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Coronavirus Pandemic

Real-world effectiveness of inactivated vaccine on COVID-19 patients with comorbidities

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Abstract

Introduction: Patients with underlying diseases do not respond adequately to vaccines. Thus, continued research on the effects of vaccination in patients with comorbidities is crucial to evaluate the necessity of vaccination in this population. This study assessed the protective effects of inactivated vaccines on the severity and prognosis of COVID-19 in patients with comorbidities.

Methodology: A real-world retrospective cohort study was conducted from April 7, 2022, to June 6, 2022, at the Fudan University Pudong Medical Center. The collected data included demographic characteristics, symptoms, clinical severity, and outcomes of the COVID-19 patients.

Results: A total of 3,996 indigenous confirmed cases and asymptomatic infections with the Omicron variant were enrolled. Of these, 1322 (33.1%) patients had chronic comorbidities. Compared to others, COVID-19 patients with comorbidities were older, had lower vaccination rates, longer days of nucleic acid conversion and hospitalization, and a higher incidence of severe-critical illness and composite endpoint. Multivariable analyses suggested that in the comorbidity group, two-dose- (odds ratio [OR] 0.38, 95% CI 0.24–0.60; OR 0.20, 95% CI 0.08–0.51) and three-dose vaccinated patients (OR 0.26, 95% CI 0.14–0.47; OR 0.21, 95% CI 0.08–0.58) had a lower risk of aggravation and the composite endpoint; similar results were observed in the non-comorbidity group.

Conclusions: Two or more doses of inactivated vaccines could prevent deterioration and poor prognosis in Omicron-infected patients, regardless of the presence of an underlying disease. Our findings support maximizing coverage with inactivated vaccines in highly vaccinated populations, such as those in China.

Key words: COVID-19; omicron variant; vaccination; comorbidity; severity; prognosis.

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is caused by the long-lasting and unstable Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. This virus has not been synonymous with safe infection, mild symptoms, or a low population mortality burden; indeed, certain patients develop severe or even critical illnesses [2,3]. Evidence suggests that either mRNA or inactivated vaccines are less effective and durable in preventing Omicron but offer protection against severe diseases and adverse events [4–6].

COVID-19 patients with comorbidities have a worse prognosis than those without comorbidities, and the prognosis worsens as the number of comorbidities increases [7–10]. Therefore, prioritization of SARS-CoV-2 vaccination in populations with underlying diseases is warranted [11]. However, it is concerning that patients with diabetes and tumors, especially those with underlying immunosuppression, will not generate an appropriate immune response to vaccination, resulting in diminished vaccine protection [8,12–15]. Continued research on the effect of the vaccine on COVID-19 patients with comorbidities is crucial to

assess the necessity of vaccination in this population [16].

In April 2022, an outbreak of COVID-19 occurred in Shanghai, with the dominant strains being Omicron BA.2 and BA.2.2. The Fudan University Pudong Medical Center, designated for COVID-19 management, is tasked with the admission and treatment of patients with COVID-19 in this area. Therefore, we conducted a real-world retrospective cohort study at this extensive medical center to assess the impact of inactivated whole-virus vaccines on the severity and outcomes of COVID-19 among patients with comorbidities.

Methodology

Patients and study design

Confirmed cases and asymptomatic infections of the Omicron variant were admitted to Fudan University Pudong Medical Center from April 7, 2022, to June 6, 2022. We conducted a retrospective cohort study to assess the protective effects of inactivated vaccines on the severity and prognosis of COVID-19 in patients with comorbidities. The primary vaccines administered in Shanghai are inactivated (Sinovac, Wuhan; Sinopharm, Wuhan; and Sinopharm, Beijing, China). The inclusion criteria encompassed confirmed cases and asymptomatic infections with the Omicron variants BA.2 and BA.2.2, whereas the exclusion criteria included significant gaps in medical records, vaccination with non-inactivated vaccines, suspected cases, and imported cases. This study received approval from the Shanghai Pudong Hospital Research Committee (No.YJXG-04). As data were collected retrospectively from patient records, the requirement for informed consent was waived.

We divided the comorbid and non-comorbid groups into subgroups based on vaccination status. Owing to the limited efficacy of the one-dose vaccine, we combined the unvaccinated and one-dose vaccine subgroups into no- or one-dose vaccine subgroups.

Case definition

Referring to the "Treatment protocol for novel coronavirus pneumonia (trial version 9)," patients with an epidemiological history, clinical symptoms, and serological or etiological evidence were defined as "confirmed cases" [17], whereas those with serological or etiological evidence but no clinical symptoms were defined as "asymptomatic infections" [18]. The confirmed cases were classified as mild, moderate, severe, or critical. To meet the sample requirements for statistical analysis, we combined these categories as asymptomatic-mild, moderate, and severe-critical.

Data collection

Data on demographic and clinical characteristics were extracted from medical records and double-verified by the investigators. The indicators included demographic factors such as sex, age, patient condition, comorbidities, and vaccination status; clinical features like common symptoms and disease severity; treatments comprising herbal remedies, invasive ventilation, and intensive care unit (ICU) admission; and outcomes, specifically cure and death. The potential symptoms encompassed fever, cough, fatigue, nasal congestion, runny nose, sore throat, headache, muscle or body aches, and diarrhea [4,19]. Comorbidities were confirmed based on the patient's self-report upon admission and included hypertension, other cardiovascular diseases, cerebrovascular diseases, diabetes, chronic respiratory diseases, chronic kidney failure, malignancy, and Alzheimer's disease [7].

Observed outcomes

The primary endpoint was a composite indicator of ICU admission, invasive ventilation, or death [7]. The secondary endpoints included symptoms, disease severity, days of nucleic acid conversion, and hospitalization.

Statistical analysis

Data were analyzed using SPSS ver. 22.0 (IBM Corp., Armonk, New York, USA). Baseline characteristics and procedural outcomes are presented as proportions of categorical variables, whereas continuous variables are expressed as means with standard deviations or medians with interquartile ranges. Statistical analysis involved the chi-square test or Fisher's exact test for comparing categorical variables and the one-way analysis of variance or the Kruskal-Wallis test for comparing continuous variables among groups based on their distribution profiles. The protective effect of inactivated vaccines was evaluated through univariate and multivariate logistic regression analyses stratified by chronic underlying conditions. Adjustment covariates included sex, age, and herbal treatment (when analyzing the composite endpoint). Participants were classified into three groups according to vaccination status. The significance levels were set at $\alpha = 0.05$ for the initial tests and $\alpha = 0.10$ for the normality tests.

Results

Characteristics of subjects with or without comorbidity

Between April 7, 2022, and June 6, 2022, a total of 3,996 individuals were confirmed as locally transmitted cases or asymptomatic carriers of the Omicron variant. Of these, 1,322 (33.1%) reported having at least one chronic comorbidity, such as hypertension (22.8%), cardiovascular disease (5.4%), and diabetes mellitus (7.6%), among others. The vaccination statuses were distributed as follows: 47.5% were either unvaccinated or received only one dose, 28.6% were fully vaccinated with two doses, and 23.8% had received three doses. Additionally, 1,777 (44.5%) patients were treated with herbal medicines. The majority of patients exhibited symptoms including runny nose, cough, or fever, whereas 57 (1.4%) experienced severe critical illness. A total of 130 patients encountered adverse outcomes, corresponding to a mortality rate of 2.0% (79/3996), as shown in Table 1.

Compared with others, COVID-19 patients with comorbidities were older, had lower vaccination rates, longer days of nucleic acid conversion and hospitalization, and a higher incidence of severe critical illness and composite endpoints involving mechanical ventilation, ICU admission, and mortality (Table 1).

Characteristics of patients with different vaccination levels

Regardless of the underlying disease status, most patients who received no or only one dose of the vaccine were older adults and had longer days to nucleic acid conversion and hospitalization, with higher rates of

Table 1. Characteristics of subjects with or without comorbidity.

Basic features	Total (n = 3996)	Non-comorbidity (n = 2674)	Comorbidity (n = 1322)	*p*
Age (years)				< 0.001
< 60	2002 (50.1)	1781 (66.6)	221 (16.7)	
≥ 60	1994 (49.9)	893 (33.4)	1101 (83.3)	
Sex (M:F)	1995: 2001	1292: 1382	703: 619	0.004
Hypertension				-
None	3085 (77.2)	-	411 (31.1)	
Mild	712 (17.8)	-	712 (53.9)	
Moderate or severe	199 (5.0)	-	199 (15.1)	
Cardiovascular diseases	216 (5.4)	-	216 (16.3)	-
Diabetes	304 (7.6)	-	304 (23.0)	-
Chronic respiratory diseases	137 (3.4)	-	137 (10.4)	-
Cerebrovascular disease	212 (5.3)	-	212 (16.0)	-
Alzheimer's disease	11 (0.3)	-	11 (0.8)	-
Chronic renal failure	59 (1.5)	-	59 (4.5)	-
Tumor history	150 (3.8)	-	150 (11.3)	-
Vaccination				< 0.001
No or 1 dose	1900 (47.5)	1001 (37.4)	899 (68.0)	
2 doses	1143 (28.6)	907 (33.9)	236 (17.9)	
3 doses	953 (23.8)	766 (28.6)	187 (14.1)	
Common symptoms				
Fever	880 (22.0)	620 (23.2)	260 (19.7)	0.012
Cough	1504 (37.6)	951 (35.6)	553 (41.8)	< 0.001
Fatigue	88 (2.2)	56 (2.1)	32 (2.4)	0.508
Nasal congestion	227 (5.7)	177 (6.6)	50 (3.8)	< 0.001
Runny nose	3884 (97.2)	2608 (97.5)	1276 (96.5)	0.068
Sore throat	582 (14.6)	406 (15.2)	176 (13.3)	0.115
Headache	152 (3.8)	112 (4.2)	40 (3.0)	0.071
Muscle or body aches	163 (4.1)	110 (4.1)	53 (4.0)	0.875
Diarrhea	86 (2.2)	38 (1.4)	48 (3.6)	< 0.001
COVID-19				< 0.001
Asymptomatic-mild	3511 (87.9)	2454 (91.8)	1057 (80.0)	
Moderate	428 (10.7)	201 (7.5)	227 (17.2)	
Severe-critical	57 (1.4)	19 (0.7)	38 (2.9)	
Herbal Treatment	1777 (44.5)	1151 (43.0)	626 (47.4)	< 0.010
Nucleic acid conversion (days)	6 (1-37)	6 (1-36)	7 (1-37)	< 0.001
Hospitalization (days)	9 (1-39)	8 (1-38)	10 (1-39)	< 0.001
Admission to ICU	65 (1.6)	16 (0.6)	49 (3.7)	< 0.001
Invasive ventilation	32 (0.8)	10 (0.4)	22 (1.7)	< 0.001
Deaths	79 (2.0)	19 (0.7)	60 (4.5)	< 0.001
Composite end-point	130 (3.3)	34 (1.3)	96 (7.3)	< 0.001

ICU: intensive care unit.

Table 2. Characteristics of patients without comorbidity at different vaccination levels.

Basic features	No or 1-dose group (n = 1001)	2-dose group (n = 907)	3-dose group (n = 766)	*p*
Age (years)				< 0.001
< 60	446 (44.6)	719 (79.3)	616 (80.4)	
≥ 60	555 (55.4)	188 (20.7)	150 (19.6)	
Sex (M:F)	452: 549	424: 483	416: 350	< 0.001
Common symptoms				
Fever	264 (26.4)	206 (22.7)	150 (19.6)	0.003
Cough	337 (33.7)	337 (37.2)	277 (36.2)	0.260
Fatigue	24 (2.4)	25 (2.8)	7 (0.9)	0.022
Nasal congestion	46 (4.6)	76 (8.4)	55 (7.2)	0.003
Runny nose	967 (96.6)	888 (97.9)	753 (98.3)	0.050
Sore throat	133 (13.3)	154 (17.0)	119 (15.5)	0.077
Headache	29 (2.9)	52 (5.7)	31 (4.0)	0.008
Muscle or body aches	30 (3.0)	47 (5.2)	33 (4.3)	0.053
Diarrhea	20 (2.0)	12 (1.3)	6 (0.8)	0.097
COVID-19				< 0.001
Asymptomatic-mild	876 (87.5)	859 (94.7)	719 (93.9)	
Moderate	108 (10.8)	47 (5.2)	46 (6.0)	
Severe-critical	17 (1.7)	1 (0.1)	1 (0.1)	
Herbal Treatment	319 (31.9)	394 (43.4)	438 (57.2)	< 0.001
Nucleic acid conversion (days)	7 (1-36)	5 (1-22)	5 (1-26)	< 0.001
Hospitalization (days)	10 (1-38)	8 (1-36)	7 (1-37)	< 0.001
Admission to ICU	13 (1.3)	2 (0.2)	1 (0.1)	0.001
Invasive ventilation	9 (0.9)	1 (0.1)	0 (0.0)	0.001
Deaths	18 (1.8)	0 (0.0)	1 (0.1)	< 0.001
Composite end-point	30 (3.0)	2 (0.2)	2 (0.3)	< 0.001

ICU: intensive care unit.

Table 3. Characteristics of patients with comorbidity at different vaccination levels.

Basic features	No or 1-dose group (n = 899)	2-dose group (n = 236)	3-dose group (n = 187)	*p*
Age (years)				< 0.001
< 60	71 (7.9)	72(30.5)	78 (41.7)	
≥ 60	828 (92.1)	164 (69.5)	109 (58.3)	
Sex (M:F)	471: 428	121: 115	111: 76	0.179
Common symptoms				
Fever	169 (18.8)	49 (20.8)	42 (22.5)	0.465
Cough	384 (42.7)	95 (40.3)	74 (39.6)	0.631
Fatigue	23 (2.6)	8 (3.4)	1 (0.5)	0.082
Nasal congestion	22 (2.4)	13 (5.5)	15 (8.0)	< 0.001
Runny nose	857 (95.3)	233 (98.7)	186 (99.5)	0.002
Sore throat	91 (10.1)	47 (19.9)	38 (20.3)	< 0.001
Headache	20 (2.2)	11 (4.7)	9 (4.8)	0.046
Muscle or body aches	31 (3.4)	8 (3.4)	14 (7.5)	0.033
Diarrhea	42 (4.7)	5 (2.1)	1 (0.5)	0.009
COVID-19				< 0.001
Asymptomatic-mild	671 (74.6)	212 (89.8)	174 (93.0)	
Moderate	192 (21.4)	23 (9.7)	12 (6.4)	
Severe-critical	36 (4.0)	1 (0.4)	1 (0.5)	
Herbal Treatment	417 (46.4)	113 (47.9)	96 (51.3)	0.460
Nucleic acid conversion (days)	8 (1-35)	6 (1-35)	5 (1-37)	< 0.001
Hospitalization (days)	11 (1-39)	9 (1-37)	7 (1-38)	< 0.001
Admission to ICU	44 (4.9)	3 (1.3)	2 (1.1)	0.004
Invasive ventilation	18 (2.0)	3 (1.3)	1 (0.5)	0.245
Deaths	56 (6.2)	2 (0.8)	2 (1.1)	< 0.001
Composite end-point	87 (9.7)	5 (2.1)	4 (2.1)	< 0.001

ICU: intensive care unit.

Table 4. Univariate and multivariate analysis of risk factors of the severity.

Variable name	Non-comorbidity		Comorbidity	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Univariate analysis				
Sex (male) [a]	0.79 (0.60, 1.05)	0.100	0.76 (0.58, 1.00)	0.053
Age (< 60 years) [a]	4.51 (3.37, 6.04)	< 0.001	3.06 (1.87, 5.00)	< 0.001
Vaccination (no or 1-dose) [a]				
2 doses	0.39 (0.28, 0.55)	< 0.001	0.33 (0.21, 0.52)	< 0.001
3 doses	0.46 (0.32, 0.65)	< 0.001	0.22 (0.12, 0.39)	< 0.001
Multivariate analysis [b]				
Sex (male) [a]	0.73 (0.55, 0.97)	0.032	0.72 (0.55, 0.95)	0.021
Age (< 60 years) [a]	3.99 (2.91, 5.45)	< 0.001	2.03 (1.21, 3.39)	0.007
Vaccination (no or 1-dose) [a]				
2 doses	0.63 (0.44, 0.91)	0.014	0.38 (0.24, 0.60)	< 0.001
3 doses	0.74 (0.51, 1.08)	0.120	0.26 (0.14, 0.47)	< 0.001

[a] Reference group of the variable is noted in parentheses. [b] Adjusted for sex and age in the multivariable models.

severe-critical illness and composite endpoints (Tables 2 and 3).

Univariable and multivariable analysis of the risk factors of the severity

Owing to the presence of only one severe-critical case in the two-dose and three-dose vaccine subgroups, these cases were combined with moderate cases to establish a moderate-severe-critical disease category for the logistic regression model, which utilized disease severity as the dependent variable. The model indicated that in the non-comorbidity group, being female (OR 0.73, 95% CI 0.55–0.97) and receiving two doses of the vaccine (OR 0.63, 95% CI 0.44–0.91) were factors associated with a reduced risk of disease aggravation, whereas individuals aged 60 years or older (OR 3.99, 95% CI 2.91–5.45) exhibited an increased risk. In the comorbidity group, being female (OR 0.72, 95% CI 0.55–0.95), receiving two doses (OR 0.38, 95% CI 0.24–0.60), and three doses of the vaccine (OR 0.26, 95% CI 0.14–0.47) were associated with a decreased risk of aggravation, whereas those aged 60 years or older (OR 2.03, 95% CI 1.21–3.39) faced a higher risk (Table 4).

Univariable and multivariable analysis of the risk factors of the composite endpoint

The binary logistic regression model revealed that within the non-comorbidity group, age (OR 5.07, 95% CI 2.03–12.69) was significantly associated with an increased risk of the composite endpoint. Conversely, two-dose vaccination (OR 0.13, 95% CI 0.03–0.54) and three-dose vaccination (OR 0.15, 95% CI 0.04–0.66) demonstrated a protective effect against this risk. In the comorbidity group, herbal treatment (OR 0.60, 95% CI 0.39–0.93), two-dose vaccination (OR 0.20, 95% CI 0.08–0.51), and three-dose vaccination (OR 0.21, 95% CI 0.08–0.58) were also found to reduce the risk of the composite endpoint (Table 5).

Discussion

During the epidemic, 3996 COVID-19 patients were admitted. Of them, 1322 patients (33.1%) had at least one underlying disease. Similar to the findings of other studies, patients with any comorbidity had greater disease severity and poorer clinical outcomes than did those without [7–10]. Weak resistance and lack of

Table 5. Univariate and multivariate analysis of the risk factors of the composite end-point.

Variable name	Non-comorbidity		Comorbidity	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Univariate analysis				
Sex (male) [a]	0.65 (0.33, 1.29)	0.221	0.76 (0.50, 1.16)	0.207
Age (< 60 years) [a]	9.58 (3.95, 23.21)	< 0.001	3.19 (1.38, 7.39)	0.007
Herbal treatment (no) [a]	0.63 (0.31, 1.30)	0.209	0.59 (0.38, 0.91)	0.016
Vaccination (no or 1-dose) [a]				
2 doses	0.07 (0.02, 0.30)	< 0.001	0.20 (0.08, 0.50)	0.001
3 doses	0.09 (0.02, 0.36)	0.001	0.20 (0.07, 0.56)	0.002
Multivariate analysis [b]				
Age (< 60 years) [a]	5.07 (2.03, 12.69)	0.001		
Herbal treatment (no) [a]			0.60 (0.39, 0.93)	0.022
Vaccination (no or 1-dose) [a]				
2 doses	0.13 (0.03, 0.54)	0.005	0.20 (0.08, 0.51)	0.001
3 doses	0.15 (0.04, 0.66)	0.012	0.21 (0.08, 0.58)	0.002

[a] Reference group of the variable is noted in parentheses. [b] Adjusted for sex, age, and herbal treatment in the multivariable models.

tolerance owing to organic weakness in patients with comorbidities are significant factors affecting the prognosis following Omicron infection [20]. Nevertheless, owing to a lack of confidence in the effectiveness of vaccination, only 17.9% of patients with multiple diseases received two-dose vaccines, and 14.1% received a booster, values much lower than the local average [21,22].

We confirmed that two or more doses of the inactivated vaccine protected against deterioration and poor prognosis, regardless of the presence or absence of an underlying disease. Compared to mRNA vaccines, inactivated vaccines induce higher expression of structural protein-specific CD4+ and CD8+ T cell responses [14,23–25]. Notably, T-cell responses may play an essential role in suppressing disease severity, thus effectively preventing adverse outcomes in COVID-19 [26–30]. Furthermore, we observed that the inactivated vaccine demonstrated a greater impact on reducing severity and a lesser effect on poor outcomes in COVID-19 patients with underlying diseases than it did in those without. Not surprisingly, although vaccination can directly modulate severity through a specific immune response, COVID-19-related clinical outcomes are further influenced by underlying diseases. Moreover, our data indicate that the two- and three-dose vaccines offer comparable protective effects in COVID-19 patients. This similarity may be attributed to the protection duration of the two-dose inactivated vaccine, which extends up to 180 days, with most patients remaining within this protection window during the COVID-19 outbreak in Shanghai [31,32]. However, with a time-dependent decline in antibodies, booster shots can improve plasma neutralization and help maintain extensively neutralizing antibodies at certain levels. Given the established tolerable safety profile of vaccines in special populations, patients with comorbidities should be encouraged to receive adequate vaccination whenever possible [33].

Furthermore, the results demonstrated that herbal therapy had a protective effect on the prognosis of patients with comorbidities. Cytokine storm, an overactive immune response characterized by the release of various mediators, such as interferons and interleukins, is one of the main pathological features of COVID-19 [34]. Some studies have shown that COVID-19 patients with underlying diseases are more likely to experience a cytokine storm [35–37]. Herbal therapy can reduce lung inflammation and injury by inhibiting the expression of pro-inflammatory factors [38,39]. Therefore, traditional Chinese medicines such as Jinhua Qing Gan granules and Huoxiang Zhengqi soft capsules are recommended for the individualized treatment of COVID-19 [40].

This study presents limitations. First, research based on a single center is subject to some selective bias, and multicenter studies are warranted. Second, as the majority of patients in this study were administered inactivated vaccines, we focused our evaluation solely on them.

Conclusions

Two or more doses of inactivated vaccines can prevent deterioration and poor prognosis in patients infected with the Omicron variant, regardless of whether they have an underlying disease. Promoting vaccination among individuals with comorbidities would be advantageous. Our findings advocate for maximizing coverage with inactivated vaccines in populations with high vaccination rates, such as those in China.

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Authors' Contributions

Study conception and design: Li-Li Gao, Hao Zhang; Administrative support: Wu-Jun Xiong, Li-Li Gao; Data acquisition: All authors; Data analysis: Hao Zhang, Hua-Fang Yan; Drafting the article or revising it critically for important intellectual content: Hao Zhang, Hua-Fang Yan; Final approval of the version: All authors.

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