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Preplanned Studies

The Associated Factors of SARS-CoV-2 Reinfection by Omicron Variant — Guangdong Province, China, December 2022 to January 2023

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Summary

What is already known about this topic?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection by variants is being reported commonly and has caused waves of epidemic in many countries. Because of dynamic zero policy, the SARS-CoV-2 reinfection was less reported in China.

What is added by this report?

SARS-CoV-2 reinfections were observed in Guangdong Province between December 2022 and January 2023. This study estimated that the reinfection incidence was 50.0% for the original strain primary infections, 35.2% for the Alpha or Delta variants, and 18.4% for the Omicron variant; The reinfection incidence within 3-6 months after primary infection by Omicron variant was 4.0%. Besides, 96.2% reinfection cases were symptomatic while only 7.7% sought medical attention.

What are the implications for public health practice?

These findings suggest a reduced likelihood of an Omicron-driven epidemic resurgence in the short term but emphasize the importance of maintaining vigilant surveillance of emerging SARS-CoV-2 variants and conducting population-based antibody level surveys to inform response preparedness.

Between December 2022 and January 2023, coronavirus disease 2019 (COVID-19) became widespread in China (*1*). This study aimed to preliminarily determine the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection during this epidemic period and identify its associated factors. A telephone survey was conducted in January 2023, focusing on patients in Guangdong, a province in southern China, who had recovered from COVID-19 after initial confirmation beginning in 2020. The study included 368 participants, aged 1–80 years.

The overall SARS-CoV-2 reinfection incidence was found to be 28.3% [95% confidence interval (*CI*): 23.7%, 33.2%]. Univariate analysis revealed that the reinfection incidence for primary cases involving the Omicron variant was significantly lower than that for primary cases involving pre-Omicron strains (χ^2=23.94, P<0.001). Additionally, the study indicated that while the majority of reinfection cases developed symptoms, only a small proportion required medical attention. These findings may contribute to a better understanding of the risk associated with subsequent epidemics and inform improved response preparedness.

In this study, SARS-CoV-2 reinfection was defined as an infection occurring more than 90 days after the onset of the primary infection or after the collection of the first positive specimen. Following the criteria established by the US CDC (*2*) and the 10th edition of the Chinese diagnosis and treatment protocol, SARS-CoV-2 reinfections were categorized as either probable or confirmed cases.

Probable cases were defined as those without a positive SARS-CoV-2 nucleic acid or antigen test result but who met at least one of the following two conditions since December 2022: 1) an acute onset or worsening of cough or loss of sense of smell/taste or 2) an acute onset or worsening of at least two of the following symptoms or signs: fever, fatigue, nasal congestion, runny nose, sore throat, myalgia, diarrhea, or conjunctivitis.

Confirmed cases were identified as those who tested positive for SARS-CoV-2 nucleic acid or antigen, irrespective of symptoms, according to self-reporting and laboratory record review.

The predominant strains of SARS-CoV-2 causing local outbreaks in Guangdong shifted from the original strain in 2020 to the Alpha and Delta variants in 2021, and the Omicron variant in 2022. This study included

local primary infection cases of COVID-19 reported between January 2020 and August 2022 in Guangzhou and Shenzhen. A total of 3,331 local recovered COVID-19 patients were sampled from cases reported in Guangzhou and Shenzhen during that time (856 in 2020, 181 in 2021, and 2,294 in 2022). The cases were selected using a systematic sampling method based on the primary infection strains.

Data on demographic characteristics, vaccination history, COVID-19-related symptoms, and laboratory test results for both primary infection and reinfection with SARS-CoV-2 were obtained through telephone surveys and the National Notifiable Disease Reporting System. The incidence of SARS-CoV-2 reinfection was calculated using the sum of confirmed and probable cases. A chi-square test was employed for univariate analysis, and logistic regression was performed separately to explore the factors influencing reinfection for individuals with primary infections caused by different strains.

All statistical analyses were carried out using R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria), and all statistical tests were two-sided with an α value of 0.05.

In this study, a total of 368 case participants were investigated, consisting of 183 males and 185 females ranging in age from 1 to 85 years old. The participants were categorized based on the type of SARS-CoV-2 infection: 68 individuals with the original strain, 88 with either the Alpha or Delta variants, and 212 with the Omicron variant. Vaccination status was also recorded, with 103 participants having completed the primary SARS-CoV-2 vaccination series and 189 having received a booster dose. The demographic and characteristic details are presented in Table 1.

A total of 104 cases were identified as SARS-CoV-2 reinfections, comprising 70 confirmed cases and 34 probable cases. The overall incidence of SARS-CoV-2 reinfection was estimated to be 28.3% (95% *CI*: 23.7%, 33.2%). When categorized by the primary infection strain, the reinfection incidences were 50.0% (95% *CI*: 37.6%, 62.4%) for the original strain, 35.2% (95% *CI*: 25.3%, 46.1%) for the Alpha or Delta variants, and 18.4% (95% *CI*: 13.4%, 24.3%) for the Omicron variant. Notably, the reinfection incidence for cases with primary Omicron variant infection was significantly lower than that for cases with primary pre-Omicron strain infections (χ^2=23.94, P<0.001). Among the 104 reinfection cases, 96.2% were symptomatic. The most common symptoms included cough (72.0%), fever (57.0%), sore throat (47.0%), and fatigue (39.0%). Only 8 (7.7%) reinfection cases sought medical attention.

Reinfections were observed during December 2022 and January 2023, with intervals between infections ranging from 3.7 to 35.5 months. For participants initially infected with the Alpha or Delta variant, all reinfections occurred more than 12 months later. Among the 212 participants infected with the Omicron variant, one case experienced reinfection within the 3 to 6 months timeframe, while 38 cases had reinfections occurring beyond 6 months following the primary infection. Additional details regarding reinfection cases are presented in Table 2.

Logistic regression analysis revealed no significant associations between gender, age, clinical manifestations of primary infection, or vaccination history and reinfection incidence. However, for cases with primary infection involving the Omicron variant, logistic regression indicated that being a medical worker and the time interval since the last infection were significant risk factors, with odds ratios (*OR*s) of 9.13 (95% *CI*: 2.70, 30.90) and 9.66 (95% *CI*: 1.12, 83.60), respectively. The results of the multivariate analysis for reinfection risk factors are presented in Table 3.

DISCUSSION

This investigation examined the SARS-CoV-2 reinfection rates and associated factors in Guangdong Province, China. All reinfections were identified during the initial wave of widespread community transmission beginning in December 2022. The findings revealed that the reinfection incidence among individuals primarily exposed to the Omicron variant was significantly lower than that of individuals exposed to pre-Omicron strains. Additionally, our study demonstrated that the majority of reinfection cases were symptomatic, but only a small percentage necessitated medical intervention.

In this study, we observed a low risk of reinfection within 3 to 6 months following primary infection by the Omicron variant. Prior research has indicated that neutralizing antibody titers in COVID-19 patients remain stable for at least 3 months post-infection (*3*–*5*). The rapid development of herd immunity across the general population of Guangdong Province can be attributed to the widespread COVID-19 outbreak from December 2022 to January 2023.

Additionally, our survey revealed a significant increase in SARS-CoV-2 reinfection incidence more

TABLE 1. Characteristics of participants according to primary infection strain of SARS-CoV-2 (*n*=368).

Characteristic	Wild type infection		Alpha/Delta infection		Omicron infection		Total	
	n	%	*n*	%	*n*	%	*n*	%
Gender								
Male	36	52.9	45	51.1	102	48.1	183	49.7
Female	32	47.1	43	48.9	110	51.9	185	50.3
Age, years								
0–17	7	10.3	14	15.9	18	8.5	39	10.6
18–59	49	72.1	51	58.0	183	86.3	283	76.9
≥60	12	17.6	23	26.1	11	5.2	46	12.5
Occupation								
Medical worker	4	5.9	3	3.4	20	9.4	27	7.3
Other	64	94.1	85	96.6	192	90.6	341	92.7
Clinical manifestation of primary infection								
Asymptomatic	13	19.1	14	15.9	47	22.2	74	20.1
Symptomatic	55	80.9	74	84.1	165	77.8	294	79.9
SARS-CoV-2 vaccination status								
Unvaccinated	0	0	4	4.5	4	1.9	8	2.2
Incomplete	7	10.3	9	10.2	9	4.2	25	6.8
Complete	12	17.6	39	44.3	52	24.5	103	28.0
Booster	34	50.0	34	38.6	121	57.1	189	51.4
No detail	15	22.1	2	2.3	26	12.3	43	11.7
Interval since last vaccination*								
Unvaccinated	0	0.0	4	4.7	4	2.2	8	2.5
<12 months	26	49.1	74	86.0	50	26.9	150	46.2
≥12 months	27	50.9	8	9.3	132	71.0	167	51.4
Reinfection status								
Non-reinfection	34	50.0	57	64.8	173	81.6	264	71.7
Reinfection	34	50.0	31	35.2	39	18.4	104	28.3
Probable case	7	10.3	6	6.8	21	9.9	34	9.2
Confirmed case	27	39.7	25	28.4	18	8.5	70	19.0

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
* Only 325 respondents had access to detailed vaccination information.

than 6 months after an initial Omicron infection. It is anticipated that epidemic levels will remain low for the next 3 to 6 months. However, as immunity declines over time, the risk of COVID-19 resurgence may increase.

Viral mutation serves as another cause for reinfection, as it can render previously established acquired immunity ineffective against new variants. Reinfections with SARS-CoV-2 original strain, Alpha, Beta, Delta, and Omicron variants have been observed in numerous countries, leading to ongoing epidemic waves. Numerous studies have demonstrated that individuals previously infected with pre-Omicron strains exhibited a higher risk of reinfection by the Omicron variant (*6*). The univariate analyses in this study revealed that the reinfection incidence following primary infections by the original strain or by the Alpha or Delta variant was significantly higher than the reinfection incidence following the primary infection by the Omicron variant.

China's dynamic COVID-zero strategy has effectively maintained low morbidity and mortality rates in the country for the past three years. However, it remains challenging to independently discern the effects of variants and time elapsed since the initial infection on SARS-CoV-2 reinfection. The SARS-

TABLE 2. Univariate analysis on the associated factors of SARS-CoV-2 reinfection, according to primary infection strain (*n*=368).

Factor	Wild type infection, *n* (%) (*N*=68)						Alpha/Delta infection, *n* (%) (*N*=88)						Omicron infection, *n* (%) (*N*=212)					
	Reinfection cases			Non-reinfection cases	χ^2	*P*	Reinfection cases			Non-reinfection cases	χ^2	*P*	Reinfection cases			Non-reinfection cases	χ^2	*P*
	Confirmed case	Probable case	Sub-total				Confirmed case	Probable case	Sub-total				Confirmed case	Probable case	Sub-total			
Gender																		
Male	11 (30.6)	4 (11.1)	15 (41.7)	21 (58.3)	2.13	0.145	14 (31.1)	2 (4.4)	16 (35.6)	29 (64.4)	0.01	0.947	9 (8.8)	13 (12.7)	22 (21.6)	80 (78.4)	1.32	0.251
Female	16 (50.0)	3 (9.4)	19 (59.4)	13 (40.6)			11 (25.6)	4 (9.3)	15 (34.9)	28 (65.1)			9 (8.2)	8 (7.3)	17 (15.5)	93 (84.5)		
Age, years																		
0–17	0 (0)	1 (14.3)	1 (14.3)	6 (85.7)			4 (28.6)	0 (0)	4 (28.6)	10 (71.4)			1 (5.6)	2 (11.1)	3 (16.7)	15 (83.3)		
18–59	25 (51.0)	5 (10.2)	30 (61.2)	19 (38.8)	9.04	0.011	17 (33.3)	5 (9.8)	22 (43.1)	29 (56.9)	3.50	0.173	16 (8.7)	19 (10.4)	35 (19.1)	148 (80.9)	0.74	0.692
≥60	2 (16.7)	1 (8.3)	3 (25.0)	9 (75.0)			4 (17.4)	1 (4.3)	5 (21.7)	18 (78.3)			1 (9.1)	0 (0)	1 (9.1)	10 (90.9)		
Occupation																		
Medical worker	4 (100.0)	0 (0)	4 (100.0)	0 (0)	2.39	0.122	1 (33.3)	0 (0)	1 (33.3)	2 (66.7)	0.30	0.586	5 (25.0)	4 (20.0)	9 (45.0)	11 (55.0)	8.55	0.004
Other	23 (35.9)	7 (10.9)	30 (46.9)	34 (53.1)			24 (28.2)	6 (7.1)	30 (35.3)	55 (64.7)			13 (6.8)	17 (8.9)	30 (15.6)	162 (84.4)		
Clinical manifestation of primary infection																		
Asymptomatic	6 (46.2)	2 (15.4)	8 (61.5)	5 (38.5)	0.86	0.355	6 (42.9)	2 (14.3)	8 (57.1)	6 (42.9)	2.46	0.117	2 (4.3)	6 (12.8)	8 (17.0)	39 (83.0)	0.08	0.783
Symptomatic	21 (38.2)	5 (9.1)	26 (47.3)	29 (52.7)			19 (25.7)	4 (5.4)	23 (31.1)	51 (68.9)			16 (9.7)	15 (9.1)	31 (18.8)	134 (81.2)		
Interval since last infection*																		
3 to 6 months	0 (0)	0 (0)	0 (0)	0 (0)	–	–	0 (0)	0 (0)	0 (0)	0 (0)	–	–	0 (0)	1 (4.0)	1 (4.0)	24 (96.0)	2.90	0.089
>6 months	27 (39.7)	7 (10.3)	34 (50.0)	34 (50.0)			25 (28.4)	6 (6.8)	31 (35.2)	57 (64.8)			18 (9.6)	20 (10.7)	38 (20.3)	149 (79.7)		
Interval since last vaccination†																		
Unvaccinated	0 (0)	0 (0)	0 (0)	0 (0)			1 (25.0)	0 (0)	1 (25.0)	3 (75.0)			0 (0)	1 (25.0)	1 (25.0)	3 (75.0)		
<12 months	11 (42.3)	2 (7.7)	13 (50.0)	13 (50.0)	0.02	0.893	23 (31.1)	5 (6.8)	28 (37.8)	46 (62.2)	2.22	0.329	4 (8.0)	6 (12.0)	10 (20.0)	40 (80.0)	0.06	0.972
≥12 months	9 (33.3)	4 (14.8)	13 (48.1)	14 (51.9)			1 (12.5)	0 (0)	1 (12.5)	7 (87.5)			14 (10.6)	13 (9.8)	27 (20.5)	105 (79.5)		

Note: "–" means not applicable.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

* The interval between non-cases is the time from the first infection to the investigation date.

† Only 325 respondents had access to detailed vaccination information.

TABLE 3. Logistic regression analysis on the associated factors of SARS-CoV-2 reinfection, according to primary infection strain (*n*=325).

Factors	Wild type		Alpha/Delta		Omicron	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Gender						
Female	Ref		Ref		Ref	
Male	0.61 (0.17, 2.16)	0.442	1.02 (0.37, 2.81)	0.968	2.32 (1.00, 5.35)	0.049
Age, years						
0–17	Ref		Ref		Ref	
18–59	6.71 (0.59, 76.04)	0.124	2.38 (0.50, 11.41)	0.277	1.69 (0.35, 8.17)	0.513
≥60	2.01 (0.14, 29.25)	0.610	0.61 (0.11, 3.49)	0.582	0.36 (0.03, 4.76)	0.436
Occupation						
Other	Ref		Ref		Ref	
Medical worker	Inf (0.68, Inf)	0.999	0.81 (0.06, 10.71)	0.870	9.13 (2.70, 30.90)	0.000
Clinical severity of first infection						
Asymptomatic	Ref		Ref		Ref	
Symptomatic	0.29 (0.05, 1.62)	0.158	0.29 (0.07, 1.18)	0.083	1.25 (0.48, 3.26)	0.654
SARS-CoV-2 vaccination status						
Incomplete	Ref		Ref		Ref	
Complete	1.53 (0.17, 13.86)	0.705	0.22 (0.04, 1.12)	0.073	0.87 (0.14, 5.29)	0.876
Booster	1.06 (0.15, 7.39)	0.951	0.19 (0.03, 1.11)	0.066	0.49 (0.08, 2.88)	0.426
Interval since last vaccination						
Nonvaccinated	−	−	Ref		Ref	
<12 months	Ref		12.46 (0.68, 228.72)	0.089	0.42 (0.02, 9.40)	0.586
≥12 months	1.15 (0.32, 4.08)	0.835	2.10 (0.06, 77.31)	0.688	0.29 (0.01, 6.64)	0.439
Interval since last infection						
3 to 6 months	−	−	−	−	Ref	
>6 months	−	−	−	−	9.66 (1.12, 83.60)	0.039

Note: "−" means not applicable; Ref means reference group.
Abbreviation: *OR*=odds ratio; *CI*=confidence interval; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

CoV-2 Omicron variant was imported into Guangdong in December 2021 and became the dominant strain in 2022. Notably, the primary infections' dominant variants shifted from Omicron BA.1 and BA.2 in early 2022 to BA.5 and BF.7 towards the end of the year. The analysis suggests that the risk of reinfection by different Omicron subvariants remains low but significantly increases after six months.

This study found that healthcare workers experienced a higher reinfection incidence than other populations, suggesting that increased professional exposure during epidemic periods may be a contributing factor (*7*).

In the present study, the majority of reinfection cases presented with symptoms; however, only a minority necessitated medical intervention, and no critical cases were detected. The findings suggest that protection conferred by a prior infection may contribute to a reduced incidence of severe illness upon reinfection, irrespective of the viral variants or the time elapsed since the previous infection. This observation is in alignment with the outcomes of other research studies (*8*–*9*). Although the study did not identify a significant association between vaccination and reinfection, prior research indicates that hybrid immunity — stemming from both a previous infection and a recent booster vaccination — offers the most effective defense against symptomatic Omicron infections (*10*).

This study has several limitations that warrant consideration. First, the study was conducted using a telephone survey, which might have introduced non-response bias compared to a face-to-face survey.

Nevertheless, we compared the demographic characteristics of the participants and the non-respondent group, finding no statistically significant differences between them. This suggests that the study maintains adequate population representation.

Second, information regarding reinfection-associated symptoms and case classification was obtained via self-report; thus, the potential underestimation of reinfection incidence may be a concern. Asymptomatic reinfections are less likely to result in laboratory testing or clinical visits and could lead to an underestimation of the actual occurrence of reinfections.

Additionally, due to the relatively limited scale of COVID-19 cases in Guangdong in the past three years, the re-exposure risk among previously infected individuals remained artificially controlled prior to adjustments in epidemic prevention policies. Consequently, nearly all exposures were concentrated in December 2022, making it challenging to differentiate reinfections based on time intervals and the influence of distinct viral variants within this investigation.

Future research should focus on conducting large-scale studies with extended follow-up periods to further elucidate the dynamics of SARS-CoV-2 reinfection.

The results of this study may enhance the assessment of potential epidemic risks and bolster response preparedness. Our findings indicate that, for at least the next three months, the likelihood of an epidemic resurgence driven by the Omicron variant in Guangdong is relatively low. Nevertheless, it remains crucial to maintain vigilant surveillance of emerging SARS-CoV-2 variants and to conduct routine population-based antibody level surveys.

Conflicts of interest: No conflicts of interest.

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Preplanned Studies

Timing and Magnitude of the Second Wave of the COVID-19 Omicron Variant — 189 Countries and Territories, November 2021 to February 2023

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Summary

What is already known about this topic?

The first nationwide wave of coronavirus disease 2019 (COVID-19), driven by the Omicron variant, has largely subsided. However, subsequent epidemic waves are inevitable due to waning immunity and the ongoing evolution of the severe acute respiratory syndrome coronavirus 2.

What is added by this report?

Insights gleaned from other nations offer guidance regarding the timing and scale of potential subsequent waves of COVID-19 in China.

What are the implications for public health practice?

Understanding the timing and magnitude of subsequent waves of COVID-19 in China is crucial for forecasting and mitigating the spread of the infection.

Due to waning immunity against coronavirus disease 2019 (COVID-19) and the ongoing emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants, another epidemic wave of COVID-19 is expected. Insights from other countries can offer valuable information on the timing and severity of the upcoming COVID-19 wave in China. In this study, we analyzed surveillance data related to COVID-19 from 189 countries that experienced two or more waves of the SARS-CoV-2 Omicron variant. The median time between the first and second wave peaks was 164 days, and between the first and third wave peaks was 247 days. The median relative peaks of the second and third waves compared to the first wave were 14.5% and 11.2%, respectively.

The relative peak of the second wave showed a significant increase in relation to the gross domestic product per capita (P<0.001), urbanization rate (P=0.003), population density (P=0.007), and proportion of older adults over 65 years (P<0.001). Meanwhile, it decreased significantly with the proportion of individuals aged 0–14 years (P<0.001). In conclusion, the historical context and progression of COVID-19 outbreaks in other countries may help inform risk assessment for future outbreaks in China. However, the timing of the next COVID-19 wave may also be influenced by several unknown factors, including the rapid viral evolution of SARS-CoV-2.

Understanding the timing and magnitude of subsequent COVID-19 waves in China is crucial for predicting and mitigating the spread of the virus. The Omicron variant, first identified in South Africa and Botswana and reported to the World Health Organization (WHO) on November 24, 2021 (*1*), has led to at least three waves of COVID-19 in Europe, the Americas, and the Western Pacific (*1*). However, due to China's zero-COVID policy and stringent nonpharmaceutical interventions, the country experienced its first nationwide COVID-19 wave caused by the Omicron variant considerably later compared to other nations. The initial and most severe nationwide wave, attributed to the SARS-CoV-2 Omicron BF.1 and BA.2.2 subvariants, subsided by January 25, 2023 in China. Nevertheless, as immunity to COVID-19 wanes (*2*) and the SARS-CoV-2 Omicron variant continues to evolve (*3*), subsequent waves are inevitable. Consequently, insights from other countries can offer valuable information regarding the timing and magnitude of future COVID-19 waves in China.

In the present study, we analyzed COVID-19 surveillance data from 237 countries to determine the timing and magnitude of the first, second, and third waves of COVID-19 attributable to the SARS-CoV-2 Omicron variant. Furthermore, we examined the correlations between these waves and socioeconomic factors. Daily confirmed COVID-19 case data for 237 countries from January 1, 2020, to February 28, 2023, were obtained from the WHO Coronavirus (COVID-19) Dashboard (*1*), and Our World in Data (*4*). Socioeconomic status data for each country were

also collected from The World Bank (*5*), encompassing gross domestic product (GDP) per capita, urbanization rate (percentage of people residing in urban areas), population density, and the proportions of individuals aged >65 years and <14 years. Given that the SARS-CoV-2 Omicron variant was initially identified in South Africa and Botswana and reported to the WHO on November 24, 2021 (*6*), our analysis focused on the period following this date.

In this study, the highest number of daily confirmed COVID-19 cases was considered the peak of a wave. The period between two consecutive waves of the SARS-CoV-2 Omicron variant was defined as the time interval between the peak timings of these waves. The relative peaks of the second and third waves were calculated by dividing the peaks of these waves by the peak of the first wave. Since the first nationwide wave of the SARS-CoV-2 Omicron variant occurred in China in January 2023, the timing of the second wave is of significant interest. Therefore, we primarily focused on the period between the first and second waves of the Omicron variant in other countries.

The definition of a COVID-19 wave within a country used in this study was similar to our previous studies on influenza (*7*). The onset timing of an epidemic wave was identified as the first seven consecutive days with a smoothed increase in daily cases exceeding a predetermined baseline. The baseline was set as the 50% quantile of the non-zero number of daily cases (*8*). The end of a wave was defined as the first of seven consecutive days with a smoothed number of daily cases below the baseline.

Due to the potential impact of fluctuations in surveillance data on estimating the peak timing and peak value of a wave, a 7-day moving average was used to smooth the COVID-19 surveillance data in this study (*7*). Spearman's correlation was utilized to characterize the relationship between socioeconomic factors and the period of peak timing between two consecutive waves or the relative peak of the second wave, as these data did not exhibit a normal distribution. Correlation analysis was performed using R software (version 4.0.3; R Core Team, Vienna, Austria). A two-sided *P*-value of 0.05 or lower was considered statistically significant.

According to the established definition of a COVID-19 wave, by March 2023, a minimum of two waves of the SARS-CoV-2 Omicron variant had transpired in 189 countries. Concurrently, at least three waves were observed in 120 countries, and over four waves occurred in 48 countries.

The peak timings of the first and second waves of the SARS-CoV-2 Omicron variant significantly varied across 189 countries. Early peak timing in the first wave did not consistently indicate early peak timing in the second wave (Figure 1). Among these countries, the duration between the peak timings of the first and second waves ranged from 15 days in El Salvador to 351 days in Eswatini, with a median of 164 days [interquartile range (IQR): 125.5–184.0] and generally followed a Weibull distribution (Figure 2A). For 55 countries (30%), the duration between the peak timings of the first and second waves was between 150 and 180 days. In only seven countries, this period was less than 60 days, possibly due to small initial wave peaks in those countries. As such, these fluctuations are important factors in understanding COVID-19 wave patterns.

In only eight countries (i.e., Japan, Somalia, Guatemala, Federated States of Micronesia, El Salvador, Solomon Islands, Cayman Islands, and Australia), the peak of the second wave was higher than that of the first wave. Conversely, in 181 countries, the second wave peak was substantially lower than the first wave peak. In these countries, on average, the second wave peak was only one-fifth of the first wave peak. The relative peak of the second wave ranged from 1.0% to 73.1%, with a median value of 14.5% (IQR: 6.9%–28.5%), following an exponential distribution (Figure 2B).

More than three waves of the Omicron variant occurred in 120 of the 189 countries. The duration between the peak timings of the first and third waves varied from 30 to 404 days, with a median of 243 days (IQR: 184.2–314.5) (Figure 2C). In 69 countries (57.5%), the duration between the peak timings of the first and third waves ranged from 200 to 320 days. Only three countries (El Salvador, Solomon Islands, and Japan) had a third wave peak higher than the first wave peak. In the other 117 countries, the relative third wave peak ranged from 1% to 83.6% with a median value of 11.2% (IQR: 4.5%–20.6%), following an exponential distribution (Figure 2D). Generally, in these 117 countries, the third wave peak was slightly lower than the second wave peak.

The interval between the peak timings of the first and second waves did not exhibit a statistically significant rank correlation with any of the five socioeconomic factors analyzed in this study (Table 1). However, the second wave's relative peak demonstrated a significant increase in association with GDP per capita (P<0.001), urbanization rate (P=0.003),

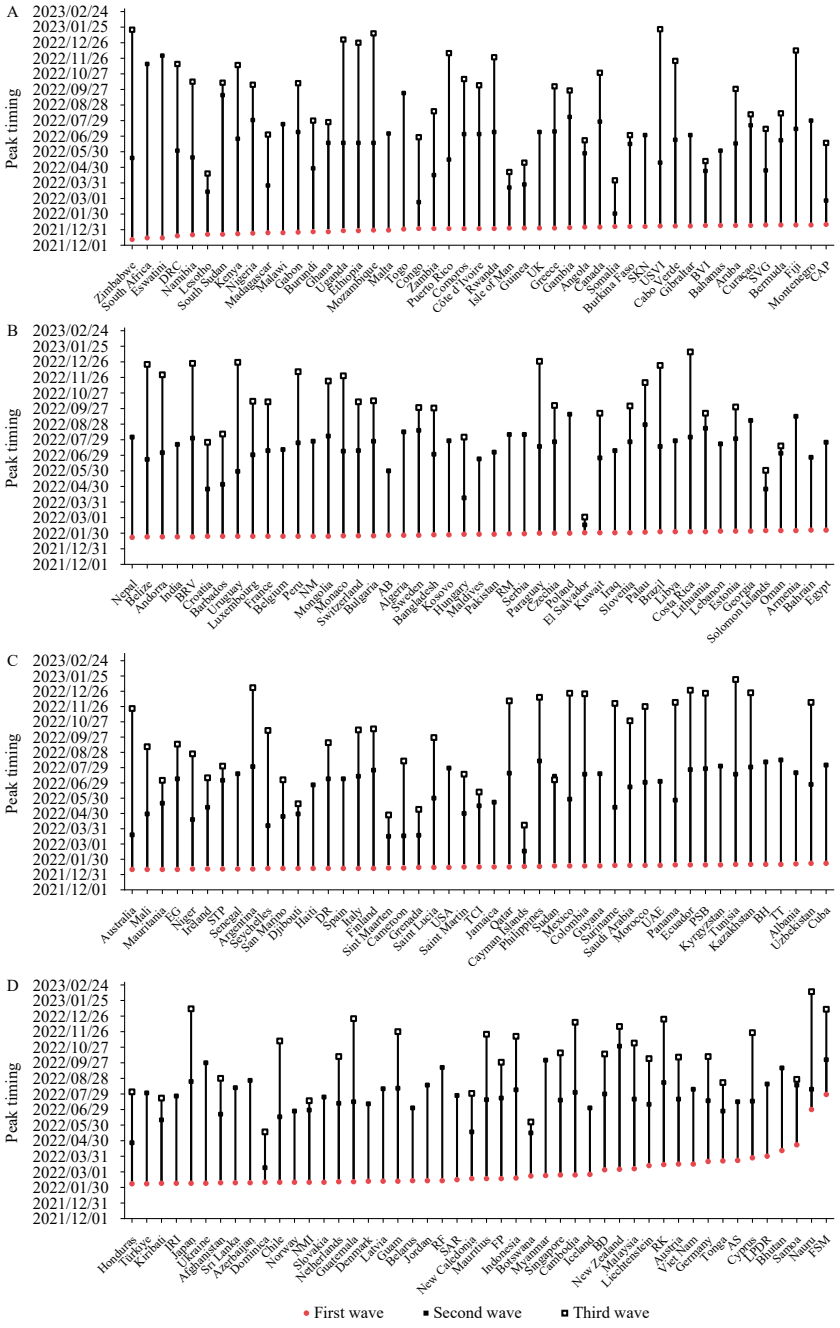

FIGURE 1. Peak timing of the first, second, and third waves of COVID-19 caused by the SARS-CoV-2 Omicron variant in 189 countries. (A) In 47 countries with the peak timing of the first waves between December 12, 2021 and January 10, 2022; (B) In 47 countries with the peak timing of the first waves between January 10, 2022 and January 22, 2022; (C) In 47 countries with the peak timing of the first waves between January 22, 2022 and February 5, 2022; (D) In 48 countries with the peak timing of the first waves between February 6, 2022 and July 28, 2022.

Note: Countries were sorted by the increased peak timing of the first waves.

Abbreviation: DRC=Democratic Republic of the Congo; UK=United Kingdom; SKN=Saint Kitts and Nevis; USVI=United States Virgin Islands; BVI=British Virgin Islands; SVG=Saint Vincent and the Grenadines; CAP=Central African Republic; EG=Equatorial Guinea; STP=Sao Tome and Principe; DR=Dominican Republic; USA=United States of America; TCI=Turks and Caicos Islands; UAE=United Arab Emirates; PSB=Plurinational State of Bolivia; BH=Bosnia and Herzegovina; TT=Trinidad and Tobago; BRV=Bolivarian Republic of Venezuela; NM=North Macedonia; AB=Antigua and Barbuda; RM=Republic of Moldova; IRI=Islamic Republic of Iran; NMI=Commonwealth of the Northern Mariana Islands; RF=Russian Federation; SAR=Syrian Arab Republic; FP=French Polynesia; BD=Brunei Darussalam; RK=Republic of Korea; AS=American Samoa; LPDR=Lao People's Democratic Republic; FSM=Federated States of Micronesia; COVID-19=coronavirus disease 2019; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

population density (P=0.007), and the percentage of older adults (>65 years; P<0.001). Conversely, it exhibited a significant decrease in relation to the proportion of individuals aged 0-14 years (P<0.001) (Table 1).

DISCUSSION

Predicting the timing and magnitude of future COVID-19 waves is crucial for efficiently preparing for and responding to potential crises. Due to the implementation of the dynamic zero-COVID policy in China, the first COVID-19 wave caused by the SARS-CoV-2 Omicron variant occurred later in China than in other countries. Consequently, insights can be gained from examining the development of outbreaks elsewhere. Our study indicates that in most countries, the second wave of COVID-19 brought on by the

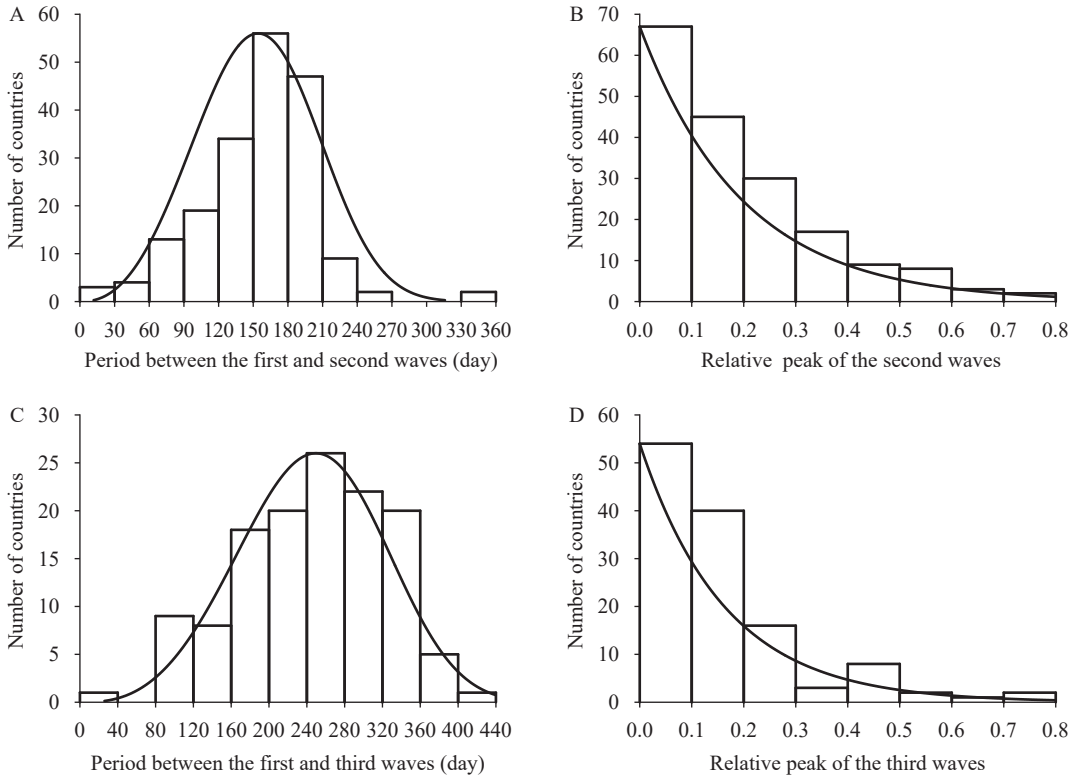

FIGURE 2. Distribution of time periods and relative peaks of the second or third waves compared to the first waves of the SARS-CoV-2 Omicron variant. (A) Distribution of the time period between the first and second waves in 189 countries; (B) Distribution of relative peak of the second waves compared to the first waves in 181 countries; (C) Distribution of the time period between the first and third waves in 120 countries; (D) Distribution of relative peak of the third waves compared to the first waves in 117 countries.
Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

TABLE 1. Correlation between socioeconomic factors and the timing and relative peak of the second compared with the first waves.

Socioeconomic factors	Peak timing		Relative peak	
	Spearman correlation	*P* value	Spearman correlation	*P* value
GDP per capita	−0.037	0.616	0.298	<0.001
Urbanization rate	0.042	0.571	0.214	0.003
Population density	−0.077	0.294	0.196	0.007
Proportion of older adults >65 years	0.127	0.081	0.307	<0.001
Proportion of <14 teenagers	−0.064	0.384	−0.347	<0.001

Abbreviation: GDP=gross domestic product.

SARS-CoV-2 Omicron variant emerged 5–7 months after the first wave, with the magnitude of the second wave being significantly lower than that of the initial wave.

In addition, our analysis revealed that the peak timing of the second COVID-19 waves in 107 out of 151 Northern Hemisphere countries occurred between June 1 and August 30, 2022, suggesting that warm weather has a limited impact on curbing the spread of the epidemic. This observation may be attributed to the fact that at the early stages of an emergent pathogen, an ample supply of susceptible individuals can constrain the influence of climatic factors (*9*).

Over three years have passed since the COVID-19 pandemic was first identified in December 2019 (*10*), yet numerous factors that could influence the transmission dynamics of SARS-CoV-2, such as viral evolution and environmental drivers, remain unclear. The median duration between the initial and subsequent waves of COVID-19 was marginally shorter than the reported immunity period — approximately 8 months of immunity via vaccination, 12 months through infection, and over 12 months with both (*1*). Furthermore, there was no statistically significant rank correlation observed between the timing of the second wave of COVID-19 and socioeconomic factors. One possible explanation for this is the rapid evolution of SARS-CoV-2, which may play a crucial role in the timing of COVID-19's second waves (*2*). If a new variant manages to evade the pre-existing immune response, even a recent infection may not guarantee protection.

The results of this study should be interpreted while bearing in mind two key limitations. Firstly, the primary source of COVID-19 surveillance data analyzed was obtained from the WHO, and potential discrepancies between different COVID-19 surveillance databases were not examined. Secondly, this investigation did not take into account certain factors that might influence the onset and intensity of subsequent waves, such as the enforcement of non-pharmaceutical interventions, including but not limited to, the regulation of international travel (*11*).

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Preplanned Studies

The Infection of Healthcare Workers and the Reinfection of Patients by Omicron Variant — Jiangsu Province, China, December 2022 to January 2023

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Summary

What is already known about this topic?

Healthcare workers (HCWs) and previously infected patients (PIPs) may experience a wave of epidemic following the modification of the country's coronavirus disease (COVID)-zero policy in China.

What is added by this report?

As of early January 2023, the initial wave of the COVID-19 pandemic among HCWs had effectively subsided, with no statistically significant differences observed in infection rates compared to those of their co-occupants. The proportion of reinfections among PIPs was relatively low, particularly in those with recent infections.

What are the implications for public health practice?

Medical and health services have resumed normal operations. For patients who have recently experienced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, appropriate relaxation of policies may be considered.

The coronavirus disease 2019 (COVID-19) emerged in December 2019 and rapidly spread across the globe (*1*–*2*). As of November 14, 2021, approximately 3.8 billion people had been infected or re-infected, accounting for 43.9% of the global population, with a peak in April 2021 (*3*). The proportion of infected individuals varied by region: 73.6% in Eastern Europe, 59.5% in Central Europe, 21.4% in Western Europe, 30.9% in North America, and 25.1% in Southern Latin America (*3*). In addition, healthcare workers (HCWs) have been identified as particularly vulnerable with a higher risk of infection compared to the general population (*4*). An Italian study also reported that HCWs were more than twice as likely to be re-infected compared to non-HCWs (*5*). These disparities between countries highlight the influence of COVID-19 treatment, host immunity characteristics, and national and local policies on transmission patterns (*6*).

In the early stages of the pandemic, the Chinese government implemented strict measures to combat the virus, successfully controlling the domestic outbreak. However, with the emergence of the Omicron variant, the virus has undergone significant changes, resulting in a reduced virulence while maintaining high infectivity (*7*). In response, the Chinese government refined its preventive strategies. On December 7, 2022, China introduced "Ten New Measures", including discontinuing region-wide mass testing and permitting home isolation or quarantine.

As the Omicron variants continue to spread in China, this study aimed to investigate the infection statuses of HCWs in a general hospital in Jiangsu Province, reinfections of previously infected persons (PIPs), as well as the impact of vaccination on infection rates. These findings could provide a theoretical basis for developing health policy. Both HCWs and PIPs represent unique population groups: the infection status of HCWs directly affects the quality of medical services, particularly during the COVID-19 pandemic (*8*), while assessing the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection is vital for understanding its burden and impact on the general population, informing appropriate mitigation policies (*9*). Therefore, conducting research on these two distinct populations bears significant practical implications.

The participants in this study comprised current HCWs in the Affiliated Taizhou People's Hospital of Nanjing Medical University and PIPs who were admitted due to COVID-19 between January 1, 2020, and December 7, 2022. The diagnosis and classification of COVID-19 rely on the updated definition provided by the World Health Organization (WHO) in their Public Health Surveillance guidelines,

as of July 22, 2022. PIPs in this investigation were individuals who had a previous positive SARS-CoV-2 RT-PCR test following clinical recovery from a COVID-19 episode and at least one negative RT-PCR result after their initial infection.

This study was conducted from January 6 to 11, 2023, utilizing electronic questionnaires to gather demographic and epidemiological data. The office of the dean at our hospital notified the department directors to organize and complete the questionnaires for HCWs. Testing and vaccination dates were obtained from the clinical laboratory information system and the public health department records within our hospital, respectively, to ensure data accuracy. For PIPs, their demographic characteristics, clinical information during hospitalization, and contact information were obtained from the information office based on case diagnoses. A total of 732 PIPs were identified, with 53 patients being excluded due to missing contact information. Following this, our team conducted telephone interviews and completed the questionnaire for the remaining PIPs.

All data were analyzed using SPSS (version 26.0, IBM Corporation, Armonk, NY, USA) and Excel (version 2010, Microsoft Corporation, Redmond, WA, USA). Qualitative data were reported as frequency (percentage) and compared using the chi-square test. Quantitative data were presented as mean±standard deviation when normality assumptions were met, and as median (interquartile range) when normality assumptions were not met.

A total of 2,347 electronic questionnaires were successfully retrieved from HCWs and included in the analysis (Table 1). Of the 2,347 HCWs surveyed, 1,975 were found to be infected, with an infection rate of 84.1%. The infection curve indicated that the first wave of the epidemic within the hospital had primarily concluded, reaching a peak in daily new cases from December 21 to 23, 2022 (Figure 1). Among the 1,975 infected HCWs, 20 (1.0%) required hospitalization, with one (0.1%) being admitted to the intensive care unit (ICU). Furthermore, 794 individuals who experienced severe symptoms during their infection underwent a hospital-organized physical examination post-recovery. Out of these individuals, 185 (23.3%) were diagnosed with pneumonia, and 5 (0.6%) had myocarditis.

In addition, there were 7,068 co-occupants of the

TABLE 1. Demographic characteristics of the subjects.

Characteristics	HCWs (*n*=2,347)	PIPs (*n*=382)
Sex (%)		
Male	548 (23.3)	220 (57.6)
Female	1,799 (76.7)	162 (42.4)
Age (years)	33 (29–42)	50 (35–58)
Times of vaccination (%)		
0	16 (0.7)	21 (5.5)
1	17 (0.7)	23 (6.0)
2	113 (4.8)	66 (17.3)
3	1,225 (52.2)	270 (70.7)
4	976 (41.6)	2 (0.5)

Abbreviation: HCWs=healthcare workers; PIPs=previously infected persons.

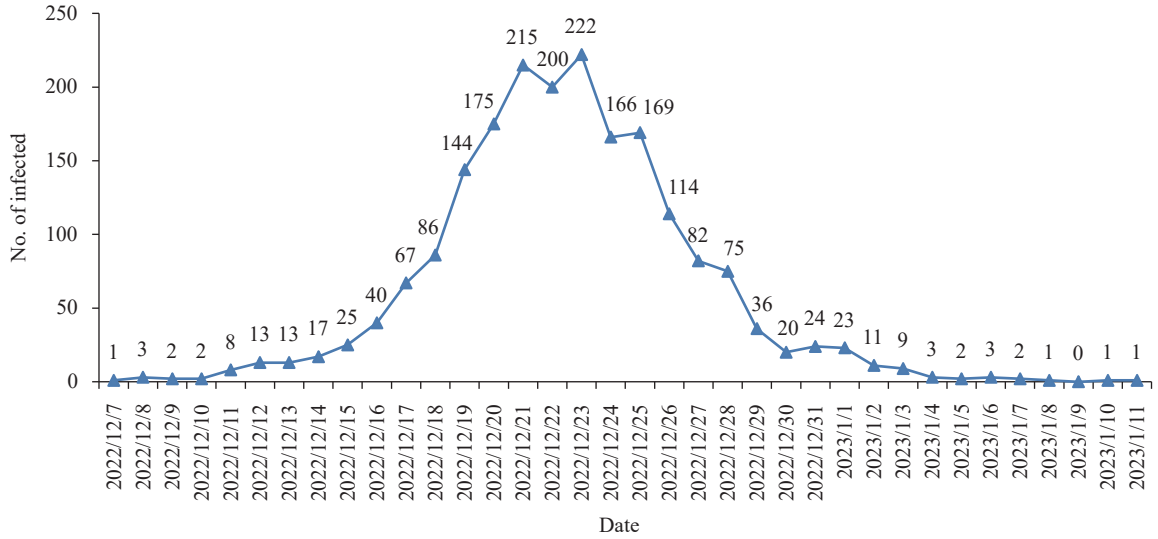

FIGURE 1. The number of healthcare workers infected with the coronavirus disease 2019 in our hospital over time.

HCWs, among whom 5,995 were infected, resulting in an infection rate of 84.8%. The infection rate did not significantly differ from that of HCWs in the same hospital (P>0.05, Figure 2). Furthermore, the secondary attack rate in families was 82.1%. Among the 1,975 medically infected individuals in our hospital, 1,018 (51.5%) were infected before the first infection of their co-resident, 188 (9.5%) were infected after their co-resident's first infection, 620 (31.4%) were infected on the same day as their co-resident's first infection, and 149 (7.5%) lived alone.

Moreover, we also explored the effect of vaccination on the rate of infection among HCWs, with a focus on the association between the number of vaccine doses, timing of the last dose, and the infection rate. It was found that receiving the fourth dose of the CanSinoBIO (viral vector) vaccine and a shorter time interval since the last dose were both significantly associated with a reduced infection rate (Table 2). Furthermore, during the initial wave of the COVID-19 pandemic, an investigation was conducted on the symptoms of 1,266 infected HCWs at our hospital. The findings indicate that the CanSinoBIO vaccine may mitigate the severity of COVID-19 symptoms, particularly fever and alterations in olfactory and gustatory function.

In order to assess hospitalized PIPs within our institution, we organized staff to conduct this survey, and the data of 382 patients were successfully collected and analyzed (Table 1). According to the WHO grading standards, only one patient was categorized as severe (grade 6), 31 as mild cases (grade 4), and the remaining 350 as mild cases (grade 3 or below). Of the 382 patients, 21 were initially infected with SARS-CoV-2 more than a year ago. After China's adjustment to the zero-COVID policy, nine were reinfected, yielding a secondary infection proportion of 42.9%. A total of 114 patients were infected between three months and one year ago, and 12 were reinfected, resulting in an infection proportion of 10.5%. About 247 patients were infected within the past three months, and none exhibited COVID-19 symptoms or tested positive for SARS-CoV-2 using the RT-PCR method. There was a significant difference observed between any two groups (P<0.05; Figure 3). All the re-infected patients had symptoms of grade 2 or less, of whom 5 were asymptomatic.

DISCUSSION

The findings in this study suggest that the first wave of the COVID-19 epidemic among HCWs has largely subsided, marked by a relatively high infection rate. Currently, medical and health services have fully

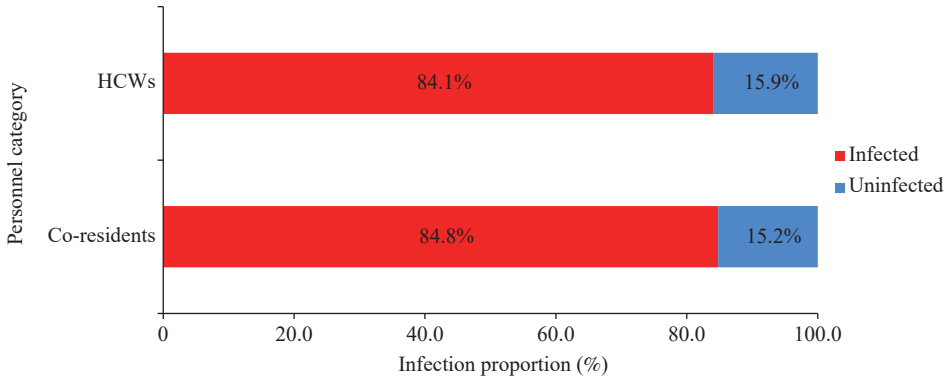

FIGURE 2. Comparison of infection between healthcare workers and co-residents.

TABLE 2. Association between vaccination and infection rates among healthcare workers [n (%)].

Vaccination		Uninfected (n=372)	Infected (n=1,975)	χ^2/z	P
Number of vaccinations	≤3	183 (13.3)	1,188 (86.7)	15.48	<0.001
	4	189 (19.4)	787 (80.6)		
Last inoculation time	<1 month	183 (19.0)	780 (81.0)	14.92	<0.001
	1 month to 1 year	35 (11.4)	271 (88.6)		
	>1 year	138 (13.8)	863 (86.2)		
	Missing	16 (20.8)	61 (79.2)		

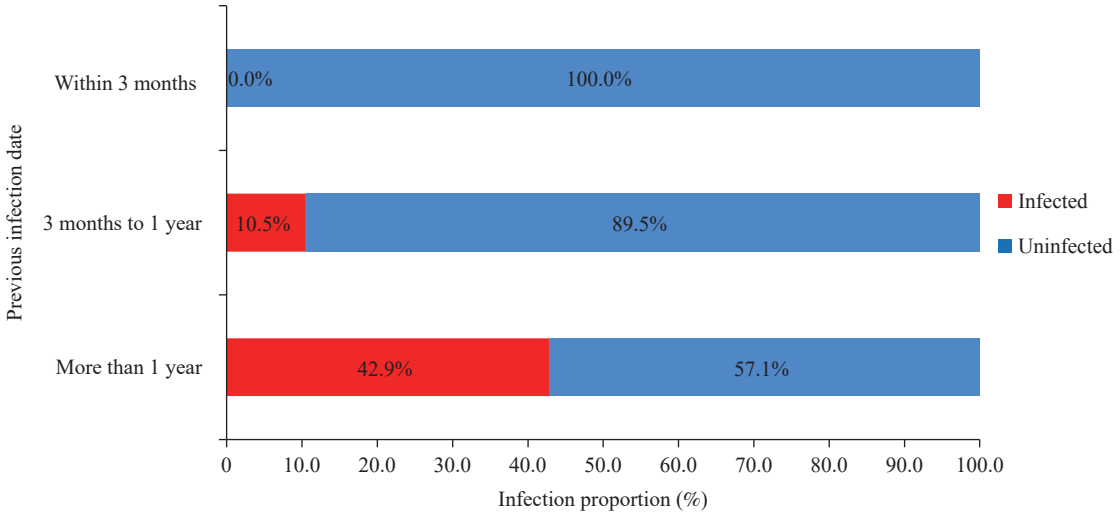

FIGURE 3. Comparison of the infections of previously infected patients.

returned to normal compared to the pre-adjustment period of the zero-COVID policy. It is strongly recommended that those who have not received the fourth vaccine dose do so as soon as possible in order to decrease infection rates. The fourth dose administered to HCWs in our hospital utilizes an adenovirus vector (CanSinoBIO), which induces robust antigen-specific humoral and cellular immune responses.

Nevertheless, during this epidemic wave, HCWs experienced an excessively high rate of SARS-CoV-2 infections in a single day, adversely impacting medical and health services. Efforts should be made to prevent such occurrences during future waves. Additionally, ensuring the timely availability of appropriate medications, such as antipyretic drugs and analgesics, is crucial in order to alleviate concerns and prevent panic before the next outbreak.

Our research indicates that the proportion of reinfection of SARS-CoV-2 is relatively low among PIPs, particularly for those with short-term recovery. This finding is consistent with previous studies (*10*). Nonetheless, the likelihood of reinfection may increase over time due to an insufficient immune response following the primary infection, which fails to provide adequate protection against subsequent infections. Furthermore, no severe cases were observed during reinfections, which could be attributed to the reduced virulence of the Omicron variant and the presence of antibodies in recovered patients. Consequently, policymakers should consider implementing less restrictive measures for individuals who have previously been infected with SARS-CoV-2, especially for those who have recovered recently.

This study examined the infection status of HCWs and the reinfection status of PIPs. Nonetheless, several limitations of this research must be acknowledged. Firstly, the study's retrospective design may have introduced a degree of recall bias, potentially compromising the accuracy of the collected data. Secondly, by drawing participants (both HCWs and PIPs) exclusively from a single hospital, the generalizability of these findings may be limited, though this does not impact the validity of the conclusions.

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Methods and Applications

Collective and Individual Assessment of the Risk of Death from COVID-19 for the Elderly, 2020–2022

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) has had profound disruptions worldwide. For a population or individual, it is critical to assess the risk of death for making preventative decisions.

Methods: In this study, clinical data from approximately 100 million cases were statistically analyzed. A software and an online assessment tool were developed in Python to evaluate the risk of mortality.

Results: Our analysis revealed that 76.51% of COVID-19-related fatalities occurred among individuals aged over 65 years, with frailty-associated deaths accounting for more than 80% of these cases. Furthermore, over 80% of the reported deaths involved unvaccinated individuals. A notable overlap was observed between aging and frailty-associated deaths, both of which were connected to underlying health conditions. For those with at least two comorbidities, the proportion of frailty and the proportion of COVID-19-related death were both close to 75 percent. Subsequently, we established a formula to calculate the number of deaths, which was validated using data from twenty countries and regions. Using this formula, we developed and verified an intelligent software designed to predict the death risk for a given population. To facilitate rapid risk screening on an individual level, we also introduced a six-question online assessment tool.

Conclusions: This study examined the impact of underlying diseases, frailty, age, and vaccination history on COVID-19-related mortality, resulting in a sophisticated software and a user-friendly online scale to assess mortality risk. These tools offer valuable assistance in informed decision-making.

INTRODUCTION

It is essential to recognize that coronavirus disease 2019 (COVID-19) presents unique characteristics, including asymptomatic predominance (*1*), asymptomatic transmissibility (*2*), and reinfection/ recurrent infection (*3*), which contribute to undetectable transmission and unforeseen risks. Consequently, it is crucial to effectively and accurately assess the risk of death for both populations and individuals in order to appropriately allocate health resources and take optimal preventive measures. However, an ideal assessment tool for this purpose remains unavailable at this time.

Several key factors including age (*4*), underlying diseases (*4*), vaccination history (*5*), and frailty (*6*) were identified as the primary factors that contribute to COVID-19-related fatalities. Notedly, underlying diseases, aging, and frailty often overlap in certain populations. Hence, understanding their interrelationship with COVID-19 mortality is crucial for predicting and assessing the risk of death.

This study analyzed clinical data and examined the associations among age, comorbidities, frailty, and vaccination history with COVID-19 mortality to create a straightforward mathematical model. Subsequently, we developed a forecasting software for population-level assessment and a web-based tool for individual risk evaluation. Our innovative tools provide reliable support for decision-making.

METHODS

Collected and Analyzed Clinical Data: Clinical data from approximately 100 million cases were collected through a comprehensive literature search using international databases and statistically analyzed. See supplementary methods for details of collection and analysis.

Development of the Locally Run Software SEIP-RA: Initially, we developed the K-SEIR-Sim software (*7*), followed by its enhancement through the creation of the SEIR-AS software (*2*). Here, we designed an improved software, SEIP-RA, which focuses on pinpointing high-risk populations. Our risk prediction

formula is incorporated into the software, allowing for corresponding recalculation of necessary results. The software is programmed in Python, with detailed formulas and parameters designed as described in Supplementary Table S1 (available in https://weekly.chinacdc.cn). The software can be freely downloaded for noncommercial use (http://peiyun.cn/download/seir_sim.files/SEIR-RA%202.64.exe).

Developed the Remotely Run Simple Tool COVID-RA: We developed a scale to assess individual risk of death by considering all critical factors contributing to mortality. This scale employs 6 questions and 14 answer choices to evaluate risk through a question-answer-score system (Supplementary Table S2, available in https://weekly.chinacdc.cn). The evaluation outcomes were categorized into low, moderate, and high risk groups. Subsequently, we converted it into an easily accessible rapid assessment tool to encourage its implementation. We incorporated this tool into a web-based platform, utilizing Python for its development, and stored the data in MySQL. The online tool in both English and Chinese languages can be accessed free of charge and without any setup requirements (http://peiyun.cn/SEIR-AS-query/).

RESULTS

Relationships between Risk Factors and the Death from COVID-19: We examined 106,103,566 COVID-19 cases from 20 countries, revealing that individuals aged over 65 years represented 76.51% of the deaths, frailty and pre-frailty (an intermediate stage between normal and frail) accounted for 83.20%, hypertension for 63.44%, cardiovascular diseases for 42.64%, dyslipidemia for 37.33%, diabetes for 35.44%, heart diseases for 28.63%, arrhythmias for 27.11%, depression for 26.84%, coronary artery disease for 25.48%, dementia for 23.18%, and renal disease for 18.86% of the fatalities (Figure 1A).

Among the elderly patients (a total of 38,645,762 cases), hyperlipidemia was present in 49.21% of the cases, hypertension in 48.22%, gastroesophageal disease in 46.98%, heart disease in 27.47%, cerebrovascular disease in 22.97%, diabetes in 20.27%, heart failure in 15.94%, depression in 14.85%, renal disease in 14.68%, and cancer in 12.91% (Figure 1B). In contrast, among patients with frailty (a total of 890,586 cases), hypertension was a factor in 63.89% of the cases, rheumatoid arthritis in 36.31%, high blood cholesterol in 36.11%, osteoporosis in 28.18%, heart disease in 26.87%, diabetes in 25.47%, depression in 23.57%, dementia in 20.13%, renal disease in 19.29%, and coronary artery disease in 18.57% (Figure 1C).

To further investigate the relationship between aging, frailty, and mortality in COVID-19 patients, we analyzed the number of underlying diseases these patients had. A nearly 75% similarity was observed in the proportion of patients with frailty who had more than two underlying diseases to that of COVID-19 related deaths with two underlying diseases (Figure 1D). In comparison, the older adult group had an approximate proportion of 62.59%. This finding suggests that the presence of two or more underlying diseases in patients with frailty can serve as a useful indicator for determining the risk of death in COVID-19 patients.

By examining clinical data and assessing the proportion of vaccination history among COVID-19-related deaths (7,348,213 total cases), we found that less than 20% of the deceased individuals were vaccinated (Figure 1E). This outcome indicates that vaccination history also serves as a valuable predictor for evaluating the risk of death in COVID-19 patients.

The Formula Proposed for Predicting the Deaths in COVID-19: Based on the analysis results and the logical relationships among population factors, we derived a mathematical formula to estimate the potential number of deaths as follows: $A = A_1 \times A_2 \times (1 - A_3) \times A_4$. This equation implies that the high-risk population (i.e., the deaths) can be calculated by multiplying the total infections by the proportion of individuals over 60 years, then by (1 – vaccination rate), and finally by the proportion of frail elderly individuals (Figure 2A). The estimated number of high-risk populations closely aligns with the actual number of COVID-19 deaths in areas with strict control measures in place, such as New Zealand, and Singapore (Figure 2B), as well as in areas with less stringent control measures, including the USA, Brazil, India, Italy, England, Germany, and Spain, Republic of Korea, Russia, Australia, Iran, Mexico, Turkey, Viet Nam, and the Netherlands (Figure 2C). To evaluate the accuracy of our prediction, we assessed the difference between our predicted values and the reported numbers of deaths. We found that the highest discrepancy was 42.06% and the lowest was 2.60%, resulting in a mean variation of 16.24% (Figure 2D).

Software Developed for Assessing the Risk of Death for a Population Suffering from COVID-19: We developed a software tool designed to assess the risk of mortality within a population, providing a reference framework for decision-making at country or regional levels. This software incorporates our risk assessment

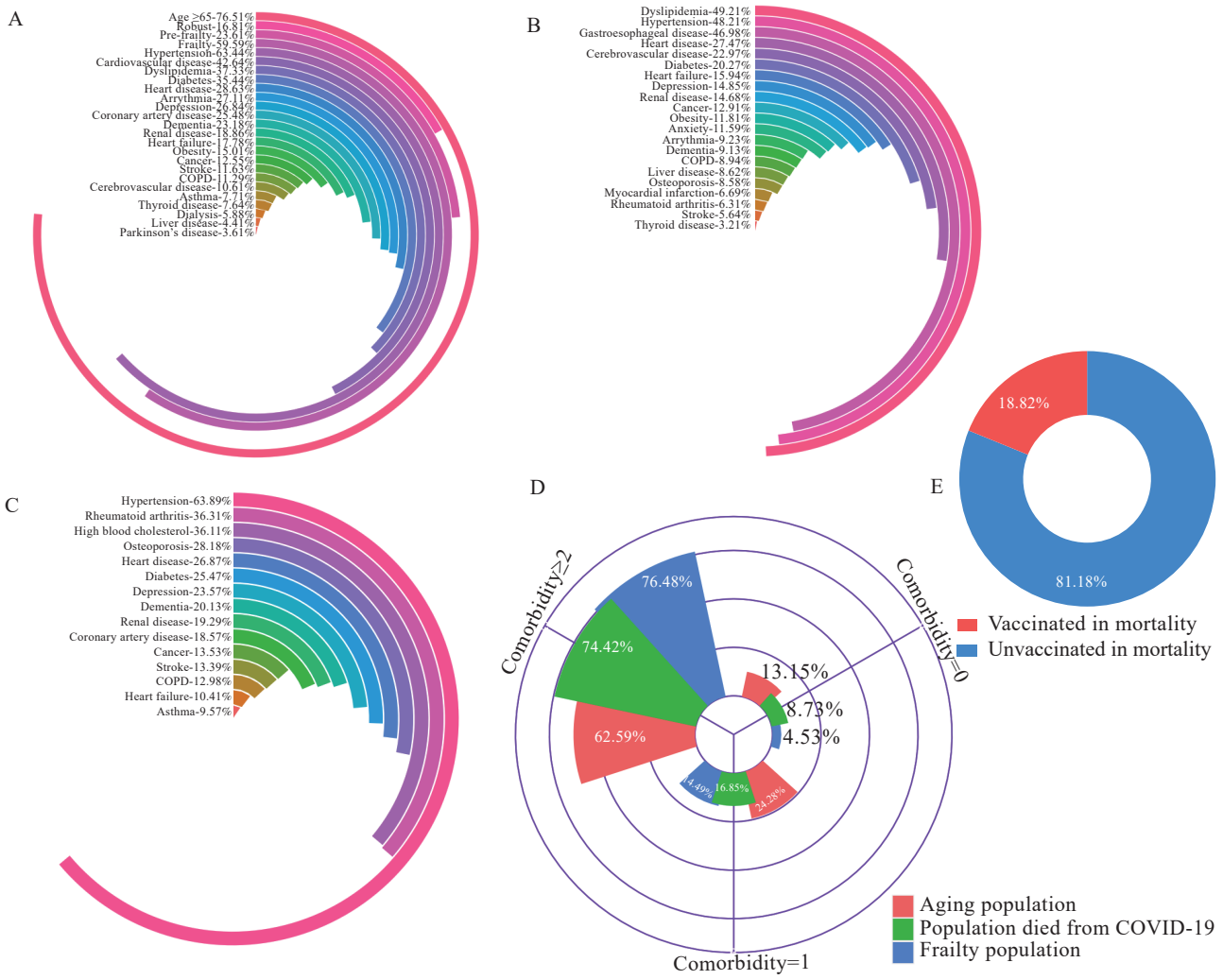

FIGURE 1. Examining the complex relationships between aging, frailty, underlying disease, and medical history and COVID-19 mortality. (A) Proportion of individuals with aging, frailty, and underlying conditions among the total cases who died of COVID-19. (B) Proportion of underlying conditions in elderly patients. (C) Proportion of various underlying conditions among patients with frailty. (D) Number of coexisting diseases and frailty syndrome correlate with the death of COVID-19. (E) Vaccination history affecting deaths of COVID-19.
Abbreviation: COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019.

formula into the traditional SEIR model, which is frequently employed for simulating the progression of an epidemic (Figure 3A). Our software offers both out-of-the-box and customizable functionality (Figure 3B). Users can input relevant epidemic parameters and click the "simulate" button to obtain the predicted total infection and death counts.

Using data from the United States between December 1, 2021 and March 1, 2022, we entered these values and executed the software. The 90-day simulation results are presented within the software interface and can be exported for further analysis (Figure 3C). We compared the predicted and reported numbers of total infections and deaths. The reported figures were 30,140,720 and 168,655, whereas the simulated figures were 30,263,302 and 186,820, respectively (Figure 3D). These findings demonstrate the practical utility of our software tool.

Scale Designed for Assessing the Risk of Death for an Individual Suffering from COVID-19: We designed a scale that considers the above main key factors that lead to COVID-19 deaths to rapidly assess the risk of death for an individual. This scale consists of four domains: frailty phenotype, comorbidity number, vaccine dose, and COVID-19 symptom (Figure 4A). We can assess the risk by way of the question and answer scoring (Figure 4B). It has 6 questions and 14 answers, and the score is rated from 0 to 6 (Supplementary Table S2). The evaluation results are as follows: low risk at <3.5; moderate risk at 3.5–5;

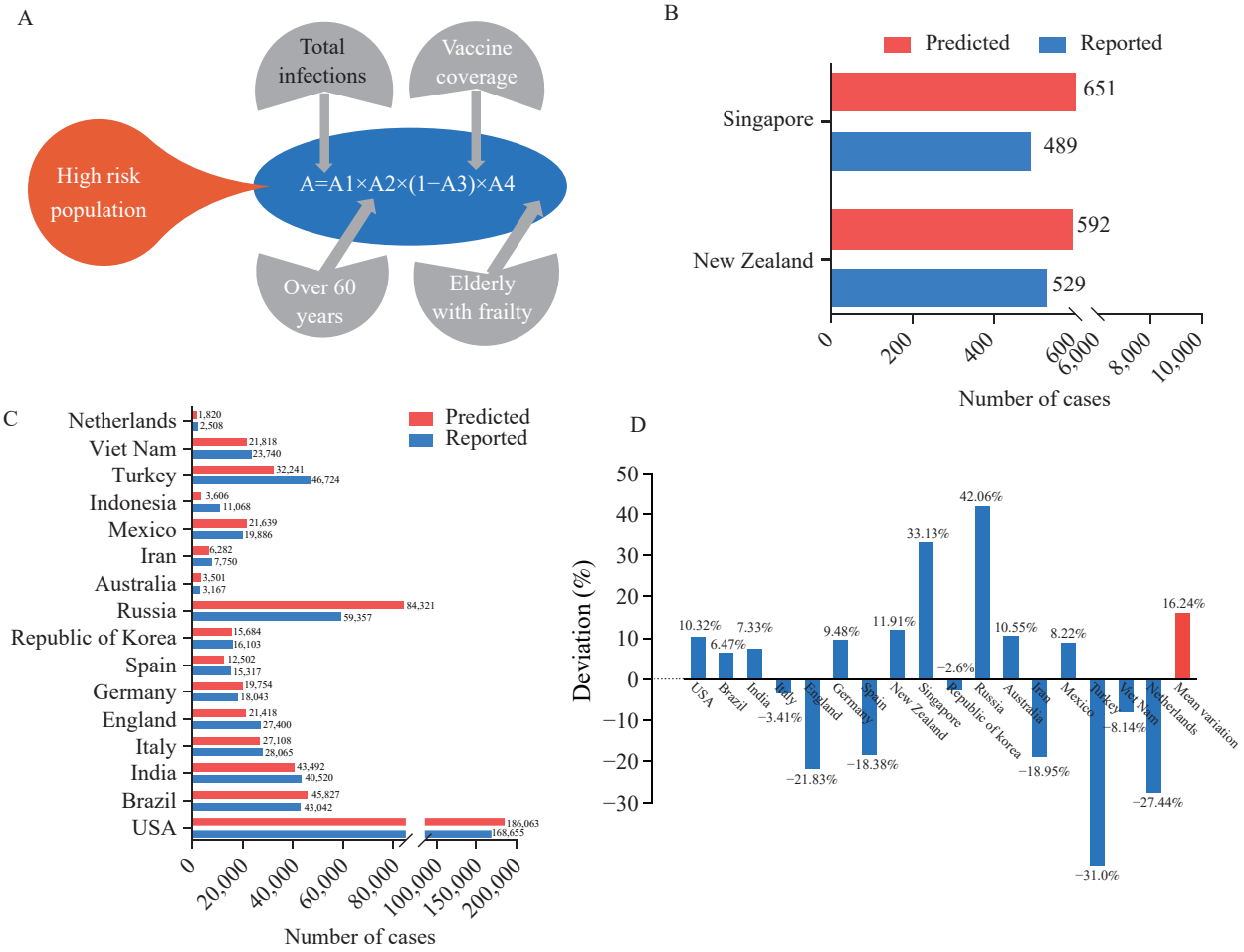

FIGURE 2. Comparison of predicted high-risk populations and actual COVID-19-related deaths. (A) Proposed formula for predicting the deaths. (B) Comparison of predicted and reported case numbers in New Zealand, and Singapore. (C) Comparison of predicted and reported COVID-19 cases in the United States, Brazil, India, Italy, United Kingdom, Germany, Spain, Republic of Korea, Russia, Australia, Iran, Mexico, Turkey, Viet Nam, and the Netherlands. (D) Bias generated by prediction for all analyzed regions.
Abbreviations: USA=the United States of America; COVID-19=coronavirus disease 2019.

and high risk at >5. Presently, we are in the information age. We have designed an online web page for risk assessment anytime and anywhere to facilitate individual prediction (Figure 4C). Completing this scale may only take 1–3 minutes due to its free and out-of-the-box availability, which will allow a simple and quick individual assessment.

DISCUSSION

Frailty characterized by a decline in physiological reserves across multiple organ systems can result in increased susceptibility to external stressors (*8*). Risk assessment based on frailty has been employed in clinical resource allocation in various fields since its introduction 20 years ago (*9*–*10*). Frailty has also been suggested as a criterion for priority access to medical care for COVID-19 patients (*10*). However, relying solely on frailty as an indicator may not be sufficient in addressing the novel epidemic strain, which is predominantly characterized by asymptomatic cases. We incorporated age, frailty, and vaccination history into our risk assessment tool to enhance its accuracy and applicability using a mathematical formula based on the product effect to estimate the number of fatalities (Figure 2A). Subsequently, we refined this formula and developed a population risk assessment software, SEIP-RA (Figure 3), by adapting our previous SEIR model (*7*) to make it more practical. The reliability of this formula was demonstrated to be accurate to 83.76% using epidemic data from 20 countries and regions (Figure 2D). Although discrepancies exist between our predictions and the available reports (Figure 2B–D), these variations can be

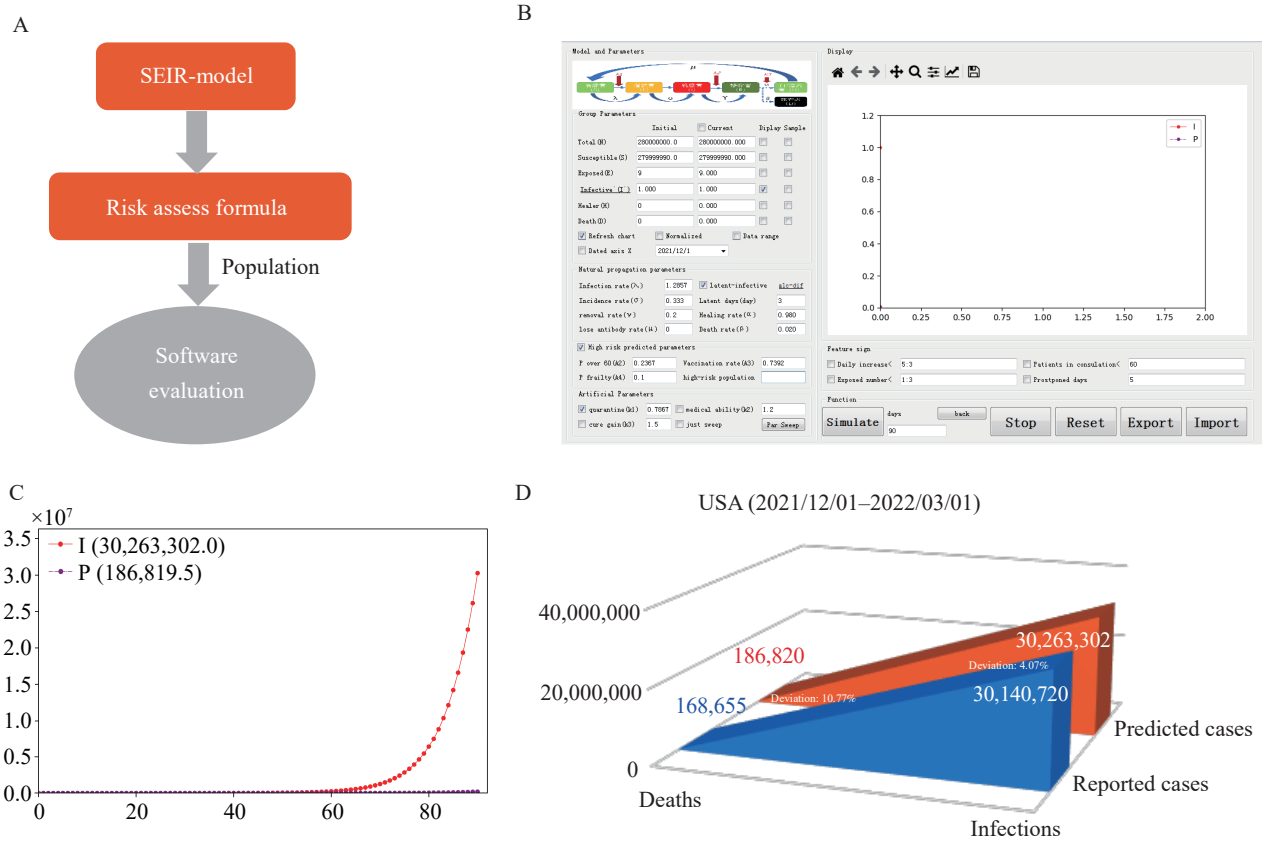

FIGURE 3. Software for population risk assessment for coronavirus disease 2019. (A) Design principle of the software. (B) Software interface and operating parameters. (C) Projected total number of infections and deaths in the United States from December 1, 2021 to March 1, 2022, utilizing predictive modeling software. (D) Comparison of predicted and reported total infections and deaths in the United States from December 1, 2021 to March 1, 2022.
Abbreviations: USA=the United States of America.

mainly attributed to the regional heterogeneity of the frailty index and the ongoing changes in vaccination rates.

For individual risk assessment, relying solely on age, frailty, and vaccination history may be inadequate. Factors such as the number of comorbidities and the presence of COVID-19 symptoms also significantly influence the severity of the disease. To improve accuracy, we integrated these two factors into our assessment tool. The tool is based on the Fried phenotype, a frailty assessment method, with the removal of complex indicators. Key risk factors, such as vaccination status and number of comorbidities, were extracted from the population level and combined with clinical symptoms of COVID-19 to create a straightforward and rapid personal risk assessment tool. The weight of each item is assigned according to the scoring system of the frailty scale (Fried phenotype) (*11*). Clearly, retrospective research methods are insufficient to rigorously verify and fine-tune the weight of each item. Further refinement will necessitate years of clinical experience in multiple countries or regions with ongoing COVID-19 outbreaks. Unfortunately, we could not provide individualized clinical data for risk assessment due to current conditions. It is our hope that widespread use of this scale will generate valuable data in the future, assisting in the tool's improvement.

In accordance with prevailing logic, factors such as aging, comorbidities, frailty, and vaccinations significantly contribute to the mortality associated with infectious diseases, irrespective of viral mutations. Consequently, our risk assessment tools remain broadly applicable. In summary, these tools may offer valuable insights for enhancing life preservation, resource allocation, cost-effectiveness, and the advancement of social and economic development.

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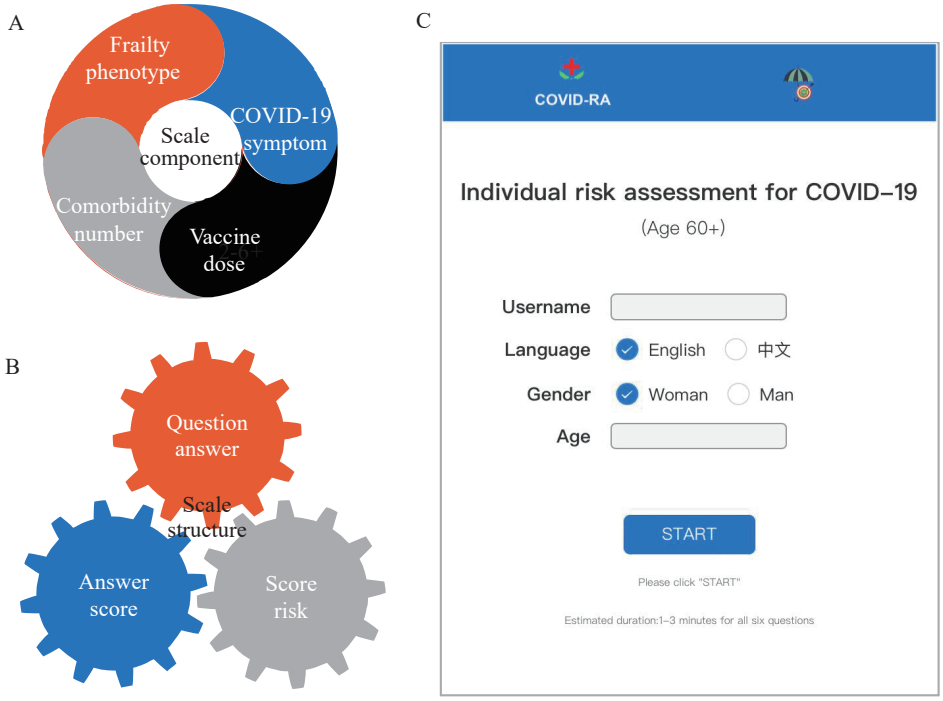

FIGURE 4. Web-based version of scale for individual risk assessment for coronavirus disease 2019 (COVID-19). (A) Scale component. (B) Scale structure. (C) Online risk assessment tool.

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SUPPLEMENTARY MATERIAL

Detailed Collection and Analysis of Clinical Data

Data on comorbidity in the aging and frailty population were collected through a comprehensive literature search. International databases, including PubMed, ScienceDirect, and EMBASE, were queried utilizing the terms: "aging" or "older," "comorbidity" or "coexisting diseases" or "multiple diseases" or "complex disease" or "underlying disease," and "frailty." The search encompassed articles published between 2010 and 2022. All retrieved articles were subjected to further exclusion criteria by removing those containing the terms "COVID-19" and "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)."

Case reports including fewer than 1,000 patients in total, or 100 frailty patients, were excluded due to insufficient sample size and a lack of representative information. Data visualization was conducted using RStudio.

Data on comorbidities in COVID-19-related fatalities were collected through a systematic literature review. The search was conducted using PubMed and EMBASE databases to gather relevant risk factor data associated with deaths in individuals infected with COVID-19. The search terms utilized were "COVID-19," "death" or "mortality," and "clinical." The inclusion criteria were articles written in English and published prior to April 1, 2022. Studies with a sample size of fewer than 100 deaths were excluded due to inadequate patient representation and insufficient data.

This study sought to gather data on the influence of frailty and vaccination status in COVID-19-related fatalities. A comprehensive literature search was conducted using both PubMed and EMBASE databases to collect information on frailty and vaccination history in COVID-19 fatalities, employing keywords such as "COVID-19," "frailty," and "vaccine." Inclusion criteria consisted of English-language articles published prior to April 1, 2022. Studies with fewer than 100 cases regarding frailty or vaccination history in COVID-19 fatalities were excluded due to an inadequate sample size and lack of representative data.

In this study, critical data — including "Total infected cases," "Population proportion over 60 years," "Vaccination rate," and "Frailty population proportion" — were collected from the top twenty countries and regions most affected by the COVID-19 pandemic to predict the high-risk population among confirmed cases. Additionally, data from Singapore, New Zealand, and other countries and regions were gathered for comparative analysis in predicting high-risk populations. Moreover, a prediction formula was developed for identifying high-risk groups, as detailed below:

$$A = A_1 \times A_2 \times (1 - A_3) \times A_4$$

where A is the predicted total number of high-risk populations; A_1 is total infections; A_2 is population proportion over 60 years; A_3 is vaccination rate among the population; and A_4 is proportion of elderly individuals with frailty. Frailty parameters were obtained from literature reports.

In the proposed prediction formula, A_1 represents the total number of infections, either known or predicted. The estimation of total infections was achieved using parameters associated with the relevant infectious disease. Values for A_2, A_3, and A_4 were obtained from publicly accessible data sources specific to each location and entered into the software for analysis. For aging populations and regions, an increase in A_2 may be observed. Additionally, A_3 may gradually rise and eventually plateau as vaccination efforts continue. Notably, the derived formula highlights the significant contribution of frailty and vaccination history to the predictive outcome, with vaccination history being particularly impactful.

Due to space limitations, all original data and references can be obtained from the first author.

SUPPLEMENTARY TABLE S1. Formulas and parameters of SEIP-RA software.

Population	Formula	Parameter
Susceptible (S)	$\frac{dS(t)}{dt} = -\lambda S(t)\, S(t)/N$	λ: Average daily infection rate *S(t)*: Number of the population (S) at time t *I(t)*: Number of the population (I) at time t *N*: Number of total populations in a certain region
Exposed (E)	$\frac{dE(t)}{dt} = \lambda S(t)\, I(t) - \sigma E(t)$	σ: Infected case per day *E(t)*: Number of the population (E) at time t
Infectious (I)	$\frac{dI(t)}{dt} = \sigma E(t) - \gamma I(t)$	γ: Average daily treatment probability for the infections
High-risk Population (P)	$P(t) = a_2(1 - a_3)a_4 \mathrm{I}(\mathrm{t})$	$P(t)$: High-risk populations at time t a_2: Rate of over 60 year a_3: Rate of vaccination a_4: Rate of frailty
	$S(0) + E(0) + I(0) + R(0) = N$	0: time $t = 0$
	$\lambda = R_0/T$	R_0: Reproducing coefficient *T*: Average infectious days
	$\sigma = 1/L$	*L:* Average latent day
	$\gamma = 1/C$	*C:* Average self-healing days
	$\lambda_k = \lambda k_1$	k_1: Interpersonal contact rate

SUPPLEMENTARY TABLE S2. Scale for individual risk assessment for COVID-19.

Domain	Question	Answer	Score
Frailty Phenotype	1. You have lost 4.5 kg or over 5.0% of your body weight in the past year.	A. Yes	1
		B. No	0
	2. You have walked less than 2 hours per week (except for quarantine or under restrictions) in the past 6 months.	A. Yes	1
		B. No	0
	3. One of the following has happened to you in the past week (*1*). I feel that I have to work hard to do everything (*2*). I cannot walk forward	A. Yes	1
		B. No	0
Comorbidity Number	4. The number of underlying diseases you suffered from the following: hypertension, obesity, hyperlipidemia, vascular disease, diabetes, depression, heart disease, Alzheimer's disease, chronic kidney disease, cancer, stroke, chronic pulmonary embolism, hemodialysis, thyroid disease, allergy, liver disease, and Parkinson's disease.	A. 0 or 1	0
		B. 2 or 3	0.5
		C. ≥4	1.5
Vaccine Dose	5. The number of COVID-19 vaccinations you have received:	A. Unvaccinated	1.5
		B. 1–2 injections	0.5
		C. ≥3 injections	0
COVID Symptom	6. Your symptoms of COVID-19 are as follows: common cold symptoms, such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, a new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.	A. No	0
		B. Yes	0.5
Score Evaluation	Low-risk: <3.5, Moderate risk: 3.5–5, High-risk: >5		

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