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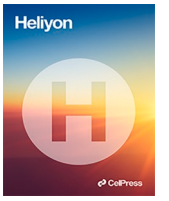

Clinical characteristics, outcomes, and risk factors of SARS-CoV-2 breakthrough infections among 572 fully vaccinated (BBIBP-CorV) hospitalized patients

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ABSTRACT

Background: Breakthrough infections have been widely reported in vaccinated individuals. However, the clinical characteristics, outcomes, and risk factors of SARS-CoV-2 breakthrough infections among fully vaccinated (BBIBP-CorV) hospitalized patients have not yet been fully elucidated.

Methods: In the single-center cohort study conducted at Xiangya Hospital of Central South University, we enrolled the hospitalized COVID-19 patients who had received full (2 doses) vaccination with the BBIBP-CorV vaccine between December 5, 2022, and January 31, 2023. We collected and analyzed information related to clinical characteristics, laboratory results, treatments, outcomes and prognostic data. Univariate and multivariable Cox regression were performed to assess the impact of clinical characteristics and laboratory results on the composite outcome (including the initiation of endotracheal intubation, non-invasive respiratory support, intensive care unit admission, and all-cause death).

Results: A total of 572 COVID-19 hospitalized patients with fully vaccinated (BBIBP-CorV) were included. The median age of the patients was 66 years (IQR 53, 74). The most common symptoms included fever (347 [60.7 %]), dry cough (401 [70.1 %]), and expectoration (333 [58.2 %]). Among those with pre-existing chronic comorbidities, 44.2 % had hypertension and 20.5 % had diabetes. Laboratory tests revealed that the majority of patients (425/549 [77.4 %]) had normal white blood cell counts. Composite outcome occurred in 11.9 % of patients, with 96.7 % of patients discharged and 3.3 % of patients died. Multivariate Cox regression analyses suggested that the NLR >4 (adjusted HR, 5.50 [95%CI: 1.56–19.47]; P = 0.008), D-dimer >0.5 mg/ml (adjusted

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HR, 2.17 [95%CI: 1.03–4.59]; P = 0.042) and procalcitonin >0.1 ng/ml (adjusted HR, 3.22 [95% CI: 1.38–7.52]; P = 0.007) were independently associated with the composite outcome.
Conclusion: Breakthrough infection after being fully vaccinated (BBIBP-CorV) is more likely to occur in older patients and patients with pre-existing chronic comorbidities. NLR >4, D-dimer >0.5 mg/ml and procalcitonin >0.1 ng/ml were independent risk factors for composite outcome.

1. Introduction

The COVID-19 epidemic has rapidly spread worldwide, placing a significant strain on limited healthcare resources with more than 760 million confirmed cases and more than 6.8 million deaths until March 19, 2023 [1]. In an effort to control the pandemic, the World Health Organization (WHO) has granted Emergency Use Listing (EUL) to 11 different vaccines, including 4 types of protein subunit vaccines, RNA vaccines, non replicating viral vector vaccines, and inactivated vaccines [2]. These vaccines offer outstanding protection against COVID-19 [3]. However, breakthrough infections still transpire in those vaccinated individuals [4–7]. Therefore, it holds great significance to elucidate the clinical characteristics and prognostic risk factors of COVID-19 patients with breakthrough infection.

BBIBP-CorV (Sinopharm) is a widely utilized inactivated vaccine, particularly in China [8]. The BBIBP-CorV vaccine is produced by infecting vero cell with SARS-CoV-2, screening for strains, purifying and culturing them, and then inactivating the virus through in vitro culture. This process helps to preserve the integrity of the viral particles, which act as immunogens in the BBIBP-CorV vaccine [9]. BBIBP-CorV was reported to reduce the rate of hospitalization for fully vaccinated participants infected with the Delta and Omicron

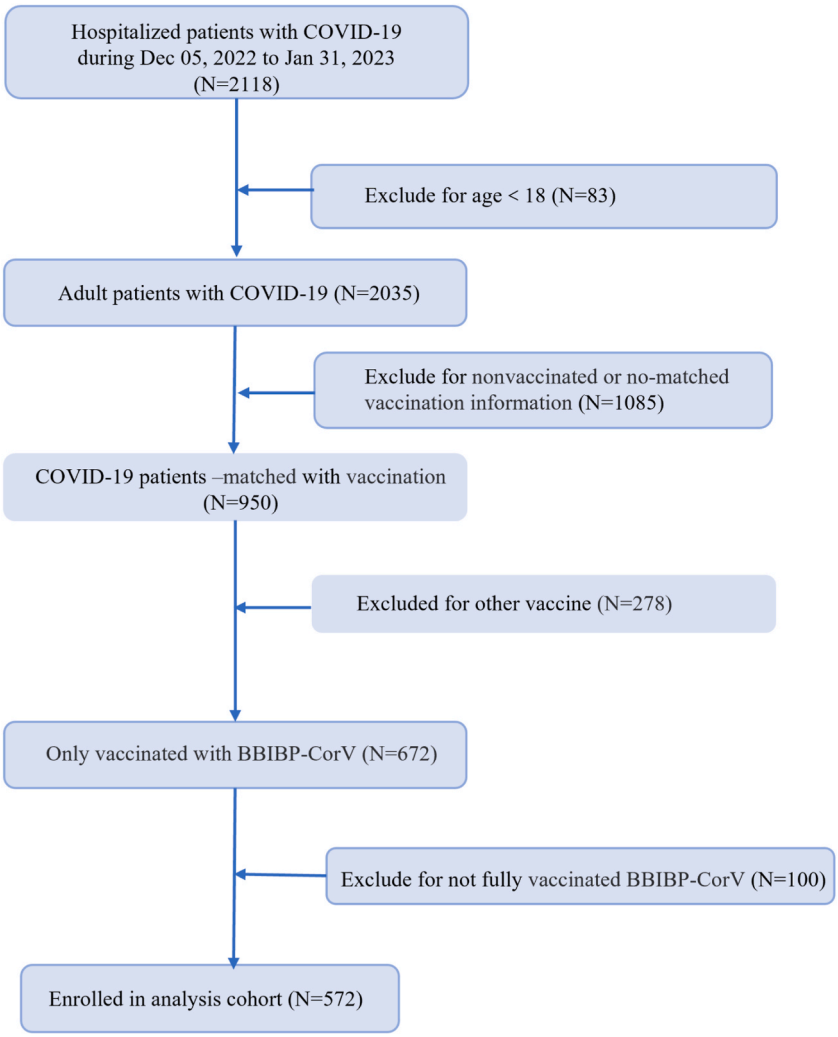

Fig. 1. The flow diagram depicting the patients screening process, including the criteria of inclusion and exclusion.

variants in United Arab Emirates [10]. Besides, a real-world study in Morocco reported that vaccine effectiveness was 88 % (95%CI, 84–91) during the first month, 87 % (95%CI: 83–90) during the second and third month, and more than 60 % even after five months against COVID-19 associated severe and critical hospitalization [11]. Consistently, a case-control study in Iran demonstrated that the maximum effectiveness of BBIBP-CorV was 85 % (95%CI: 77–91 %) in preventing regular hospitalization 151 days after receiving the second dose [12]. However, these studies focused primarily on the vaccine effectiveness against hospitalization, and failed to assess prognostic risk factors for breakthrough infections in hospitalized patients who were fully vaccinated (BBIBP-CorV). In addition, ethnic disparities and the prevalence of new variants in China highlight the importance of summarizing clinical characteristics and outcomes in these patients.

To fill the gap, we here aimed to provide insight into the clinical characteristics, outcomes, and risk factors of 572 fully vaccinated (BBIBP-CorV) hospitalized patients with COVID-19 in China. These findings will contribute to a better understanding of disease management and treatment strategies for patients with breakthrough infection.

2. Methods

2.1. Study design and patients

This is a single-center, retrospective cohort study in Xiangya Hospital of Central South University from December 5, 2022, to January 31, 2023. We included all hospitalized patients with fully (2 doses) vaccinated (inactivated, BBIBP-CorV) and positive for SARS-CoV-2 infection using RT-PCR. Participants under the age of 18 years were excluded from the study. The flow diagram depicting the patients screening process, including the criteria of inclusion and exclusion, is presented in Fig. 1. The study was approved by the institutional review committee of Xiangya Hospital of Central South University (202002024). As the retrospective cohort study involved anonymous patient data, individual informed consent was not required.

Table 1
Demographic, clinical characteristics of hospitalized patients with COVID-19 after inactivated vaccine (BBIBP-CorV) vaccination.

Characteristics	Total (N = 572)	No composite outcome (n = 504)	Composite outcome (n = 68)
Time from full vaccination to breakout infection (month)	16 (15, 18)	17 (16, 18)	16 (15, 18)
Age (year)			
median (IQR)	66.0 (53.0, 74.0)	65.0 (53.0, 74.0)	70.5 (54.5, 80.0)
≥65	350 (61.2)	204 (40.5)	18 (26.5)
Sex, n (%)			
Male	315 (55.1)	264 (52.4)	51 (75.0)
Female	257 (44.9)	240 (47.6)	17 (25.0)
Symptoms			
Fever	347 (60.7)	303 (60.1)	44 (64.7)
Dry cough	401 (70.1)	354 (70.2)	47 (69.1)
Expectoration	333 (58.2)	296 (58.7)	37 (51.7)
Poor appetite	229 (40.0)	202 (40.1)	27 (39.7)
Polypnea	220 (38.5)	177 (35.1)	43 (63.2)
Fatigue	172 (30.1)	151 (30.0)	21 (30.9)
Stuffiness	132 (23.1)	120 (23.8)	12 (17.6)
Myalgia	79 (13.8)	68 (13.5)	11 (16.2)
Comorbidities			
Hypertension	253 (44.2)	210 (41.7)	43 (63.2)
Coronary disease	106 (18.5)	87 (17.3)	19 (27.9)
Diabetes mellitus	117 (20.5)	98 (19.4)	19 (27.9)
COPD	28 (4.9)	23 (4.6)	5 (7.4)
Asthma	7 (10.4)	6 (10.7)	1 (9.1)
Nervous System disease	53 (12.0)	42 (10.9)	11 (20.4)
Infectious diseases	44 (10.0)	42 (10.9)	2 (3.7)
Urinary system diseases	42 (9.5)	31 (8.0)	11 (20.4)
Cancer	45 (7.9)	37 (7.3)	8 (11.8)
Immune system disease	21 (4.8)	16 (4.1)	5 (9.3)
Medication, n (%)			
Steroids	107 (18.7)	88 (17.5)	19 (27.9)
Antibiotics	200 (35.0)	173 (34.3)	23 (39.7)
Azvudine	126 (22.0)	114 (22.6)	12 (17.6)
Paxlovid	145 (25.3)	118 (23.4)	27 (39.7)
Oxygen support, n (%)			
Nasal cannula	417 (72.9)	383 (76.0)	34 (50.0)
Mask oxygen	29 (5.1)	0 (0)	29 (42.6)
High-flow oxygen	28 (4.9)	0 (0)	28 (41.2)
Invasive mechanical ventilation	20 (3.5)	0 (0)	20 (29.4)
Prognosis, n (%)			
Died	19 (3.3)	0 (0)	19 (27.9)

IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

2.2. Data source

Health records of hospitalized COVID-19 patients were obtained from the electronic inpatient system of Xiangya Hospital of Central University. These records included demographic characteristics, admission date, time from symptom occurrence to admission, pre-existing conditions, prescription and drug dispensing records, laboratory results, admission to the ICU, and date of discharge or death. As we stated previously, the health records were linked with vaccination records from the Department of Immunization, Center for Disease Control and Prevention of Hunan Province using unique identification numbers (China Identity Card) [13]. Data collection was performed consecutively until the predetermined time point. The composite outcome considered in this study encompassed the initiation of endotracheal intubation, non-invasive respiratory support, intensive care unit admission, and all-cause death, whichever came first.

2.3. Statistical analysis

Descriptive data were presented as the median, interquartile range (IQR), and proportions. Demographic characteristics and laboratory results that could affect the outcome were involved in univariate Cox regression model to determine potential prognostic risk factors of fully vaccinated (BBIBP-CorV) hospitalized patients with breakthrough infection. Multivariate Cox regression analysis was further performed to identify the independent risk factors if the statistically significant factors ($p < 0.05$) in the univariate analysis [14–16]. All statistical analyses and graphical representations were performed using R version 4.2.1 and SPSS version 26.0 (IBM, United States). P value < 0.05 was considered statistically significant.

3. Result

3.1. The characteristics of the patients of COVID-19

We enrolled a total of 572 patients for the study, with 68 patients belonging to the composite outcome group and 504 patients belonging to the no composite outcome group. The demographic and clinical characteristics of these patients are summarized in Table 1. The median time from full vaccination to breakthrough infection of patients is 16 months (IQR 15, 18). The median age of the patients was 66 years (IQR 53, 74), with 61.2 % of them being aged older 65 years or older. Among the patients, 315 (55.1 %) were male. Notably, patients with composite outcome were generally older than those with no composite outcome, with median ages of 70.5 years (IQR 54.5, 80.0) and 65.0 years (IQR 53.0, 74.0), respectively.

The most common symptoms at onset were fever (347 [60.7 %]), dry cough (401 [70.1 %]), expectoration (333 [58.2 %]), poor appetite (229 [40 %]), polypnea (220 [38.5 %]), and fatigue (172 [30.1 %]). It is worth mentioning that the proportion of patients with polypnea symptoms in the composite outcome group was significantly higher compared to that in the no composite outcome group (43 [63.2 %] vs. 177 [35.1 %]).

Most of patients had pre-existing chronic comorbidities, including hypertension (253 [44.2 %]), coronary disease (106 [18.5 %]), diabetes mellitus (117 [20.5 %]), chronic obstructive pulmonary disease (28 [4.9 %]), asthma (7 [10.4 %]), nervous system diseases (53 [12.0 %]), infectious diseases (44 [10.0 %]), urinary system diseases (42 [9.5 %]), cancer (45 [7.9 %]), and immune system disease (21 [4.8 %]). We observed a higher prevalence of patients with composite outcomes of chronic disease compared to those with no composite outcomes, involving hypertension (43 [63.2 %] vs. 210 [41.7 %]), coronary disease (19 [27.9 %]) vs. 87 [17.3 %]) and diabetes mellitus (19 [27.9 %]) vs. 98 [19.4 %]).

Among the patients who received medication treatments, 107 (18.7 %) patients were administered with steroids, 200 (35 %) received antibiotics, 126 (22 %) received Azvudine and 145 (25.3 %) were treated with Paxlovid. Notably, a higher percentage of patients with composite outcome received steroids (19 [27.9 %] vs. 88 [17.5 %]) and Paxlovid (27 [39.7 %] vs. 118 [23.4 %]) compared to patients with no composite outcome. As for oxygen support, 417 (72.9 %) patients utilized nasal cannula, with a greater proportion observed among no composite outcome group compared to composite group (383 [76.0 %] vs. 34 [50.0 %]). On the

Table 2
Laboratory characteristics of hospitalized patients with COVID-19 after inactivated vaccine (BBIBP-CorV) vaccination.

Variable, Median (IQR)	Total (N = 572)	No composite outcome (n = 504)	Composite outcome (n = 68)
White blood cell (10^9/L)	5.8 (4.5, 7.7)	5.7 (4.5, 7.3)	7.1 (5.5, 11.0)
Blood platelet (10^9/L)	205 (152, 274)	210 (153, 276)	176 (136, 260)
Lymphocyte (10^9/L)	1.1 (0.7, 1.4)	1.1 (0.8, 1.5)	0.7 (0.4, 1.1)
Serum creatinine (μmol/L)	67.1 (54.0, 84.0)	65.0 (53.8, 83.0)	76.2 (59.3, 122.5)
BUN (mmol/L)	5.2 (4.0, 7.2)	5.1 (3.9, 6.9)	7.3 (5.3, 10.4)
Lactate dehydrogenase (U/L)	199 (167, 259)	193 (164, 238)	261 (201, 380)
Troponin (U/L)	0.004 (0.001, 0 .010)	0.003 (0.001, 0.010)	0.012 (0.006, 0.033)
Albumin (g/L)	35.4 (32.1, 38.2)	35.7 (32.6, 38.4)	31.4 (28.3, 36.2)
D-dimer (mg/L)	0.17 (0.08, 0.39)	0.16 (0.08, 0.37)	0.32 (0.17, 0.80)
Procalcitonin (ng/ml)	0.05 (0.04, 0.10)	0.05 (0.04, 0.07)	0.19 (0.06, 0.76)

IQR, interquartile range; BUN, Blood urea nitrogen.

contrary, the utilization of mask oxygen account for 29 (5.1 %); high-flow oxygen was administered to 28 (4.9 %) of the patients; 20 (3.5 %) required invasive mechanical ventilation, and all of the above patients were from the composite outcome group. Finally, the results showed death occurred in 19 (3.3 %) of total patients and 19 (27.9 %) of patients with composite outcome.

3.2. Laboratory characteristics of hospitalized patients with COVID-19 after inactivated vaccine (BBIBP-CorV) vaccination

The laboratory characteristics of hospitalized patients with COVID-19 after inactivated vaccine (BBIBP-CorV) vaccination were present in Table 2. Blood cell tests revealed that the median white blood cell (WBC) count was higher in patients with composite outcomes compared to those with no composite outcomes (7.1 [5.5, 11.0] $\times 10^9$/L vs. 5.7 [4.5, 7.3] $\times 10^9$/L). It is worth noting that patients in the composite outcome group exhibited lymphocyte median counts (0.7 [0.4, 1.1] $\times 10^9$/L) below the normal range, whereas the median counts of blood platelets (205 [152, 274] $\times 10^9$/L), serum creatinine (67.1 [54.0, 84.0] μmol/L), BUN (5.2 [4.0, 7.2] mmol/L), troponin (0.004 [0.001, 0.010] U/L), albumin (35.4 [32.1, 38.2] g/L) and D-dimer (0.17 [0.08, 0.39] mg/L) are within the normal range. Noticeably, patients in the composite outcome group exhibited the median counts of lactate dehydrogenase (261 [201, 380] U/L) and procalcitonin (0.19 [0.06, 0.76] ng/ml) beyond the normal range, while those median counts of patients in the no composite outcome group are within the normal range of values.

3.3. Cox regression analysis of factors associated with composite outcome among fully vaccinated (BBIBP-CorV) inpatients

Univariable Cox regression was employed to identify potential factors associated with the composite outcome among fully vaccinated (BBIBP-CorV) inpatients. Age >65 years old, white blood cell count >9.5 $\times 10^9$ cells/L, lymphocytes <1.1 $\times 10^9$ cells/L, NLR >4, serum creatine >111 μmol/L, blood urea nitrogen >9.5 mmol/L, lactate dehydrogenase >245 U/L, troponin >0.02 U/L, D-dimer >0.5 mg/ml and procalcitonin >0.1 ng/ml were associated with composite outcome (Table 3). However, the female patients were found to have a lower likelihood of experiencing the composite outcome compared to males. Multivariate Cox regression were further conducted to identify the independent prognostic risk factor of the composite outcome in fully vaccinated (BBIBP-CorV) hospitalized patients with breakthrough infection. The results indicated that NLR >4 (adjusted HR, 5.50 [95%CI:1.56–19.47]; P = 0.008), D-dimer >0.5 mg/ml (adjusted HR, 2.17 [95%CI: 1.03–4.59]; P = 0.042) and procalcitonin >0.1 ng/ml (adjusted HR, 3.22

Table 3
Cox regression analysis of factors associated with composite outcome among fully vaccinated (BBIBP-CorV) inpatients.

	Univariable HR (95%CI)	p value	Multivariable HR (95%CI)	p value
Age, years (≥65)	1.79 (1.05, 3.07)	**0.034**		
Female sex (vs male)	0.41 (0.24, 0.71)	**0.001**		
Comorbidity	1.14 (0.63, 2.05)	0.668		
White blood cell count ($\times 10^9$ cells/L)				
<3.5	0.59 (0.18, 1.92)	0.382		
3.5–9.5	1 (ref)			
>9.5	3.52 (2.12, 5.85)	**<0.001**		
Lymphocytes ($\times 10^9$ cells/L)				
≥1.1	1 (ref)			
<1.1	2.78 (1.62, 4.77)	**<0.001**		
NLR				
≤4	1 (ref)			
>4	4.28 (2.37, 7.73)	**<0.001**	5.50 (1.56, 19.47)	**0.008**
Platelets ($\times 10^9$ cells/L)				
≥125	1 (ref)			
<125	1.46 (0.80, 2.67)	0.222		
Serum creatine (μmol/L)				
≤111	1 (ref)			
>111	2.72 (1.57, 4.73)	**<0.001**		
Blood urea nitrogen (mmol/L)				
≤9.5	1 (ref)			
>9.5	3.52 (2.09, 5.92)	**<0.001**		
Lactate dehydrogenase (U/L)				
≤245	1 (ref)			
>245	3.39 (2.03, 5.68)	**<0.001**		
Troponin (U/L)				
≤0.02	1 (ref)			
>0.02	2.65 (1.33, 5.28)	**0.006**		
D-dimer (mg/mL)				
≤0.5	1 (ref)			
>0.5	2.56 (1.54, 4.25)	**<0.001**	2.17 (1.03, 4.59)	**0.042**
Procalcitonin (ng/ml)				
≤0.1	1 (ref)			
>0.1	6.00 (3.44, 10.47)	**<0.001**	3.22 (1.38, 7.52)	**0.007**
Antiviral therapy	1.45 (0.90, 2.34)	0.128		

NLR, neutrophil-lymphocyte ratio.

[95%CI: 1.38–7.52]; P = 0.007) were associated with remarkably higher risks of the composite outcome and identified as independent risk factors for composite outcome (Table 3).

4. Discussion

More than three years into the pandemic, many studies have highlighted the importance of widespread vaccination [17]. Inactivated vaccines are known to be highly immunogenic and capable of inducing robust humoral responses [18]. Previous studies have reported a significant reduction in the risk of developing symptomatic COVID-19 in vaccinated adults with inactivated COVID-19 vaccine [19,20]. Nevertheless, Omicron, a variant of the SARS-CoV-2 virus strain, appears to be more transmissible and pose a great threat to the Chinese population, with the changing of prevention and control measures in China [21]. Disturbingly, breakthrough infections have been observed as a growing trend [4,22]. With the changing of prevention and control measures in China, breakthrough infections loom as a formidable threat [13].

Several invaluable studies have primarily delved into the protective efficacy of BBIBP-CorV vaccine [23–25]. However, the clinical characteristics, outcomes, and risk factors of SARS-CoV-2 breakthrough infections among fully vaccinated (BBIBP-CorV) hospitalized patients were still not clarified. To our knowledge, our study firstly provided a comprehensive description of the clinical characteristics and analyzed the prognostic risk factors of the composite outcomes in 572 fully vaccinated (BBIBP-CorV) hospitalized patients with breakthrough infection.

We discovered that these patients with breakthrough infections were generally older and the most common symptoms were fever and dry cough, which is consistent with previous research [26,27]. We also found that a high proportion of patients had pre-existing comorbidities, suggesting that patients with underlying comorbidities might have a lower vaccine effectiveness against hospitalization. In addition, two previous retrospective studies conducted in Wuhan showed that the mortality of unvaccinated inpatients at the beginning of the COVID-19 epidemic reached 21.9 % (44/201) and 28.3 (54/191), respectively [28,29]. Similarly, a retrospective study in Italy found that unvaccinated hospitalized patients accounted for 26 % of ICU deaths (405/1581) [30]. However, we found a much lower proportion of composite outcomes in fully vaccinated (BBIBP-CorV) hospitalized patients with breakthrough infection. This disparity can be explained, at least in part, by changes in the strain and the protective effects of the vaccine [31].

In addition, we also identified 11 risk factors for composite outcome by univariate Cox regression analysis. Older age (>65) and male were identified as prognostic risk factors, indicating a higher likelihood of experiencing the composite outcome among these hospitalized patients. Notably, age and gender were also associated with poor prognosis among unvaccinated infected individuals [28,30,32]. These findings highlight the importance of timely diagnosis and active attention to the predictive value of these demographics for their prognosis. Through multivariate Cox regression analysis, NLR >4, D-dimer >0.5 mg/ml and procalcitonin >0.1 ng/ml were significantly and independently associated with composite outcome. These findings were also consistent with unvaccinated patients, suggesting that inflammatory markers and coagulation indicators were predictive for both vaccinated and unvaccinated patients [33,34].

Admittedly, this study has several limitations. Firstly, this was a single-center retrospective study conducted in Hunan Province with relatively small sample size, which could restrict the generalizability of the findings in yellow race. Secondly, there are lots of missing data, including body mass index, pulmonary computerized tomography at admission, immune-related tests and COVID-19 antibody titers, so we did not include these indicators in our study, which could cause certain bias in our conclusions. Thirdly, we just focus on the hospitalized patients with breakthrough infections. Further clinical studies are needed to clarified the clinical characteristics, outcomes, and risk factors of SARS-CoV-2 breakthrough infections among non-hospitalized patients. Finally, this study did not compare the vaccine effectiveness between vaccinated and unvaccinated COVID-19 patients, due to several accessible outcomes on this regard.

5. Conclusion

Breakthrough infection after being fully vaccinated (BBIBP-CorV) is more likely to occur in older patients and patients with pre-existing chronic comorbidities. NLR >4, D-dimer >0.5 mg/ml and procalcitonin >0.1 ng/ml were independent risk factors for composite outcome.

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Ethics statement

Our research has been approved by the institutional review committee of Xiangya Hospital of Central South University (202002024). All patients in the retrospective cohort study were anonymous, and the individual informed consent was not required.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Peilin Liu: Writing – original draft. **Yuming Sun:** Software, Formal analysis, Data curation. **Guangtong Deng:** Writing – review & editing, Resources, Project administration, Methodology, Data curation, Conceptualization.

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.

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