The Open Public Health Journal
DOI: 10.2174/0118749445407906250910095505, 2025, 18, e18749445407906
ISSN: 1874-9445
1

RESEARCH ARTICLE OPEN ACCESS

Comparison of COVID-19 Prevalence and Clinical Presentation During Pre- and Post-Vaccination Eras in Iran

Mohammad Reza Hedayati-Moghaddam[1], Raheleh Miri[1], Arman Mosavat[1], Moein Farshchian[2], Azam Shafaei[1,3], Maryam Shahi[1,3], Sanaz Ahmadi Ghezeldasht[1] and Reza Jafarzadeh Esfehani[1,*]

[1]*Blood Borne Infections Research Center, Academic Center for Education, Culture and Research (ACECR), Razavi Khorasan, Mashhad, Iran*
[2]*Stem Cells and Regenerative Medicine Research Department, Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan, Mashhad, Iran*
[3]*Clinical Laboratory Diagnostic Center, Academic Center for Education, Culture and Research (ACECR), Razavi Khorasan, Mashhad, Iran*

Abstract:

Introduction: Since the emergence of COVID-19, SARS-CoV-2 variants have exhibited distinct clinical presentations, influenced by viral evolution and the impact of vaccination. This study compared the prevalence of COVID-19 and symptom profiles during pre- and post-vaccination periods in Iran, focusing on changes driven by variants (*e.g.*, Delta, Omicron) and nationwide immunization efforts.

Method: A cross-sectional study was conducted on 7,051 individuals systematically sampled from 85,262 patients referred to a COVID-19 diagnostic center in northeast Iran (September 2020–March 2022). The data included demographics, symptoms (such as fever, cough, and dyspnea), comorbidities, and PCR results. The pre-vaccination period (waves 3–5) was compared to the post-vaccination period (wave 6, dominated by Omicron) using statistical analyses that included chi-square tests, logistic regression, and the Bonferroni correction.

Results: SARS-CoV-2 prevalence was 44.6% (95% CI: 43.3–45.8%), declining from 47.2% (pre-vaccination) to 30.4% (post-vaccination; $p < 0.001$). Symptomatic individuals had higher infection rates (55.5% *vs*. 28.2%; $p < 0.001$). Post-vaccination, respiratory symptoms (fever, cough, dyspnea) increased 1.3–1.8-fold among PCR+ cases ($p < 0.001$), while anosmia/ageusia remained stable ($p = 0.879$). Logistic regression identified male sex, symptom presence (except sore throat), and epidemic wave as significant predictors of PCR positivity.

Discussions: The Omicron wave, despite high vaccine coverage, showed a reduction in overall cases but an increase in respiratory symptoms, suggesting that vaccine-mediated attenuation of severity occurred without curbing transmissibility. Findings align with global reports of Omicron's upper respiratory tropism but contrast with studies noting reduced fever.

Conclusion: COVID-19 clinical presentations in Iran shifted post-vaccination, with Omicron associated with milder but more respiratory symptoms. Public health strategies should adapt testing protocols to prioritize respiratory symptoms and emphasize variant-specific boosters.

Keywords: COVID-19, Epidemiology, Iran, Impact of vaccination, Risk factors, SARS-CoV-2.

*Address correspondence to this author at the Blood Borne Infections Research Center, Academic Center for Education, Culture and Research (ACECR), Razavi Khorasan, Azadi-Square, Ferdowsi University Campus, 9177949367, Mashhad, Iran; E-mails: drrezajafarzadeh@yahoo.com-jafarzadeh@acecr.ac.ir

Cite as: Hedayati-Moghaddam M, Miri R, Mosavat A, Farshchian M, Shafaei A, Shahi M, Ghezeldasht S, Esfehani R. Comparison of COVID-19 Prevalence and Clinical Presentation During Pre- and Post-Vaccination Eras in Iran. Open Public Health J, 2025; 18: e18749445407906. http://dx.doi.org/10.2174/0118749445407906250910095505

Received: April 28, 2025
Revised: June 18, 2025
Accepted: June 25, 2025
Published: September 16, 2025

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) has had a profound impact on global health since its emergence in late 2019. As a highly contagious viral infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), COVID-19 has led to significant morbidity and mortality worldwide [1]. During the course of the disease, individuals may experience a range of symptoms, from mild to severe, with asymptomatic cases also being reported [2]. Common symptoms include fever, cough, fatigue, sore throat, and loss of taste or smell [3]. In severe cases, the disease can lead to complications such as pneumonia, Acute Respiratory Distress Syndrome (ARDS), multiple organ failure, and death [4]. Older adults and individuals with pre-existing chronic diseases are at a higher risk of severe illness and death [5].

Since the onset of the pandemic, several variants of SARS-CoV-2 have emerged with varying degrees of transmissibility, virulence, and consequences. Some variants, such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529), were classified as variants of concern [6, 7]. The clinical manifestations of COVID-19 have evolved. Initially, the prevalence of taste or smell loss was reported to be high; however, the frequency of this symptom decreased afterwards, and upper respiratory symptoms, such as sore throat and cough, increased in prevalence [8]. It has been reported that different variants of SARS-CoV-2 may be associated with specific symptoms. For instance, the wild-type variant was associated with symptoms such as fever, respiratory and gastrointestinal manifestations, and loss of taste and smell. In contrast, the Omicron variant was associated with symptoms including a sore throat and headaches [9]. Recent studies confirm that Omicron BA.1/BA.2 subvariants disproportionately cause upper respiratory symptoms compared to earlier variants [10].

Furthermore, the predominant clinical symptoms were influenced by the introduction of different types of vaccines against SARS-CoV-2. As more individuals are vaccinated, the overall severity of the disease is expected to decrease, resulting in a milder course for most infected individuals [11]. Post-vaccination behavioral changes, such as reduced testing of mild cases and altered healthcare-seeking behaviors, may also introduce bias to symptom profiles. Therefore, further research is necessary to monitor changes in the clinical features of SARS-CoV-2 infection and to predict future shifts in the virus's behavior.

Iran was among the first countries to experience the quick spread of the SARS-CoV-2 infection. Since the first confirmed case of COVID-19 in February 2020, Iran has experienced seven outbreak waves of this infection up to late summer 2022 [12]. To the best of our knowledge, a comparison of the clinical presentation of different SARS-CoV-2 variants has not been previously reported among the non-hospitalized population in Iran. This cross-sectional study aimed to evaluate the prevalence and risk factors of COVID-19, as well as the associated clinical manifestations, among the Iranian population during different epidemic periods. We emphasized the changes in COVID-19 epidemiology following the country's widespread national immunization against the infection after the fifth wave, which was primarily caused by the delta variant in Iran.

2. MATERIAL AND METHODS

Among the available clinical records of 85,262 individuals referred to the Central Laboratory of ACECR, Razavi Khorasan Branch, Mashhad, Iran, we had access to the clinical records of 85,262 individuals who were referred to the Central Laboratory of the ACECR, Razavi Khorasan Branch, Mashhad, Iran. Using pilot data, we estimated a 45% prevalence rate for each wave of SARS-CoV-2 infection in our population. Considering a 95% confidence coefficient ($\alpha = 0.05$) and a 5% prevalence rate as the confidence interval ($d = 0.0225$), we needed to enroll 1878 people in the survey for each of the third to sixth waves of the pandemic. Thus, we calculated a total sample size of 7512 cases and attempted to select 6-10% of the total population for each wave. Using a systematic random sampling method, we selected a sample of 7051 individuals who were referred between September 2020 and March 2022 (Fig. **1**, Table **1**). We considered the last COVID-19 wave as the post-vaccination period, as it occurred at a time when widespread national immunization had been implemented in Iran. By January 2022 (onset of the sixth wave), approximately 70% of Iran's eligible population had received a minimum of two doses of the Sinopharm, AstraZeneca, or COVIran Barekat vaccines [13]. Individual vaccination status was unavailable in the registry. The presence of chronic diseases, including cardiovascular, hypertension, kidney disorders, respiratory diseases, diabetes, obesity, transplantation, malignancy, stroke, and sickle cell anemia, was assessed by a self-reported survey. The assessment of symptoms was conducted through the implementation of structured questionnaires, which were administered during the course of clinical visits.

2.1. Data Collection Method

The records encompassed demographic data, such as age and gender, as well as a self-reported history of underlying chronic disease and COVID-19-associated clinical symptoms, including fever, chills, sore throat, cough, dyspnea, and loss of taste or smell. Two nasopharyngeal swab samples were collected from each participant by trained staff and transferred to a Viral Transport Medium (VTM) solution tube. SARS-CoV-2 RNA was extracted from the samples (MedNet EC-REP GmbH, Bioperfectus Technologies, Germany), and a real-time polymerase chain reaction (PCR) test was then performed (COVID-19 OneStep RT-PCR kit, Pishtazteb, Iran) using a Rotor-Gene Q Thermocycler (QIAGEN).

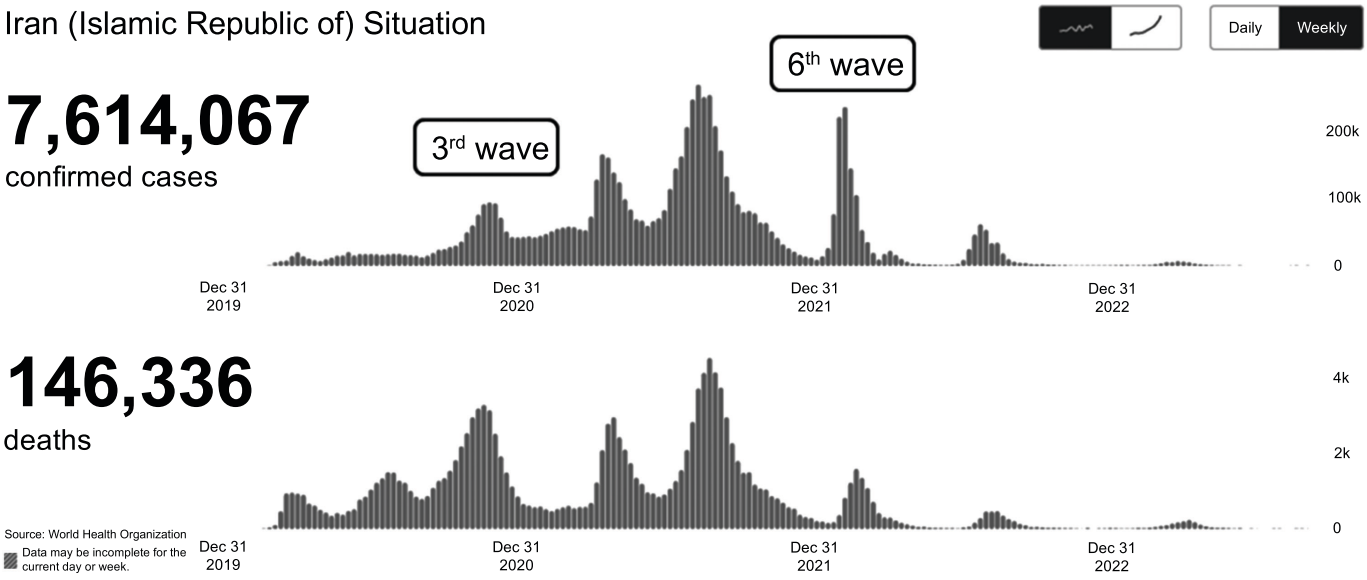

Fig. (1). The weekly trend of all confirmed outpatient and hospitalized COVID-19 cases and deaths in Iran from the beginning of the epidemic in February 2020 to September 2023. Shaded areas denote pre-vaccination (waves 3–5, Alpha/Delta variants) and post-vaccination (wave 6, Omicron variant) periods (Source: World Health Organization, https://covid19.who.int/region/emro/country/ir, Accessed: 15 September 2023).

Table 1. Details of sampling in different COVID-19 epidemic periods.

-		Sample Size	
COVID-19 Wave	**Total Cases (n)**	**n**	**%**
Third Wave			
22 Sep. 2020- 21 Oct. 2020	7182	717	10.0
22 Oct. 2020- 20 Nov. 2020	12819	1278	10.0
20 Nov. 2020- 20 Dec. 2020	7354	735	10.0
Total	27355	2730	10.0
Fourth Wave			
21 Mar. 2021- 20 Apr. 2021	4955	366	7.4
21 Apr. 2021- 21 May 2021	5541	607	11.0
Total	10496	973	9.3
Fifth Wave			
22 Jun. 2021- 22 Jul. 2021	7030	499	7.1
23 Jul. 2021- 22 Aug. 2021)	16504	1255	7.6
23 Aug. 2021- 22 Sep. 2021	11883	498	4.2
Total	35417	2252	6.4
Sixth Wave*			
21 Jan. 2022- 19 Feb. 2022	6353	737	11.6
20 Feb. 2022- 20 Mar. 2022	5641	359	6.4
Total	11994	1096	9.1
All periods	85262	7051	8.3

*The period after the widespread implication of COVID-19 vaccines in Iran

2.2. Statistical Methods

The data were analyzed using SPSS 19.0 software (IBM Corp., NY) by chi-square test, and the pairwise comparison of column proportions was performed using the Bonferroni correction to indicate significant differences. Missing data were excluded pairwise, and effect sizes (odds ratios, ORs) with 95% Confidence Intervals (CIs) are reported for key comparisons, along with p-values. The binary logistic regression model was employed to predict the likelihood of infection, with the analysis informed by demographic and clinical data. A p-value < 0.05 was considered statistically significant.

2.3. Ethics Approval and Consent to Participate

The present cross-sectional study was approved by the Ethics Committee of the Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch (ethics approval code: IR.ACECR.JDM.REC.1401.100). Written informed consent was obtained from the patients.

3. RESULTS

Among the 7051 individuals, 4411 (62.6%) were male, and 2640 (37.4%) were female. The mean age of the study population was 37.8 ± 14.2 years (range: 1-96 years). The majority of participants (62.0%, 3856/6224) reported at least one COVID-19-associated clinical symptom, and 31.7% (1876/5910) reported a family history of such symptoms. As Table **2** shows, the predominant symptom was cough (42.3%, 2465/5827), while anosmia or ageusia (20.4%) was the least prevalent. The most pervasive chronic comorbidities were cardiovascular diseases (4.4%, 236/5379), followed by hypertension (4.2%, 236/5379), kidney disorders (3.6%, 194/5342), and respiratory diseases (3.5%, 188/5358).

SARS-CoV-2 infection was documented among 3142 individuals (44.6%, 95% CI: 43.3%-45.8%). A marginal disparity in infection rates was observed between males and females (46.4% *vs*. 41.5%; $p < 0.001$). Moreover, individuals who tested positive for SARS-CoV-2 using a PCR test were slightly younger than those without infection (37.4 ± 13.8 *vs*. 38.2 ± 14.5 years, p = 0.029). The infection rates in the third, fourth, fifth, and sixth disease waves were calculated as 45.5% (95% CI: 43.7%-47.4%), 47.7% (95% CI: 44.5%-50.9%), 48.9% (95% CI: 46.9%-51.0%), and 30.4% (95% CI: 27.7%-33.2%), respectively ($p < 0.001$). Expectedly, the prevalence of COVID-19 was found to be significantly higher in symptomatic individuals compared to those without any clinical presentation (55.5% and 28.2%, respectively, $p < 0.001$). Besides, individuals diagnosed with COVID-19 were more likely to report a family history of disease-associated symptoms than those with a negative PCR result (39.1% and 25.9%, respectively, $p < 0.001$). As Table **2** indicates, the prevalence of all six clinical symptoms among individuals infected with SARS-CoV-2 was found to be 1.5–2 times higher compared to uninfected individuals ($P < 0.001$). Furthermore, individuals with confirmed COVID-19 had substantially higher rates of kidney and respiratory diseases than those without the infection (4.3% *vs*. 3.1%, P = 0.029 and 4.4%

Table 2. The frequency of COVID-19-associated clinical symptoms and the underlying chronic conditions among the study population.

Variables	Total Population					-		-		-
	Frequency		Missing		Valid Data	COVID-19 Negative		COVID-19 Positive		-
Clinical Symptoms	**n**	**%**	**n**	**%**	**%**	**n**	**%**	**n**	**%**	***p*-Value***
Fever	2067	29.3	1313	18.6	36.0	831	26.1	1236	48.4	< 0.001
Chill	1712	24.3	1428	20.5	30.4	708	22.5	1004	40.6	< 0.001
Sore throat	2159	30.6	1265	17.9	37.3	982	30.3	1177	46.2	< 0.001
Cough	2465	35.0	1224	17.4	42.3	1057	32.5	1408	54.8	< 0.001
Dyspnea	1338	19.0	1479	21.0	24.0	632	20.1	706	29.1	< 0.001
Loss of taste or smell	1121	15.9	1561	22.1	20.4	440	14.3	681	28.2	< 0.001
Clinical conditions										
Cardiovascular disease	236	3.3	1672	23.7	4.4	120	4.0	116	4.9	0.083
Hypertension	224	3.2	1665	23.6	4.2	127	4.2	97	4.1	0.942
Kidney diseases	194	2.8	1709	24.2	3.6	95	3.1	99	4.3	0.029
Respiratory diseases**	188	2.7	1693	24.0	3.5	86	2.8	102	4.4	0.003
Diabetes mellitus	161	2.3	1690	24.0	3.0	96	3.2	65	2.8	0.416
Severe obesity	77	1.1	2026	28.7	1.5	41	1.4	36	1.6	0.586
Organ transplantation	26	0.4	1721	24.4	0.5	16	0.5	10	0.4	0.611
Malignancy	23	0.3	1733	24.6	0.4	11	0.4	12	0.5	0.394
Stroke	20	0.3	2035	28.9	0.4	7	0.2	13	0.6	0.056
Sickle cell anemia	13	0.2	1877	26.6	0.3	9	0.3	4	0.2	0.346

* Chi-square test

** Including asthma

vs. 2.8%, P = 0.003, respectively). Based on binary logistic regression analysis, participants' sex, the presence of all six COVID-19 clinical symptoms except sore throat, a family history of SARS-CoV-2 symptoms, and the epidemic period were found to be associated with a higher probability of a positive result in a viral PCR test (Table **3**). Among the 6224 people who responded to questions regarding SARS-CoV-2-related symptoms, the infection rates exhibited an increase from 46.6% in the third wave to 49.1% in the fifth wave, followed by a subsequent decrease to 31.0% in the sixth wave ($p < 0.001$). The pairwise comparison revealed that the percentages of cases of COVID-19 in the third to fifth waves are not significantly different; however, the percentage in the sixth wave is significantly different from those in the other categories (Fig. **2A**). Among the clinically symptomatic subgroup, however, the sixth wave demonstrated the highest frequency of confirmed cases (65.0%) ($p < 0.001$). On the other hand, the highest (44.2%) and lowest (7.4%) rates of infection among the clinically symptomless subgroup were detected in the fifth and sixth waves, respectively ($p < 0.001$). The pairwise comparisons demonstrated that the percentages observed in the fourth and fifth waves differed significantly from those in the third and sixth waves, yet did not differ from each other (Figs. **2B** and **C**).

Table 3. Logistic regression analysis for COVID-19-associated risk factors.

Variable	OR	95% CI for OR	*p*-Value
Age	1.001	0.996-1.005	0.74
Sex	1.200	1.053-1.368	< 0.01
COVID-19 symptoms in the family	1.258	1.080-1.466	< 0.01
Fever	1.752	1.470-2.088	< 0.001
Chill	1.335	1.112-1.603	< 0.01
Sore throat	1.078	0.912-1.275	0.38
Cough	1.671	1.419-1.968	< 0.001
Dyspnea	0.753	0.624-0.910	< 0.01
Loss of smell or taste	1.530	1.267-1.848	< 0.001
Respiratory diseases	0.766	0.519-1.132	0.18
Kidney diseases	1.120	0.787-1.594	0.53
COVID-19 epidemic periods			
Third wave	1.0		
Fourth wave	1.318	1.087-1.597	< 0.01
Fifth wave	1.190	1.024-1.383	0.02
Sixth wave	0.519	0.427-0.632	< 0.001

OR: Odds ratio; CI: Confidence Interval.

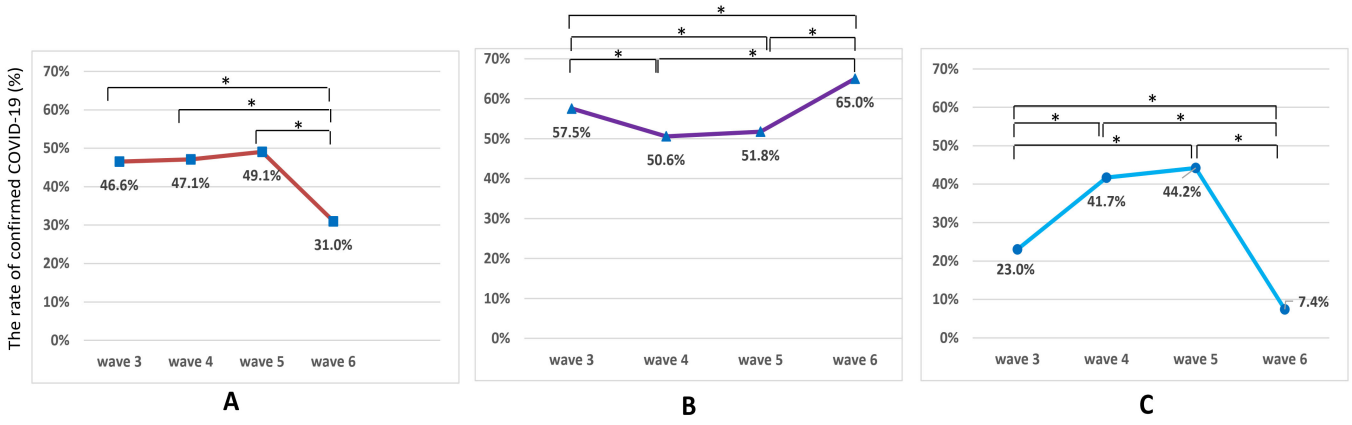

Fig. (2). The rate of confirmed COVID-19 during the different epidemic periods in Iran among the total population (**A**), people with COVID-19-related symptoms (**B**), and the clinically symptomless group (**C**). *$p < 0.05$; tests are adjusted using the Bonferroni correction. Bars represent percentages of participants.

The rate of SARS-COV-2 infection decreased considerably from 47.2% (95% CI: 45.9%-48.5%) in the pre-vaccination period (the third to fifth waves) to 30.4% (95% CI: 27.7%-33.2%) in the post-vaccination period (the sixth wave, $p < 0.001$). Furthermore, the percentages of symptomatic participants differ significantly between the two time periods (65.7% *vs*. 41.0%; $p < 0.001$). The incidence of a family history of COVID-19 symptoms in the first period (33.8%) was found to be considerably higher than in the subsequent period (20.2%; $p < 0.001$).

Among the clinically symptomless subgroup, the frequency of confirmed COVID-19 cases in the post-vaccination period showed approximately a five-fold reduction compared to the pre-vaccination period (7.4% *vs*. 34.5%, $p < 0.001$). Conversely, within the symptomatic subgroup, the infection rate increased substantially from 54.4% in the first period to 65.0% in the second period ($p < 0.001$, Fig. **3**). Table **4** shows, during both the pre- and post-vaccination periods, the most prevalent clinical manifestations among the total participants were cough (43.6% and 35.2%, respectively) and sore throat (37.8% and 34.8%, respectively). Among the group without COVID-19, the rates of all assessed symptoms, including fever, chills, sore throat, cough, dyspnea, and loss of taste or smell, were significantly lower in the post-vaccination period than in the earlier period (all $p < 0.001$). In contrast, among individuals diagnosed with COVID-19, the frequency of fever, chill, cough, sore throat, and dyspnea demonstrated a 1.3–1.8-fold increase during the post-vaccination period (all $p < 0.001$). The investigation revealed no statistically significant differences in the incidence of taste or smell loss between the two study periods (p = 0.879).

4. DISCUSSIONS

The present study evaluated the COVID-19-related clinical characteristics of the population referred to a medical diagnosis center in northeast Iran during the different epidemic periods of the disease. The prevalence of COVID-19 was documented among 44.6% of the total participants; this figure increased from 45.5% in the third wave to 48.9% in the fifth, followed by a precipitous decline to 30.4% during the sixth wave.

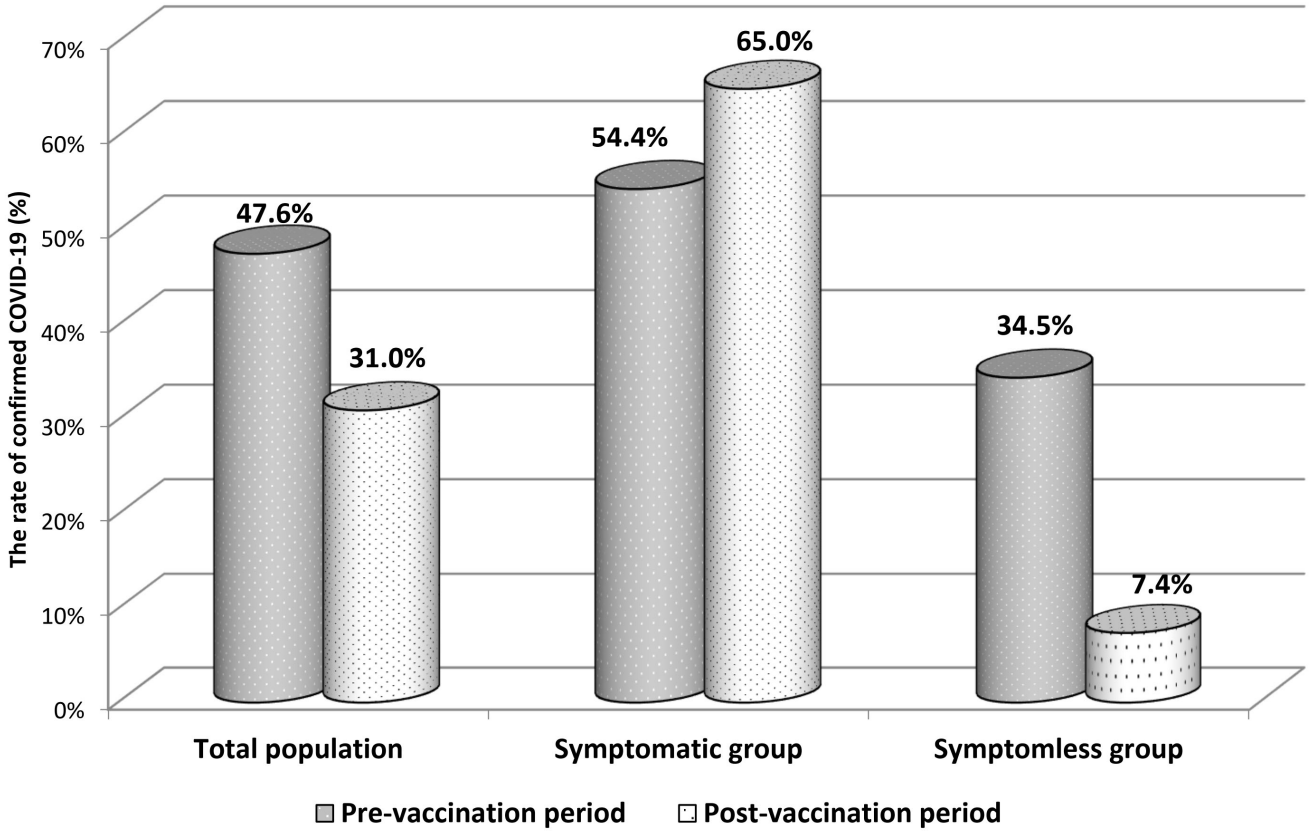

Fig. (3). The rate of confirmed COVID-19 in the pre- and post-vaccination periods in Iran among the total study population, people with COVID-19-related symptoms, and the clinically symptomless group.

Table 4. The frequency of COVID-19-associated clinical symptoms during pre- and post-vaccination eras in Iran.

	Total Population			COVID-19 Negative			COVID-19 Positive		
	Pre-vaccination	Post-vaccination	p-Value*	Pre-vaccination	Post-vaccination	*p*-Value*	Pre-vaccination	Post-vaccination	
Variables	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	*p*-Value*
Fever	1817 (37.6)	250 (27.6)	< 0.001	750 (29.4)	81 (12.8)	< 0.001	1067 (46.8)	169 (61.7)	< 0.001
Chill	1487 (31.4)	225 (25.3)	< 0.001	635 (25.1)	73 (11.7)	< 0.001	852 (38.6)	152 (57.4)	< 0.001
Sore throat	1839 (37.8)	320 (34.8)	0.088	874 (33.6)	108 (17.0)	< 0.001	965 (42.5)	212 (75.2)	< 0.001
Cough	2141 (43.6)	324 (35.2)	< 0.001	946 (36.1)	111 (17.4)	< 0.001	1195 (52.2)	213 (75.5)	< 0.001
Dyspnea	1159 (24.7)	179 (20.2)	0.004	563 (22.3)	69 (11.1)	< 0.001	596 (27.5)	110 (42.0)	< 0.001
Loss of taste or smell	1002 (21.7)	119 (13.6)	< 0.001	394 (16.0)	46 (7.4)	< 0.001	608 (28.2)	73 (28.6)	0.879

* Chi-square test

Note: Participants could report multiple symptoms.

Since its emergence, COVID-19 has undergone genetic evolution, resulting in numerous variants with distinct attributes from the original strain [14]. Different viral variants, such as the Alpha, Beta, Gamma, and Delta variants, have garnered attention due to their increased transmissibility and potential to evade immune responses [15]. These variants have been associated with a range of symptoms and severity levels. The Alpha variant was first identified in September 2020 in the United Kingdom. Patients infected with this variant presented a higher prevalence of symptoms, including cough, sore throat, myalgia, and fatigue [16].

The Delta variant, initially reported in India in October 2020, has demonstrated a doubling in its contagiousness compared to previous variants and has been linked to an increased risk of severe disease outcomes. According to a study by Mahase *et al*., the Delta variant is associated with a 60% higher hospitalization rate compared to previous variants [17]. Moreover, the probability of admission to the Intensive Care Unit and the fatality risk associated with the Delta variant have been reported to be higher than those of previous variants [19].

Our finding of marginally younger age among SARS-CoV-2-positive individuals aligns with the prioritized vaccination of elderly/ chronically ill groups, thereby shifting infections toward younger, less vaccinated individuals. The Delta variant exhibited clinical symptoms similar to those of previous variants [19]. However, this assertion is not universally accepted, as evidenced by the findings of some studies. Torjesen *et al*. reported that individuals infected with the Delta variant have a lower chance of experiencing a loss of taste or smell [20].

The subsequent variant of concern was Omicron, first described in late November 2021 [18]. In comparison to the Delta variant, the Omicron variant has been observed to affect the upper respiratory tract predominantly. It has been reported to be more transmissible, accompanied by a lower hospital admission rate [21, 22]. The present study examined the various COVID-19 epidemic periods in the country driven by the essential variants, including Alpha, Delta, and Omicron variants [23].

Furthermore, vaccination efforts against COVID-19 have played a significant role in determining the clinical manifestation of the disease over time. A body of research has demonstrated that immunization reduces the severity of illness and hospitalization rates among vaccinated individuals. In Iran, the immunization process against COVID-19 began in March 2021, initially targeting medical staff and subsequently prioritizing elderly individuals and those with underlying chronic diseases or disabilities. In the summer of 2021, there was a substantial increase in vaccination coverage coinciding with the peak of the fifth wave, and it was expanded to include all populations in the country [12].

The findings of the present study revealed that the prevalence rates of all related clinical symptoms among the COVID-19-negative group were higher in the period preceding the administration of the vaccine, which was caused by the alpha or delta variants of the virus. On the other hand, the presentation of febrile infections accompanied by chills and respiratory symptoms among people with a positive SARS-CoV-2 PCR test result became significantly more prevalent following the implementation of the country's vaccination program against the virus, predominantly attributable to the Omicron variant. Similarly, Li *et al*. conducted a comparative study of 384 Omicron cases and 103 Delta cases from China, reporting that these variants exhibited distinct clinical presentation [24]. Their report indicated that people infected with the Omicron variant are more likely to experience a fever. This finding aligns with our study, which showed a heightened frequency of fever among individuals with confirmed COVID-19 during the sixth wave, attributed to the Omicron variant.

Our findings are consistent with those reported by Yang *et al*., who noted that individuals infected with the Omicron variant were more likely to be asymptomatic or develop sore throats, and less likely to experience anosmia or ageusia compared to those infected with the Beta and Delta variants [25]. While our study found similar results regarding sore throat, we did not find a significant difference in the rate of loss of taste or smell between individuals infected during the pre-Omicron and Omicron waves. Bouzid *et al*. compared the clinical characteristics

exhibited by 818 individuals infected with the Delta variant and 898 infected with the Omicron variant, as referred to in Paris emergency departments [26]. Contrary to the findings of our study, they reported that patients infected with the Delta variant were more prone to manifest symptoms such as fever, cough, and dyspnea, while exhibiting a reduced likelihood of experiencing chills.

5. LIMITATIONS

The present study has its limitations. First, individual vaccination status and viral variant data (*e.g.*, genomic sequencing) were unavailable, precluding direct analysis of vaccine efficacy or variant-specific symptom profiles. Second, self-reported symptoms and comorbidities may introduce recall bias. Third, the single-center design limits generalizability to regions with differing demographics or vaccination timelines. Fourth, asymptomatic cases may be underrepresented due to testing biases during later waves.

CONCLUSION

The present study demonstrated distinct shifts in COVID-19 clinical presentations across epidemic waves in Iran. The Omicron-dominated sixth wave, emerging amid high vaccine coverage, showed a 36% reduction in overall cases but a 1.3–1.8-fold increase in respiratory symptoms (*e.g.*, cough, dyspnea) among confirmed infections compared to pre-vaccination periods. This suggests that vaccine-mediated attenuation of severity is accompanied by persistent transmissibility of newer variants. These findings highlight the need for: (1) variant-adapted boosters to address evolving symptomatology, (2) public education on changing symptom profiles (*e.g.*, prioritizing sore throat/dyspnea testing), and (3) longitudinal surveillance to monitor post-acute sequelae in vaccinated populations. Future research should integrate viral sequencing and individual vaccination records to disentangle the interactions between immunity and variants.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: R.E. and M.H.M.: Study concept; R.M.: Methodology; A.M.: Validation; M.F.: Data analysis or interpretation; A.S.: Writing - original draft preparation; M.S.: Writing the paper; S.G.: Data collection.

LIST OF ABBREVIATIONS

COVID-19	=	Corona Virus Diseases 2019
SARS-CoV-2	=	Syndrome Coronavirus 2
ARDS	=	Acute Respiratory Distress Syndrome
VTM	=	Viral Transport Medium
CIs	=	Confidence Intervals

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the Academic Center for Education, Culture and Research (ACECR), Razavi Khorasan, Iran (ethic approval code: IR.ACECR.JDM.REC.1401.100).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent has been taken from the patients.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

This study was supported financially by the Medical Vice-Chancellor of the Iranian Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch, Mashhad, Iran.

CONFLICT OF INTEREST

Dr. Reza Jafarzadeh Esfehani is the Editorial Advisory Board member of the Open Public Health Journal.

ACKNOWLEDGEMENTS

The authors thank the personnel of the Internal Medicine Clinic and Central Laboratory of the Iranian Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch, Mashhad, Iran, for their valuable help and support.

REFERENCES

[1] Sharma A, Ahmad Farouk I, Lal SK. COVID-19: A review on the novel coronavirus disease evolution, transmission, detection, control and prevention. Viruses 2021; 13(2): 202. http://dx.doi.org/10.3390/v13020202 PMID: 33572857

[2] Shahgolzari M, Yavari A, Arjeini Y, *et al*. Immunopathology and Immunopathogenesis of COVID-19, what we know and what we should learn. Gene Rep 2021; 25: 101417. http://dx.doi.org/10.1016/j.genrep.2021.101417 PMID: 34778602

[3] Viner RM, Ward JL, Hudson LD, *et al*. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Arch Dis Child 2021; 106(8): 802-7. http://dx.doi.org/10.1136/archdischild-2020-320972 PMID: 33334728

[4] Ramadori GP. SARS-CoV-2-infection (COVID-19): Clinical course, viral acute respiratory distress syndrome (ARDS) and cause(s) of death. Med Sci 2022; 10(4): 58. http://dx.doi.org/10.3390/medsci10040058 PMID: 36278528

[5] Fallah-Aliabadi S, Fatemi F, Heydari A, *et al*. Social vulnerability indicators in pandemics focusing on COVID-19: A systematic literature review. Public Health Nurs 2022; 39(5): 1142-55. http://dx.doi.org/10.1111/phn.13075 PMID: 35388516

[6] Jafari AS, Mozaffari Nejad AS, Faraji H, *et al*. Diagnostic challenges in fungal coinfections associated with global COVID-19. Scientifica 2025; 2025(1): 6840605. http://dx.doi.org/10.1155/sci5/6840605 PMID: 40370518

[7] Lorente-González M, Suarez-Ortiz M, Landete P. Evolution and clinical trend of SARS-CoV-2 variants. Open Respir Arch 2022; 4(2): 100169.
http://dx.doi.org/10.1016/j.opresp.2022.100169 PMID: 37497318

[8] Looi M-K. How are covid-19 symptoms changing?. BMJ 2023; 380: p3.
http://dx.doi.org/10.1136/bmj.p3

[9] Kirca F, Aydoğan S, Gözalan A, Kayipmaz AE, Özdemir FAE, Tekçe YT. Comparison of clinical characteristics of wild-type SARS-CoV-2 and Omicron. Rev Assoc Med Bras (1992) 2022 Nov 21; 68(10): 1476-80.
http://dx.doi.org/10.1590/1806-9282.20220880 PMID: 36417656

[10] Shrestha LB, Foster C, Rawlinson W, Tedla N, Bull RA. Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission. Rev Med Virol 2022; 32(5): 2381.
http://dx.doi.org/10.1002/rmv.2381 PMID: 35856385

[11] Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: Systematic review. BMJ Med 2023; 2(1): 000385.
http://dx.doi.org/10.1136/bmjmed-2022-000385 PMID: 36936268

[12] Gouya MM, Seif-Farahi K, Hemmati P. An overview of Iran's actions in response to the COVID-19 pandemic and in building health system resilience. Front Public Health 2023; 11: 1073259.
http://dx.doi.org/10.3389/fpubh.2023.1073259 PMID: 36817898

[13] Afshari P, Alavi SM, Abedi P, Beheshtinasab M, Dashtpayma S, Amiri H. Exploring the underlying factors of COVID-19 vaccination hesitancy in Ahvaz, Iran: A comprehensive cross-sectional study. Clin Exp Vaccine Res 2023; 12(2): 127-33.
http://dx.doi.org/10.7774/cevr.2023.12.2.127 PMID: 37214142

[14] Khandia R, Singhal S, Alqahtani T, *et al*. Emergence of SARS-CoV-2 Omicron (B.1.1.529) variant, salient features, high global health concerns and strategies to counter it amid ongoing COVID-19 pandemic. Environ Res 2022; 209: 112816.
http://dx.doi.org/10.1016/j.envres.2022.112816 PMID: 35093310

[15] Lazarevic I, Pravica V, Miljanovic D, Cupic M. Immune evasion of SARS-CoV-2 emerging variants: What have we learnt so far? Viruses 2021; 13(7): 1192.
http://dx.doi.org/10.3390/v13071192 PMID: 34206453

[16] Jewell BL. Monitoring differences between the SARS-CoV-2 B.1.1.7 variant and other lineages. Lancet Public Health 2021; 6(5): e267-8.
http://dx.doi.org/10.1016/S2468-2667(21)00073-6 PMID: 33857454

[17] Mahase E. Delta variant: What is happening with transmission, hospital admissions, and restrictions? BMJ 2021; 373(1513): n1513.
http://dx.doi.org/10.1136/bmj.n1513 PMID: 34130949

[18] Hoteit R, Yassine HM. Biological properties of SARS-CoV-2 variants: Epidemiological impact and clinical consequences. Vaccines 2022; 10(6): 919.
http://dx.doi.org/10.3390/vaccines10060919 PMID: 35746526

[19] Samieefar N, Rashedi R, Akhlaghdoust M, Mashhadi M, Darzi P, Rezaei N. Delta variant: The new challenge of COVID-19 pandemic, an overview of epidemiological, clinical, and immune characteristics. Acta Biomed 2022; 93(1): 2022179.
PMID: 35315394

[20] Torjesen I. Covid-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ 2021; 373(1445): n1445.
http://dx.doi.org/10.1136/bmj.n1445 PMID: 34088699

[21] Hui KPY, Ho JCW, Cheung M, *et al*. SARS-CoV-2 Omicron variant replication in human bronchus and lung *ex vivo*. Nature 2022; 603(7902): 715-20.
http://dx.doi.org/10.1038/s41586-022-04479-6 PMID: 35104836

[22] Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 omicron variant severity in Ontario, Canada. JAMA 2022; 327(13): 1286-8.
http://dx.doi.org/10.1001/jama.2022.2274 PMID: 35175280

[23] Sadeghi K, Zadheidar S, Zebardast A, *et al*. Genomic surveillance of SARS-CoV-2 strains circulating in Iran during six waves of the pandemic. Influenza Other Respir Viruses 2023; 17(4): 13135.
http://dx.doi.org/10.1111/irv.13135 PMID: 37078070

[24] Li Q, Liu X, Li L, *et al*. Comparison of clinical characteristics between SARS-CoV-2 Omicron variant and Delta variant infections in China. Front Med 2022; 9: 944909.
http://dx.doi.org/10.3389/fmed.2022.944909 PMID: 36313994

[25] Yang W, Yang S, Wang L, *et al*. Clinical characteristics of 310 SARS-CoV-2 Omicron variant patients and comparison with Delta and Beta variant patients in China. Virol Sin 2022; 37(5): 704-15.
http://dx.doi.org/10.1016/j.virs.2022.07.014 PMID: 35948265

[26] Bouzid D, Visseaux B, Kassasseya C, *et al*. Comparison of patients infected with Delta versus Omicron COVID-19 variants presenting to Paris emergency departments: A retrospective cohort study. Ann Intern Med 2022; 175(6): 831-7.
http://dx.doi.org/10.7326/M22-0308 PMID: 35286147