, W., Chen, X., Zhang, B., Wang, G., Zhang, W., 2022. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. Int. J. Infect. Dis. 114, 252–260. https://doi.org/10.1016/j.ijid.2021.11.009.