Vaccine: X 15 (2023) 100377

Contents lists available at ScienceDirect

Vaccine: X

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

Disease severity of COVID-19 in different phases of the pandemic: Do healthcare workers have better outcomes?

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ARTICLE INFO

Keywords:
COVID-19 Pandemic
Vaccine
Disease severity
Healthcare workers

ABSTRACT

Background: This study aimed to characterize and compare the demographics, clinical profile, and COVID-19 outcomes between healthcare workers (HCWs) and non-HCWs COVID-19 patients diagnosed in different phases of the pandemic defined by the vaccine rollout policy and different variants that circulated in South Carolina (SC).

Methods: Extracted from the statewide electronic health record data, we analyzed the clinical outcome of 34,502 HCWs and 1,071,020 non-HCWs adults diagnosed with SARS-CoV-2 between March 2, 2020 to April 14, 2022. Logistic regression models were used to explore the association between different pandemic phases and COVID-19 severity-related outcomes.

Results: Substantial reductions in mortality were observed following the vaccine rollout in non-HCWs and HCWs. Compared to the pre-vaccination period, non-HCWs patients diagnosed during post-vaccination with Alpha predominance (adjusted odds ratio [aOR]: 1.10; 95%CI: 1.04–1.16) were more likely to be hospitalized, but the reduced mortality rates were observed in all post-vaccination periods. Regarding HCWs, a reduced mortality rate was only observed in the pre-Alpha (aOR: 0.33; 95%CI: 0.13–0.84) and Omicron periods (aOR: 0.21; 95%CI: 0.05–0.89).

Conclusions: The declining protection effect of vaccines informs the importance of early promotion of the booster dose of the COVID-19 vaccine for HCWs who have more occupational exposure.

Introduction

SARS-CoV-2, the virus that causes COVID-19, has rapidly evolved over time, with new viral strains appearing at regular and frequent intervals. The new strains/mutations of the virus, which lead to "waves" of viral spread and mortality, have been termed as variants of concern (VOCs) by WHO and have become major concerns [1,2]. Meta-analyses and observational studies have shown that the VOCs increase the risk of disease severity and death compared to other non-VOC variants, including the original Wuhan or "wild-type" variant [3–9]. In South Carolina (SC), the first COVID-19 case was recorded in March 2020, and the epidemic in SC was characterized by several major phases by different VOCs, including wild-type (late 2020 to March 2021), Alpha (late March to June 2021), Delta (June to early December 2021), and Omicron (late December 2021 till present) variants [10]. Patients infected with different VOCs may present different patterns of transmissibility, symptoms, severity, and immune response that develops following infection and possibly from vaccination [3,11,12]. With the

Abbreviations: HCWs, healthcare workers; SC, South Carolina; VOCs, variants of concern; DHEC, Department of Health and Environmental Control; CRF, Case Report Form; RUCA, Rural-Urban Commuting Area; CCI, Charleson Comorbidity Index.

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https://doi.org/10.1016/j.jvacx.2023.100377
Received 17 May 2023; Received in revised form 21 August 2023; Accepted 25 August 2023
Available online 26 August 2023

Table 1
Sociodemographic Distribution of HCW vs non-HCW COVID-19 population.

Characteristic	Overall N = 1,105,522	Non-HCW n = 1,071,020 (96.88%)	HCW n = 34,502 (3.12%)	p-value[3]
Age group (years)				<0.0001
18–49	676,798 (61.22)	652,266 (60.90)	24,532 (71.10)	
50–64	251,168 (22.72)	242,675 (22.66)	8,493 (24.62)	
65+	177,556 (16.06)	176,079 (16.44)	1,477 (4.28)	
Sex[1]				<0.0001
Female	611,205 (55.44)	581,452 (54.45)	29,753 (86.30)	
Male	488,642 (44.33)	483,946 (45.31)	4,696 (13.62)	
Other/Unknown	2,579 (0.23)	2,550 (0.24)	29 (0.08)	
Race[1]				<0.0001
White	657,907 (59.55)	636,766 (59.49)	21,141 (61.29)	
Black	278,732 (25.23)	266,968 (24.94)	11,764 (34.11)	
Asian	12,540 (1.13)	12,071 (1.13)	469 (1.36)	
Other/Unknown	155,680 (14.09)	154,563 (14.44)	1,117 (3.24)	
Ethnicity[1]				<0.0001
Not Hispanic or Latino	790,391 (74.29)	759,236 (73.74)	31,155 (90.95)	
Hispanic or Latino	59,271 (5.57)	58,079 (5.64)	1,192 (3.48)	
Unknown	214,239 (20.14)	212,332 (20.62)	1,907 (5.57)	
Residence				<0.0001
Rural	158,203 (14.31)	152,680 (14.26)	5,523 (16.01)	
Urban	947,319 (85.69)	918,340 (85.74)	28,979 (83.99)	
CCI score[2]				<0.0001
0	846,240 (76.55)	818,762 (76.45)	27,478 (79.64)	
1	78,253 (7.08)	75,209 (7.02)	3,044 (8.82)	
≥2	181,029 (16.37)	177,049 (16.53)	3,980 (11.54)	
Symptom				<0.0001
Asymptomatic	714,088 (64.59)	709,102 (66.21)	4,986 (14.45)	
Mild	290,755 (26.30)	269,078 (25.12)	21,677 (62.83)	
Moderate/Severe	100,679 (9.11)	92,840 (8.67)	7,839 (22.72)	
Hospitalization				<0.0001
No	1,071,166 (96.89)	1,037,355 (96.86)	33,811 (98.00)	
Yes	34,356 (3.11)	33,665 (3.14)	691 (2.00)	
Mortality				<0.0001
No	1,091,790 (98.76)	1,057,356 (98.72)	34,434 (99.80)	
Yes	13,732 (1.24)	13,664 (1.28)	68 (0.20)	

Note: [1]The sample size of these variable is not equal to the total sample size due to the missing data.
[2] CCI: Charlson Comorbidity Index.
[3] All p-values came from the Chi-square test.

effective and durable COVID-19 vaccine development, evidence suggests that the number of severe COVID-19 outcomes has greatly reduced following the vaccine rollout policy [8,9]. However, the evaluation of the impact of the COVID-19 vaccine rollout policy implementation on the adverse COVID-19 outcomes during different emerging variants circulating in the US has not been explored in depth.

Healthcare workers (HCWs), essential to the nation's pandemic response, are at high risk of COVID-19 infection at work, and a substantial portion may experience severe illness if infected [13]. Protecting healthcare workers from COVID-19 infection is a priority to maintain a safe and functioning healthcare system [14]. Thus, it is important to understand the pathophysiology of the infection towards HCWs and determine what the predisposing factors exposing HCWs to more risk of adverse COVID-19 outcomes are. According to a literature review that described the health-related issues among HCWs during the COVID-19 pandemic, existing efforts focus more on mental health disorders (e.g., stress, anxiety) [15]. In addition, much of the evidence on the impact of the COVID-19 pandemic on HCWs, including infection rates, risk factors, and well-being, comes from international studies [16] or US studies limited to single hospitals or health systems [17–19]. A large-scale US study with a representative sample is warranted to better describe and compare the clinical characteristics of COVID-19 outcomes and the impact of VOCs among HCWs and non-HCWs.

To address these knowledge gaps, this study aims to evaluate and characterize the impact of the COVID-19 vaccine implementation policy on the adverse COVID-19 outcomes in the context of different emerging variants circulating in SC. In this study, we compare the demographics, clinical profiles, and severity of COVID-19 between adult non-HCWs and HCWs COVID-19 patients diagnosed in different phases of the pandemic defined by the vaccine rollout policy and different variants that circulated in SC.

Materials and methods

Data source

SC Law and Regulations require mandatory reporting of COVID-19 infection to Department of Health and Environmental Control (DHEC) [20–22]. Data for this study were derived from the SC statewide Case Report Form (CRF) ("Human Infection with 2019 Novel Coronavirus Case Report Form") for SARS-CoV-2 infection issued by SC DHEC [23]. The CRF contains information about lab-confirmed and probable cases of COVID-19, including the case classification and identification, hospitalization, ICU and death information, case demographics, clinical course, symptoms, past medical history, and social history. A total of 1,105,522 adult COVID-19 patients (age ≥ 18 years old), including 34,502 HCWs and 1,071020 non-HCWs, who meet the standardized surveillance case definition for COVID-19[23] between March 2, 2020 and April 14, 2022 were included in the current study. The huge disproportion in the number of HCWs and non-HCWs was partially due to that only around 1.94% of the total population in SC were health professions [24]. The study protocol received approval from the institutional review board at the University of South Carolina and relevant SC state agencies (IRB approval number: Pro00100854).

Measures

Case demographics and clinical symptoms

Information on social demographics included age (e.g., 18–49, 50–64 years old), sex (e.g., female, male, transgender), race (e.g., White, Black), ethnicity (e.g., Hispanic/Latino, non-Hispanic/Latino), and residential status. Residential status was defined according to the Rural-Urban Commuting Area (RUCA) codes as urban areas (i.e., urban focused) or rural areas (i.e., large rural city/towns or small and isolated rural towns focused) [25]. The overall comorbidity burden of each participant was measured through the Charleson Comorbidity Index, one of the most widely used and validated comorbidity scoring algorithms to measure comorbidity status in the healthcare database [26]. Each comorbid disease category was extracted based on the International Classification of Disease 10th revision (ICD-10) [26]. The comorbidity diagnosis codes were retrieved from the all-payer claims (UB-92) database from RFA. For symptomatic patients, the CRF documented specific symptoms that were experienced during the illness, such as

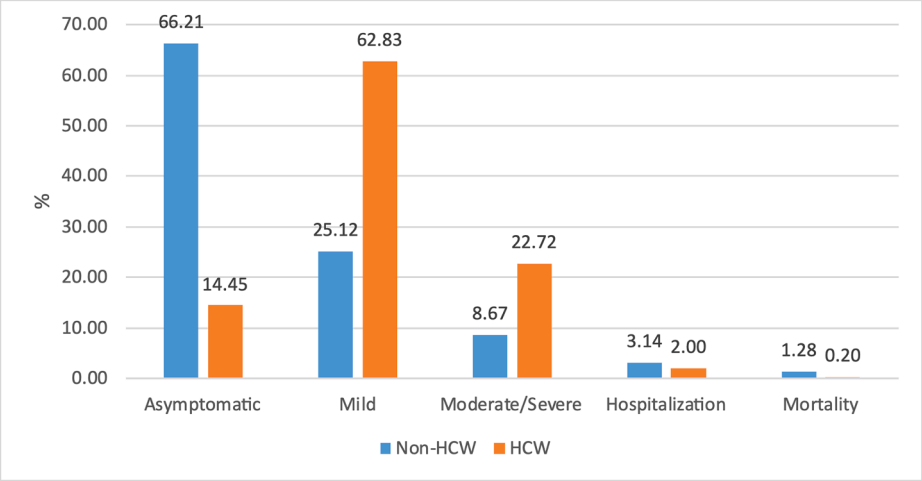

Fig. 1. Percentages of severity, hospitalization, and mortality among non-HCW and HCW COVID-19 patients in South Carolina.

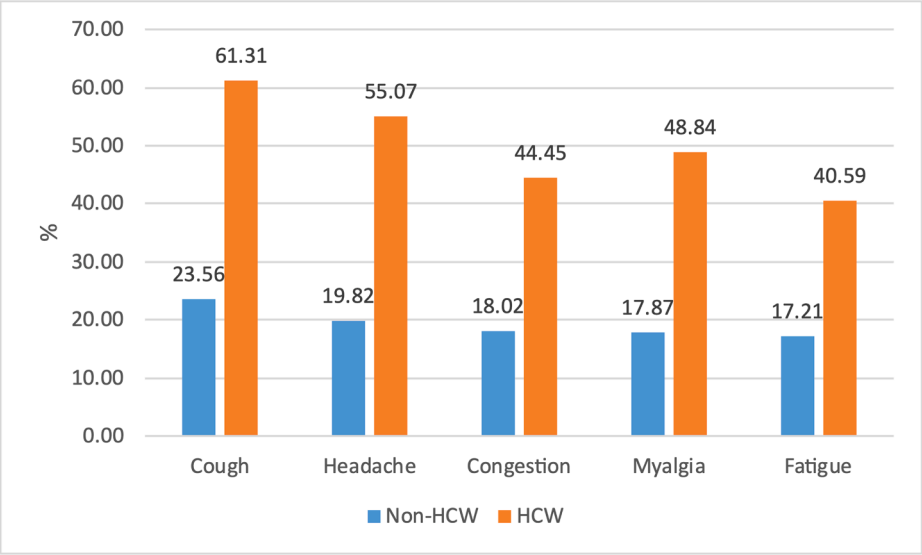

Fig. 2. Top 5 symptoms among non-HCW and HCW COVID-19 patients in South Carolina.

fever, chills, muscle aches, new olfactory and taste disorders.

Different VOCs of COVID-19 and vaccine administration milestones/ periods

According to the US COVID-19 vaccine milestones, the COVID-19 vaccine was first rolled out in December 2020 as the emergency use authorization purpose, where HCWs are one of the target populations. Since March 2021, the COVID-19 vaccine eligibility has been expanded to all Americans along with the development of different vaccine products [27]. Based on the milestone of the national implementation of COVID-19 mitigation measures [28] and different predominant variants in SC [29], we categorized the study periods for non-HCWs who tested positive into four time windows, i.e., pre-vaccination period (March 4, 2020-March 17, 2021), post-vaccination + Alpha dominant period (March 18-June 30, 2021), post-vaccination + Delta dominant period (July 1, 2021-November 30, 2021), and post-vaccination + Omicron (December 1, 2021-April 14, 2022). For HCWs, the ending time point of the pre-vaccination period was different from the general adult population because of the early rollout of Emergency Authorization Use of the COVID-19 vaccine for essential workers [27]. Thus, we split the time into five windows: pre-vaccination period (March 4, 2020-December 14, 2020), post-vaccination + pre-Alpha dominant period (December 15, 2020-February 28, 2021), post-vaccination + Alpha dominant period (March 1, 2021-June 30, 2021), post-vaccination + Delta dominant period (July 1, 2021-November 30, 2021), and post-vaccination + Omicron dominant period (December 1, 2021-April 14, 2022).

Outcomes

We analyzed three distinct outcomes: disease severity, hospitalization, and mortality of COVID-19. Information about symptoms (e.g., fever, headache, and fatigue) specified on the CRF form were collected from medical records of patients. Each symptom had three responses, i.e., 'Yes', 'No', 'Unknown'. Based on different presenting symptoms of COVID-19 patients, disease severity was categorized into three groups. Specifically, COVID-19 patients with no symptoms were categorized as asymptomatic; individuals who have any of the various mild signs and symptoms of COVID-19 (e.g., fever, headache, loss of taste and smell) were categorized as mild; whereas COVID-19 patients with difficulty breathing or developed pneumonia or acute respiratory distress syndrome were categorized as moderate/severe illness. In each phase of interest, the most severe symptoms in the most recent COVID-19 diagnosis were used to define disease severity. In the CRF, hospitalization

Table 2
Sociodemographic Distribution of Separate COVID-19 Phases among Healthcare Workers[1].

Characteristic	Pre-vaccination n = 14,707 (37.21%)	Post-vaccination + Pre-Alpha n = 7,837 (19.83%)	Post-vaccination + Alpha n = 2,105 (5.33%)	Post-vaccination + Delta n = 4,958 (12.54%)	Post-vaccination + Omicron n = 9,920 (25.10%)	P-value
Age group (years)						<0.0001
18–49	10,137 (68.93)	5,494 (70.10)	1,663 (79.00)	3,698 (74.59)	7,341 (74.00)	
50–64	3,839 (26.10)	1,962 (25.04)	397 (18.86)	1,094 (22.06)	2,266 (22.84)	
65+	731 (4.97)	381 (4.86)	45 (2.14)	166 (3.35)	313 (3.16)	
Sex[3]						<0.0001
Female	12,631 (86.10)	6,802 (86.87)	1,896 (90.11)	4,283 (86.46)	8,667 (87.43)	
Male	2,039 (13.90)	1,028 (13.13)	208 (9.89)	671 (13.54)	1,246 (12.57)	
Race						<0.0001
White	8,475 (57.66)	4,911 (62.68)	1,200 (57.01)	3,409 (68.76)	6,005 (60.54)	
Black	5,605 (38.14)	2,570 (32.80)	807 (38.34)	1,309 (26.40)	3,494 (35.22)	
Asian	212 (1.44)	85 (1.09)	28 (1.33)	56 (1.13)	132 (1.33)	
Other/Unknown	406 (2.76)	269 (3.43)	70 (3.32)	184 (3.71)	289 (2.91)	
Ethnicity						<0.0001
Not Hispanic or Latino	1,3291 (90.85)	7,061 (90.95)	1,929 (92.03)	4,513 (91.71)	9,068 (91.97)	
Hispanic or Latino	511 (3.49)	262 (3.37)	97 (4.63)	179 (3.64)	333 (3.38)	
Unknown	828 (5.66)	441 (5.68)	70 (3.34)	229 (4.65)	459 (4.65)	
Residence						<0.0001
Rural	2,433 (16.54)	1,291 (16.47)	350 (16.63)	675 (13.61)	1,629 (16.42)	
Urban	12,274 (83.46)	6,546 (83.53)	1,755 (83.37)	4,283 (86.39)	8,291 (83.58)	
CCI score[2]						<0.0001
0	11,989 (81.52)	6,332 (80.80)	1,655 (78.62)	3,801 (76.66)	7,600 (76.61)	
1	1,201 (8.17)	594 (7.58)	216 (10.26)	528 (10.65)	1,005 (10.13)	
≥2	1,517 (10.31)	911 (11.62)	234 (11.12)	629 (12.69)	1,315 (13.26)	
Symptom						<0.0001
Asymptomatic	2,414 (16.41)	1,735 (22.14)	365 (17.34)	885 (17.85)	3,615 (36.44)	
Mild	8,363 (56.87)	4,543 (57.97)	1,262 (59.95)	3,181 (64.16)	5,238 (52.80)	
Moderate/Severe	3,930 (26.72)	1,559 (19.89)	478 (22.71)	892 (17.99)	1,067 (10.76)	
Hospitalization[4]						<0.0001
No	14,278 (97.08)	7,728 (98.61)	2,066 (98.15)	4,882 (98.47)	9,881 (99.61)	
Yes	429 (2.92)	109 (1.39)	39 (1.85)	76 (1.53)	39 (0.39)	

Note: [1]The sum sample size of three phases is not equal to the overall sample size due to that some HCWs were diagnosed with COVID-19 repeatedly across periods.
[2] CCI: Charlson Comorbidity Index.
[3] Some unknown category was not listed due to the small sample size (less than 5).
[4] Per SC DHEC data use policy to protect patient privacy, mortality frequency was not reported in this table due to the small cell size (less than 10).

Table 3
Odds Ratio of Health Outcomes by Phases Among non-HCW and HCW Population.

Population	COVID Phases	Mild		Moderate/Severe		Hospitalization		Mortality	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Non-HCW	Pre-vaccine	reference	.	reference	.	reference	.	reference	.
	Post-vaccine & Alpha	1.866 (1.825,1.908)	<0.0001	1.751 (1.699,1.803)	<0.0001	1.099 (1.043,1.158)	0.0004	0.659 (0.598,0.726)	<0.0001
	Post-vaccine & Delta	0.506 (0.5,0.513)	<0.0001	0.423 (0.415,0.431)	<0.0001	0.958 (0.928,0.99)	0.0096	0.857 (0.818,0.898)	<0.0001
	Post-vaccine & Omicron	0.269 (0.266,0.273)	<0.0001	0.165 (0.161,0.168)	<0.0001	0.408 (0.393,0.422)	<0.0001	0.283 (0.267,0.299)	<0.0001
HCW	Pre-vaccine	reference	.	reference	.	reference	.	reference	.
	Post-vaccine & Pre-Alpha	0.659 (0.613,0.707)	<0.0001	0.474 (0.435,0.517)	<0.0001	0.519 (0.411,0.656)	<0.0001	0.327 (0.127,0.837)	0.0198
	Post-vaccine & Alpha	1.23 (1.071,1.413)	0.0035	0.971 (0.828,1.138)	0.7144	0.763 (0.532,1.094)	0.1414	0.979 (0.297,3.224)	0.9723
	Post-vaccine & Delta	1.411 (1.276,1.559)	<0.0001	0.827 (0.735,0.931)	0.0016	0.695 (0.533,0.906)	0.0072	1.751 (0.926,3.311)	0.0851
	Post-vaccine & Omicron	1.33 (1.221,1.449)	<0.0001	0.555 (0.498,0.618)	<0.0001	0.223 (0.151,0.33)	<0.0001	0.212 (0.051,0.886)	0.0336

Note: all the models were adjusted for key demographics, i.e., age, gender, race, ethnicity, CCI score, and disease severity.

was measured with one question, i.e., "Was the patient hospitalized?" with the responses categorized as 'Yes', 'No', and 'Unknown'. For patients with no response to this question, we also treated them as unknown. Then we dichotomized the hospitalization status as 1 if the response is 'Yes', else, it was defined as 0, indicating no hospital admission. For patients with multiple hospitalization records, we selected the encounter in which the most severe outcome was observed (e.g., ICU visit, respiratory support), then the longest visit, and finally, the most recent visit. Similarly, death was measured using the question, i.e., "Did the patient die as a result of this illness?" with the response categories as 'Yes", "No' and 'Unknown'. We use a similar strategy to define a patient's death status where 1 indicates death and 0 indicates alive, which includes alive and unknown.

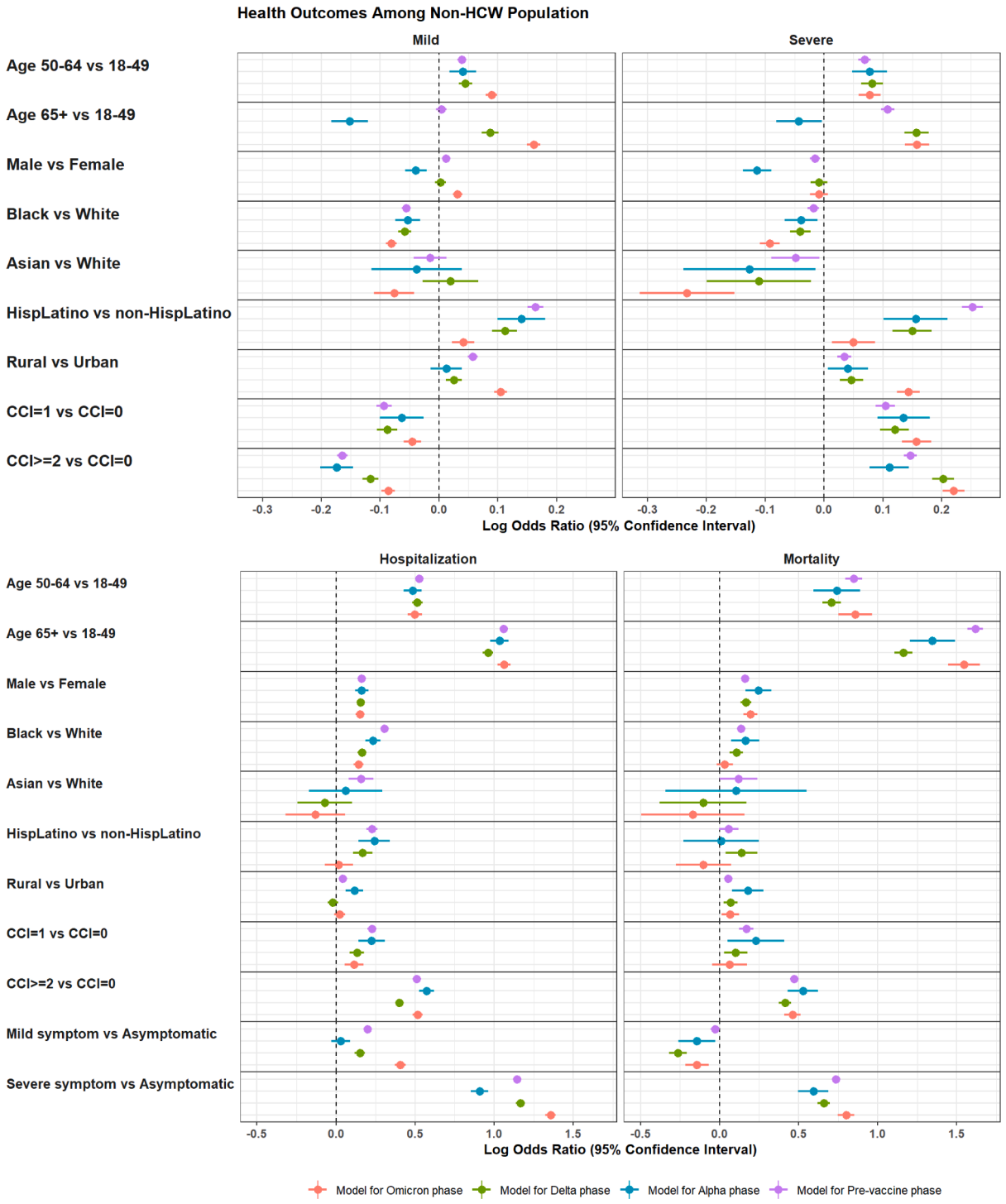

Fig. 3. Odds Ratios and 95% CI for illness severity, hospitalization, and mortality at separate COVID-19 phases among statewide non-healthcare workers (n = 1,071,020) COVID-19 patients in South Carolina, March 2, 2020- April 14, 2022.

Statistical analysis

Descriptive statistics were used to characterize the disease severity and clinical outcomes for COVID-19 cases. We used the Chi-square test to compare differences between groups. We used logistic regression models to explore the association between different phases of COVID-19 occurrence and symptom severity, hospitalization, and death outcomes for the non-HCWs adult population and HCWs, accounting for underlying individual-level variables, such as socio-demographics and comorbidities. Bar charts were used to display the percentage of severity, hospitalization, mortality, and the top 5 symptoms among non-HCWs and HCWs COVID-19 patients in South Carolina. We also analyzed the temporal trend of biweekly COVID-19 mortality along with different phases of the pandemic in the context of the COVID-19 vaccine rollout policy and different variants circulating in the area. For the display of the biweekly mortality in different phases, we used Loess (Local regression) as the smoothing method, with a degree of smoothing (spam) of 0.75. We reported odds ratios (OR) and 95% confidence intervals (95% CI) for each model in tables and forest plots. P-value less than 0.05 was considered statistically significant. All statistical analyses

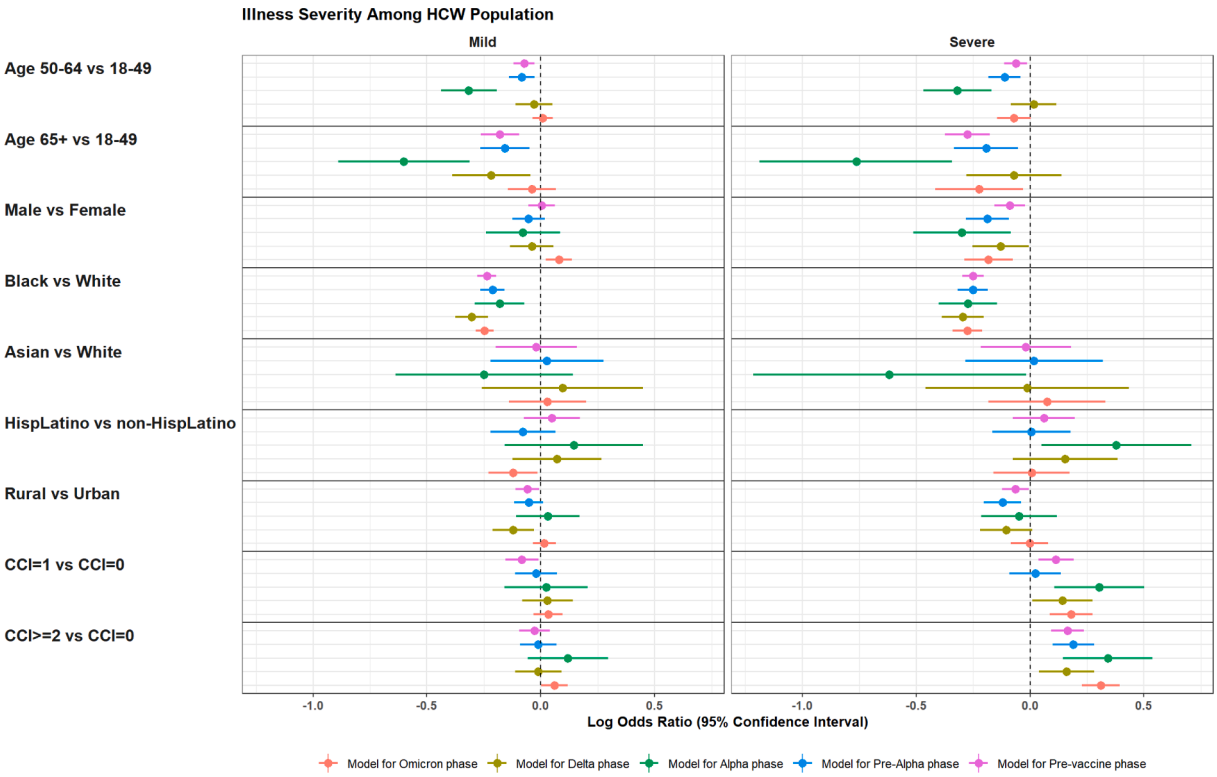

Fig. 4. Odds Ratios and 95% CI for illness severity at separate COVID-19 phases among statewide healthcare workers (n = 34,502) COVID-19 patients in South Carolina, March 2, 2020- April 14, 2022. *Note: mortality was not drawn due to the smaller number of deaths at phases Pre-Alpha, Alpha, Delta, and Omicron.*

were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC) and R software (version 3.6.2).

Results

Overall demographics and disease symptoms

Among a total of 1,105,522 adult COVID-19 patients, 61.22% were aged 18–49 years old, 55.44% were female, and 59.55% were White (Table 1). The demographic distributions of HCWs and non-HCWs were mostly similar except that HCWs were generally younger (65+: 4.28% vs 16.44%), predominantly were female (86.3% vs 54.45%), and occupied a high percentage of Black (34.11% vs 24.94%) than non-HCWs (Table 1). As presented in Fig. 1, HCWs had a much lower percentage of asymptomatic illness than the non-HCWs (14.45% vs 66.21%), yet a much higher percentage of mild (62.83% vs 25.12%), moderate/severe (22.72% vs 8.67%) illness after contracting COVID-19. Nevertheless, HCWs had a lower rate of hospitalization (2.00% vs 3.14%) and death (0.2% vs 1.28%) from COVID-19. Fig. 2 illustrates the five top common symptoms among HCWs and non-HCWs, including cough, headache, myalgia, fatigue, and congestion. The non-HCWs share the leading symptoms with HCWs, although HCWs reported a higher percentage in each category.

Disease severity in different COVID-19 pandemic phases among HCWs

Among HCWs, individuals diagnosed in phase 5 (Omicron dominance period) reported a higher proportion of asymptomatic illness (36.44% vs 16.41%–22.14%) than those diagnosed in other phases. Those diagnosed in the pre-vaccination period reported the highest proportion of moderate/severe symptoms (26.72% vs 10.76%–22.71%) and hospitalization rate (2.92% vs 0.39%-1.85%) (Table 2).

Clinical outcomes comparison in different COVID-19 pandemic phases

Among non-HCWs, individuals diagnosed during post-vaccination when Alpha was the dominant variant were more likely to exhibit mild (aOR: 1.87; 95%CI: 1.83–1.91) or moderate/severe symptoms (aOR: 1.75; 95%CI: 1.70–1.80) and being hospitalized (aOR: 1.10; 95% CI: 1.04–1.16) but less likely to die from COVID-19 (aOR: 0.66; 95%CI: 0.60–0.73) than during the pre-vaccination period. In contrast, non-HCWs who were diagnosed when Delta became the dominant variant in SC were less likely to present with mild (aOR were 0.51; 95%CI: 0.50–0.51), or moderate/severe illnesses (aOR: 0.42; 95%CI: 0.42–0.43), be hospitalized (aOR: 0.96; 95%CI: 0.93–0.99) and die (aOR: 0.86; 95%CI: 0.82–0.90). Individuals diagnosed during the Omicron dominant period showed similar patterns of clinical outcomes to that during the Delta dominance when compared to the pre-vaccination period, except that significant declining of mortality were found in the Omicron dominance but not in the Delta dominance (Table 3).

Among HCWs, individuals diagnosed in the post-vaccination & pre-Alpha period had lower odds risk of each outcome (mild: (aOR: 0.66, 95%CI: 0.61–0.71); moderate/severe: (aOR: 0.47, 95%CI: 0.44–0.52); hospitalization (aOR: 0.52. 95%CI: 0.41–0.66); and death (aOR: 0.33, 95%CI: 0.13–0.84, p = 0.07)) when compared to the pre-vaccination period. However, no significant difference in the risk of moderate/severe, hospitalization, and mortality was found in the Alpha dominance. Individuals diagnosed in the Delta and Omicron period had a comparable risk of health outcomes (higher odds of mild; lower odds of moderate/severe and hospitalization) than the pre-vaccination period, except that no significant differences in mortality was found in Delta (aOR: 1.75, 95%CI: 0.93–3.31) dominance (Table 3). When analyzed in separate models with different phases, the demographic and comorbid risk factors for the outcomes were similar across different phases in both HCWs and non-HCWs (Figs. 3-5).

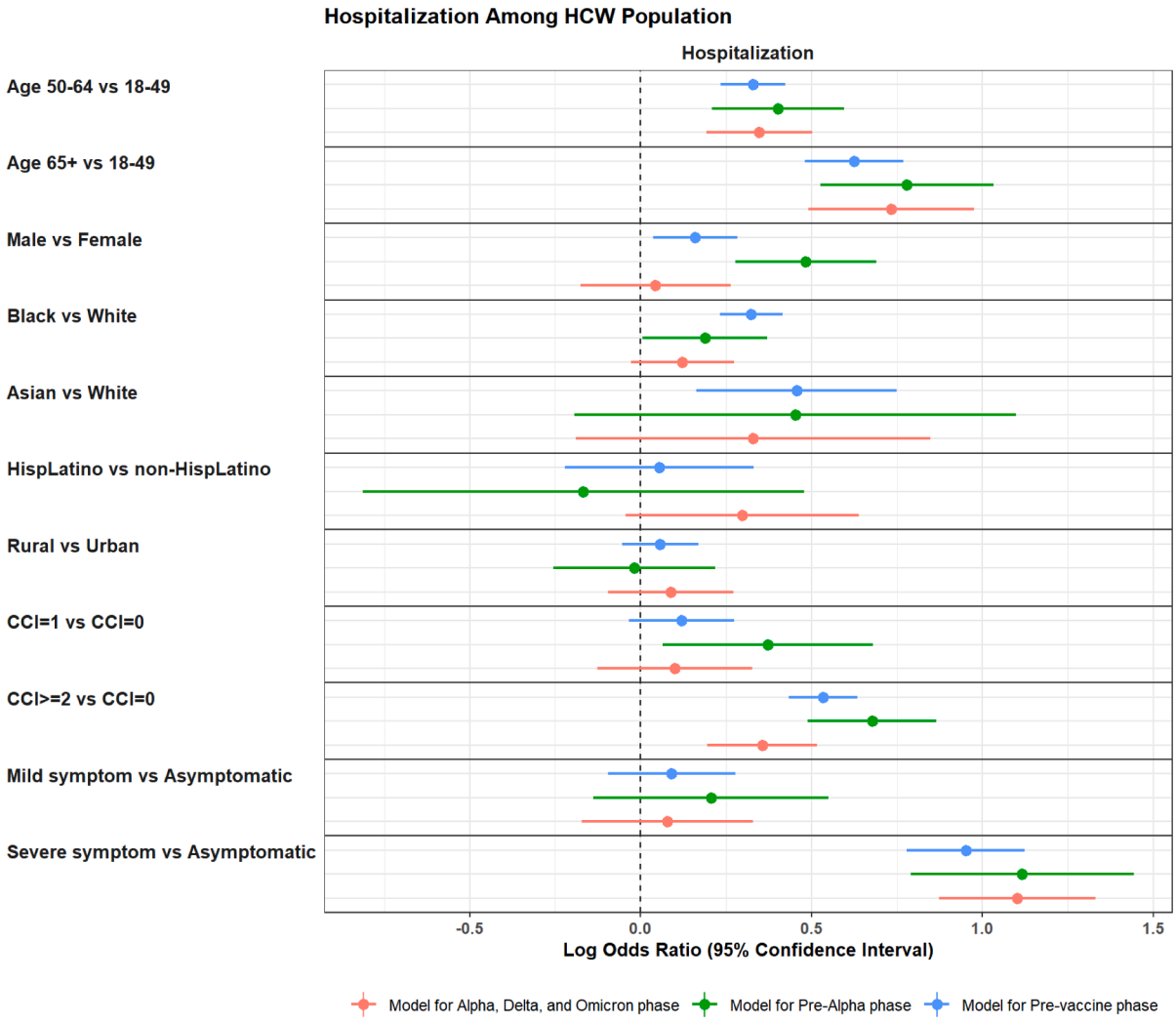

Fig. 5. Odds Ratios and 95% CI for hospitalization at separate COVID-19 phases among statewide healthcare workers (n = 34,502) COVID-19 patients in South Carolina, March 2, 2020- April 14, 2022.

Temporal trend of incident COVID-19 mortality

As displayed in Fig. 6, a general declining trend was observed in non-HCWs across the four phases. Accordingly, the implementation of vaccination rollout was consistently associated with substantial reductions in the incidence of COVID-19 mortality in the post-vaccination, at least during the Alpha dominant period (March 18-June 30, 2021). When Delta became the dominant variant in the vaccination era, the mortality gradually started to increase again (June 30, 2021-October 14, 2021) and then decreased through the Omicron period, suggesting the potentially more severe outcomes due to the Delta variant than the Alpha variant. Despite this, the incidence was still lower than in the pre-vaccination period. The temporal pattern of mortality incidence was generally similar in HCWs compared to non-HCWs, but in the pre-vaccination period, HCWs started off with a relatively lower mortality incidence and with a decreasing trend at a smaller magnitude than non-HCWs (Fig. 6).

Discussion

This large statewide cohort study spanning a 2-year period is by far one of the largest real-world pieces of evidence to compare the demographics, clinical profile, and outcomes of COVID-19 patients diagnosed in different phases of the pandemic. The findings demonstrated the protective effect of the vaccines among both the non-HCWs and HCWs. Yet, the protective effect on mortality diminished in the Alpha and Delta dominant periods among HCWs. This might be due to greater pathogenicity of the emerging variants or suboptimal response to vaccination and waning immunity. In addition, during each phase, no substantial differences were observed with regard to the impact of key demographic distribution (e.g., age, sex, race/ethnicity) and the level of comorbidity burden on the COVID-19 outcomes between vaccination rollout periods and variants circulating during a given phase.

In general, substantial reductions in mortality were observed following the implementation of the first vaccine rollout among both the non-HCWs and HCWs, although a fluctuation was observed during the Alpha and Delta dominant period in HCWs. The substantial reduction of incident COVID-19 mortality in the post-vaccination period demonstrated the protection of the vaccines but also raised the possibility that greater spread at the beginning of the pandemic could have induced some protection at the population level, resulting in a milder second wave [30]. Moreover, the vaccine effectiveness might be compromised when Alpha and Delta became the dominant variant. In adjusted models for HCWs, the comparisons between several phases showed that the variants of the Alpha dominant and Delta dominant were associated with a diminished protection effect on COVID-19 related mortality, indicating either the more pathogenicity of the emerging variants (Delta) [5–9] or suboptimal response to vaccination and waning immunity [31–34]. The declining protection effect from the vaccine informs the importance of early promotion of the booster dose of the

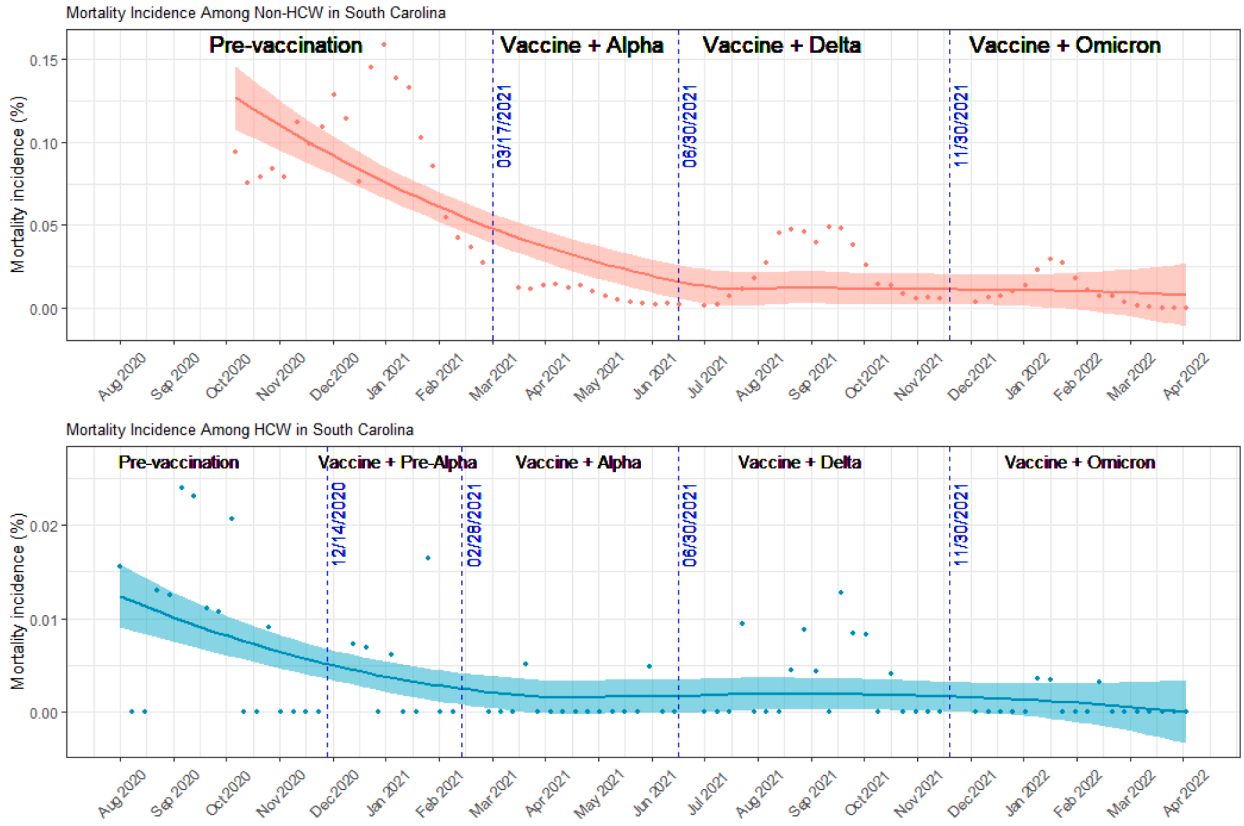

Fig. 6. Mortality incidence among non-HCW COVID-19 patients and HCWs in different COVID-19 phases.

COVID-19 vaccine for HCWs who have more occupational exposure.

For non-HCWs, individuals diagnosed in post-vaccination era (Alpha, Delta, and Omicron dominance) had a lower risk of COVID-19 mortality although they were all more likely to be hospitalized in the Alpha dominant period. The combined findings of higher percentage of mild/moderate illness and hospital admission but a low mortality rate in the Alpha period could contribute to the partial protection of the vaccine, incomplete vaccine update, or prior partial immunity due to prior infection. At the beginning stage of the vaccine rollout policy, vaccine uptake was slow, and many had not received full vaccination when the next wave of COVD-19 variants began to emerge. During the Delta and Omicron dominance period there was a wider coverage of vaccines and increasing number of fully vaccine population.

HCWs are at a high risk for COVID-19 exposure, but rates of COVID-19 illness were low [35]. The combined findings of low asymptomatic infections but higher percentage of mild and moderate/severe illnesses among HCWs corroborate with an Israeli study [36] and provide evidence supporting the necessity of national personal protection equipment (PPE) policy when caring for COVID-19 patients. Furthermore, high health care accessibility might be one of the reasons for such outcome as mass testing of symptomatic and asymptomatic HCWs has been recommended as means to reduce nosocomial transmission. The low hospitalization and mortality rate in HCW might be due to a more robust uptake if vaccination amongst HCW either due to a greater willingness to be vaccinated or mandatory vaccination policies in health care settings [37]. While it is predicted that COVID-19 will persist with sporadic waves, it will be important to continue to ensure that there are enough resources to safely meet urgent future needs of the health care system.

There are several limitations that need to be acknowledged in our study. First, our results might be biased due to RFA's use of randomly shifted (perturbed) dates of service (e.g., COVID-19 diagnosis), which limits our ability to produce accurate temporal results during analysis. However, the shifted dates of service only range from 1 to 14 days, we assume that the impact should be minimal and unlikely to change our conclusions. Second, using the study periods to roughly estimate the population-level vaccine protection in the context of different dominant variants might introduce biased results. Future studies should consider the individual-level genomic sequence data (with specific variant infection) and antibody responses to vaccination data to confirming the findings. Third, vaccination effectiveness and distinct variants spread are the only two factors among other variables affecting COVID-19 severity across different populations. Access to care may vary according to the phases of the epidemic and potentially influence the severity of the disease. Furthermore, we did not provide information on the duration of symptoms which could differ by variants. Given the shorter follow up time, we also did not include vaccine booster effect in the analysis. Despite of these limitations, our study is still one of the largest clinical studies to date that compared the clinical profiles of COVID-19 patients diagnosed in different waves of the pandemic.

Conclusions

Our findings add to the growing literature studying the impact of SARS-CoV-2 variants on COVID-19 outcomes in humans. The general decline of the incident COVID-19 mortality might partially prove the protective effect of COVID-19 vaccines on prior infection. Yet, the slight change of disease severity by different variants might be a complex effect of the vaccine protection and the high transmissibility and pathogenicity of the emerging variants. The declining protective effect from the vaccine among HCWs during the Alpha and Delta dominant periods informs the importance of early promotion of the booster dose of the COVID-19 vaccine for HCWs. Future studies are warranted to include the individual level vaccine status including vaccine booster effect in the analysis.

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

The authors do not have permission to share data.

Acknowledgements

The authors thank the SC Department of Health and Environmental Control (DHEC), the office of Revenue and Fiscal Affairs (RFA), and other SC agencies for contributing the data in South Carolina.

Funding sources

This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health [grant number R01AI127203-4S1 to XL and R21AI170159-01A1 to XY]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contribution

XY conceptualized the study design. XY and FS wrote the first draft and critical revision of the manuscript. JZ set up the statistical test design. HG and SC conducted the data analysis, which was reviewed and verified by JZ. XY prepared tables and figures with input from HG. SW provided clinical input. JZ, SW, BO, and XL reviewed and edited the manuscript. Authorship was determined using ICMJE recommendations.

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