Received: 8 March 2021 | Revised: 31 March 2021 | Accepted: 1 April 2021

DOI: 10.1002/jmv.26996

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Non-life-threatening adverse effects with COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms

Renuka Ananth Kalyan Kadali[1,2] | Ravali Janagama[3] | Sharanya Peruru[4] | Viswanath Gajula[5] | Rajasekhar R. Madathala[6] | Nikhita Chennaiahgari[7] | Srikrishna V. Malayala[8]

[1]Department of Internal Medicine, Harnett Health System, Affiliated with Cape Fear Valley Health System, Lillington, North Carolina, USA

[2]Department of Internal Medicine, Campbell University Jerry M. Wallace School of Osteopathic Medicine, Lillington, North Carolina, USA

[3]Kidzcare Pediatrics, Sanford, North Carolina, USA

[4]Department of Statistics, North Carolina State University, Raleigh, North Carolina, USA

[5]Department of Pediatrics, Division of Pediatric Critical Care Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA

[6]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

[7]Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

[8]Department of Internal Medicine, Temple University Hospital, Philadelphia, Pennsylvania, USA

Correspondence
Renuka A. K. Kadali, Department of Internal Medicine, Harnett Health System and Campbell University School of Osteopathic Medicine, 215 Brightwater Dr, Lillington, NC 27546, USA.
Email: Renuka.Kadali@harnetthealth.org and dr.kadali1982@gmail.com

Ravali Janagama, Department of Pediatrics, Kidzcare Pediatrics, 145 W Main St, Sanford, NC 27332.
Email: ravalirao@yahoo.com

Abstract

There are concerns regarding the side effects of the new coronavirus disease 2019 (COVID-19) mRNA-1273 vaccine among healthcare workers (HCWs) in the United States. The objective of the study was to investigate the side effects of the mRNA-1273 vaccine with detailed review of organ systems. A randomized, cross-sectional study using an independent online survey questionnaire was conducted to collect responses from HCWs. Of all participants, 87.8% (1116/1271) provided complete responses. Of them, 38.7% (432/1116) received the mRNA-1273 vaccine, among which, 89.35% were females; 425 of these 432 mRNA-1273 vaccine recipients (98.34%) reported at least one or more symptoms. The results were classified based on the frequency of symptoms reported postvaccination. Of these, 254/432 (58.8%) were able to continue their daily routine activities. 108/432 (25%) temporarily had trouble to perform daily activities, 120/432 (27.78%) required transient time off from work, 17/432 (3.94%) required help from an outpatient provider, 1/432 (0.23%) required help from emergency department, and none of them were hospitalized. Despite the wide array of self-reported symptoms, 97.02% of the HCWs did not intend to skip the second dose of vaccine. Among all the symptoms reported, localized pain, generalized weakness, headache, myalgia, chills, fever, nausea, joint pains, sweating, localized swelling at the injection site, dizziness, itching, rash, decreased appetite, muscle spasm, decreased sleep quality, and brain fogging were the most commonly reported symptoms (in descending order of occurrence). Most of the symptoms reported were nonlife threatening. Despite the wide array of self-reported symptoms, there appears to be a higher acceptance for this vaccine.

KEYWORDS

adverse events, COVID, COVID-19, Moderna, mRNA-1273, side effects, symptoms, SARS-CoV-2, vaccine

Renuka Ananth Kalyan Kadali and Ravali Janagama have contributed equally as first authors to this study and writing this manuscript.

1 | INTRODUCTION

Severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2) were thought to have emerged in China, with bats as their original carriers.[1] SARS-CoV-2 is transmitted via respiratory droplets from face-to-face contact or contaminated surfaces. Although the role of aerosol spread in humans remains unclear, this mode of transmission is still a major concern.[2] Common symptoms in hospitalized patients with coronavirus disease 2019 (COVID-19) infection include fever, dry cough, shortness of breath, fatigue, myalgia, nausea, vomiting or diarrhea, headache, weakness, anosmia, ageusia, and rhinorrhea.[3] Common complications[4–10] with COVID-19 infection include pneumonia, acute respiratory distress syndrome, acute liver failure, cardiac abnormalities with troponin elevation, acute heart failure dysrhythmias, myocarditis, prothrombotic coagulopathy resulting in venous and arterial thromboembolic events, acute renal failure, neurologic manifestations, including impaired consciousness and acute cerebrovascular disease such as stroke, and shock. The overwhelming systemic inflammation and multiorgan failure with high mortality is secondary to "cytokine storm syndrome" (pediatric inflammatory multisystem syndrome in children, which is an immune deregulation characterized by perpetuated activation of lymphocytes and macrophages, resulting in secretion of large quantities of cytokines).[11,12] As of February 22, 2021, the number of deaths related to COVID-19 infection in the United States was 500 000.[13]

The Moderna COVID-19 mRNA-1273 vaccine was authorized by the Food and Drug Administration (FDA) in the United States to prevent COVID-19 infection on December 18, 2020. On December 19, 2020, the Advisory Committee on Immunization Practices issued an interim recommendation for the use of a two-dose regimen of mRNA-1273 vaccine (which was shown to have 94.1% efficacy in prevention of COVID-19 illness, including severe disease) in persons aged 18 years or older.[14–16] The first phase of the vaccination program was primarily focused on healthcare workers (HCWs) nationwide (who were at the forefront and took the vaccine as a challenge) and on long-term care facility (LTCF) residents. The Moderna COVID-19 vaccine, mRNA-1273 (100 μg) is administered intramuscularly as a series of two doses (0.5 ml each), given 28 days apart.[17] A large population-based study described that allergic reactions to vaccines generally occur at a rate of 1.31 (95% confidence interval, 0.90–1.84) cases per million vaccine doses, with no fatalities reported.[18] Current reports from the Centers for Disease Control and Prevention (CDC) suggest that anaphylactic reactions to the mRNA-1273 vaccine may occur more frequently than to other vaccines.[19]

Overall, the COVID-19 messenger RNA (mRNA)-based vaccination program has generated many concerns, questions, and continuing arguments about the safety issues of both new mRNA vaccines among HCWs and the general population in the United States. However, there are limited data and literature on the side effects that specifically focus on a detailed review of organ systems and the demographic factors, such as age, gender, education level, and ethnicity. The objective of the present study was to analyze the safety and more detailed side effect profile of the mRNA-1273 vaccine using a self-reported online survey questionnaire among HCWs. Therefore, we chose a random population of HCWs and investigated the side effects of these vaccines using responses from the survey questionnaire (consisting of a more detailed review of organ systems in comparison to what the CDC is collecting through the Vaccine Adverse Event Reporting System [VAERS]).[20]

2 | METHODS

2.1 | Design and sample selection

After obtaining Institutional Review Board approval for this study, we conducted a cross-sectional study by circulating an independent online survey questionnaire through an internet-based survey platform called "Survey Monkey," which gathered anonymous responses from HCWs from healthcare communities or groups representing various parts of the country during the early phase of COVID-19 vaccination. No personal identifications were obtained. Survey Monkey weblink was distributed to (1) coordinators of healthcare institutions and (2) communities of HCWs via social media. Informed consent was obtained at the beginning of the survey. Participants who voluntarily agreed and consented to proceed and who chose to receive one of the two mRNA-based COVID-19 vaccines were automatically allowed to move forward to answer subsequent questions about the side effects and other variables. Those who chose "None of them" were diverted to a disqualified page. The study obtained feedback in anonymous mode regarding the side effects and benefit profile during the postvaccination period.

2.2 | Inclusion criteria

This study included the healthcare providers and workers in healthcare settings (Phase 1a vaccine recipients who may be exposed to suspect or confirmed COVID-19 patients or infective materials) that have received one or two doses of the mRNA-based COVID-19 vaccine.

2.3 | Exclusion criteria

(1) Those who received one or two doses of the mRNA-based COVID-19 vaccine but belong to one of the following:
(a) Phase 1a "long-term care facility" residents and staff.
(b) Phase 1b population (nonphase 1a persons aged ≥75 years and nonhealthcare frontline essential workers).
(c) Phase 1c population (nonphase 1a persons aged 65–74 years and nonphase 1a persons aged 16–64 years with medical conditions that increase the risk for severe COVID-19).

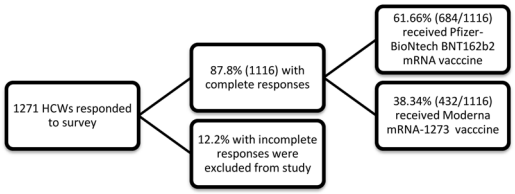

FIGURE 1 Classification of survey responses (attached below). HCWs, healthcare workers; mRNA, messenger RNA

(d) Other general population.

(2) Those who did not receive mRNA-based COVID-19 vaccine.

2.4 | Duration of study

The "Survey Monkey" weblink was left open and kept active to collect responses for approximately 4 weeks. The responses were collected between January 24, 2021 and February 24, 2021.

We obtained responses from 1271 HCWs (Figure 1) who reported receiving one or two doses of either BNT162b2 or mRNA-1273 vaccines. Out of 1271 responses, 1116 were complete responses. Only the complete responses related to the mRNA-1273 vaccine were included in the final analysis of this study (Figure 1).

3 | RESULTS

This study primarily focused on the mRNA-1273 vaccine. Of the 1116 respondents who completed the survey, 38.7% (432) received the mRNA-1273 vaccine, and the remaining received the BNT162b2 vaccine (Figure 1). Among the responses from mRNA-1273 vaccine recipients, 6.02% belong to the age group between 18 and 30 years, 42.36% between 31 and 40 years, 22.22% between 41 and 50 years, 19.21% between 51 and 60 years, 8.33% between 61 and 70 years, and 1.85% between 71 and 80 years. The calculated average age of these participants is 43.76 years. Of the responses, 89.35% were from females and the remaining were from males. The majority of respondents have a higher level of education, with either a doctoral or a professional medical degree or a master's degree (Table 1). Table 1 also shows the distribution of ethnicity among the respondents who received the mRNA-1273 vaccine.

A total of 81.71% of the HCWs (353/432) who received the mRNA-1273 vaccine took both doses, but the remaining 18.29% took only the first dose. Those who received mRNA-1273 vaccine reported the following symptoms based on their complete review of organ systems. A detailed report of the event rate in the descending order of occurrence is displayed in Table 2. At least one or more of the system-based symptoms were reported: localized symptom/s, 415/432 (96.06%); generalized symptom/s, 292/432 (67.59%); musculoskeletal symptom/s, 270/432 (62.5%); gastrointestinal symptom/s, 153/432 (35.4%);

TABLE 1 Demographic data and effect on activity or need for medical attention after administration of mRNA-1273 vaccine

	Percentage responded	Number responded
Age group (in years)		
18–30	6.02%	26
31–40	42.36%	183
41–50	22.22%	96
51–60	19.21%	83
61–70	8.33%	36
71–80	1.85%	8
Gender		
Female	89.35%	386
Male	10.42%	45
No response	0.23%	1
Ethnicity		
White	83.80%	362
Hispanic or Latino	3.70%	16
Black or African American	1.85%	8
Native American or American Indian	0.00%	0
Asian	9.49%	41
Pacific Islander	0.23%	1
Choose not to answer	1.85%	8
Other (please specify below)	1.16%	5
Level of education (answered by only 336 respondents)		
Doctorate/professional medical degree	55.65%	187
Master's degree	33.33%	112
Bachelor's degree	6.85%	23
Associate degree	3.27%	11
High school graduate	0.89%	3
Effect on activity or need for medical attention		
Temporarily had trouble to perform regular daily living activities	25.00%	108
Required transient time off from work	27.78%	120
Required to seek help from outpatient provider	3.94%	17
Required to seek help from emergency department provider	0.23%	1
Required to hospitalize and subsequent inpatient care	0.00%	0

TABLE 2 Event rate based on the descending order of occurrence

Symptom/sign/adverse event (after the first and or second dose)	Percentage reported in descending order (*n* = number of respondents with event)
Reported with most frequency	
Sore arm/pain	94.21% (407)
Generalized weakness/fatigue	65.74% (284)
Headache	59.26% (256)
Muscle pain	54.17% (234)
Chills	52.78% (228)
Fever	35.65% (154)
Nausea	26.62% (115)
Arthritis/joint pains	24.77% (107)
Sweating	18.52% (80)
Swelling	15.05% (65)
Dizziness	14.58% (63)
Itching	14.58% (63)
**Rash	13.43% (58)
Decreased appetite	13.19% (57)
Muscle stiffness/spasm	11.11% (48)
Decreased sleep quality	10.65% (46)
Brain fogging	9.95% (43)
Reported with moderate frequency	
Flushing	9.03% (39)
Heat/cold intolerance	8.56% (37)
Palpitations	8.1% (35)
Diarrhea	7.87% (34)
Nasal stuffiness	6.48% (28)
Sore throat	6.02% (26)
Abdominal pain	5.56% (24)
Anxiety	4.86% (21)
Feelings of joy/relief/ gratitude	4.86% (21)
Increase in sleep	4.86% (21)
Cough	3.47% (15)
Eye pain	3.47% (15)
Residual skin discoloration	3.47% (15)
Vertigo like symptoms	3.47% (15)
Heartburn	3.24% (14)
Increased thirst	3.24% (14)
Tingling	3.24% (14)
Vomiting	3.01% (13)
Runny nose	2.78% (12)
Ringing sensation in ears	2.31% (10)
Shortness of breath	2.31% (10)
Blood pressure changes	2.08% (9)
Reported with rare frequency	
Chest pain	1.85% (8)
Constipation	1.62% (7)
Decrease in memory	1.62% (7)
Ear pain	1.62% (7)
Food intolerance	1.62% (7)
Hives	1.62% (7)
Increased appetite	1.62% (7)
Increased urine production	1.62% (7)
Depression	1.39% (6)
Numbness	1.39% (6)
Urgent need to urinate	1.16% (5)
Extremely rare frequency	
Atopic eczema	0.93% (4)
Blurring of vision	0.93% (4)
Incoordination	0.93% (4)
Manic/hyper manic mood changes	0.93% (4)
Syncope	0.93% (4)
Tremor	0.93% (4)
Flashing lights	0.69% (3)
Frequent urination at night	0.69% (3)
Hay fever	0.69% (3)
Fainting	0.69% (3)
Pain or burning on urination	0.69% (3)
Extremity weakness	0.69% (3)
Psychological stress	0.69% (3)
Asthma exacerbation	0.46% (2)
Behavioral changes	0.46% (2)
Bleeding	0.46% (2)
Blood in urine	0.46% (2)
Change in hearing	0.46% (2)
Swelling in mouth/throat	0.46% (2)
Anaphylaxis	0.23% (1)
Bleeding gums	0.23% (1)
Decreased urine stream	0.23% (1)
Double vision	0.23% (1)

(Continues)

(Continues)

TABLE 2 (Continued)

Symptom/sign/adverse event (after the first and or second dose)	Percentage reported in descending order (*n* = number of respondents with event)
Hoarseness	0.23% (1)
Incontinence of urine	0.23% (1)
Nose bleeds	0.23% (1)
Problems swallowing	0.23% (1)
Seizures	0.23% (1)
Swelling of lips or tongue	0.23% (1)

**Rash reported as both localized side effect and allergic side effect.

psychological/psychiatric symptom/s, 105/432 (24.3%); endocrine symptom/s, 95/432 (21.99%); head/ear/eyes/nose/throat symptom/s, 88/432 (20.37%); neurological symptom/s, 72/432 (16.67%); cardiovascular symptom/s, 52/432 (12.04%); respiratory symptom/s, 26/432 (6.01%); allergic (other than localized/generalized rash), 20/432 (4.63%); and urinary symptom/s, 11/432 (2.55%) (Table 3).

3.1 | Generalized symptoms

The generalized symptoms that were primarily reported are generalized weakness or fatigue in 65.74% (284), headache in 59.26% (256), chills in 52.78% (228), fever in 35.65% (154), sweating in 18.52% (80), dizziness in 14.58% (63), and flushing in 9.03% (39) of the recipients (432).

3.2 | Localized symptoms

Approximately 94.21% (407/432) of HCWs reported sore arm or pain at the injection site as their primary localized side effect, followed by swelling by 15.05% (65), itching by 14.58% (63), rash** by 13.43% (58), lymphadenopathy (axillary or regional or cervical or ipsilateral supraclavicular) by 4.17% (18), residual skin discoloration by 3.47% (15), and bleeding by 0.46% (2) of the recipients (432).

3.3 | Musculoskeletal symptoms

Myalgia (muscle pain) was reported by 54.17% (234), arthritis or joint pain by 24.77% (107), and muscle stiffness/spasm by 11.11% (48) of the recipients (432).

3.4 | Gastrointestinal symptoms

Nausea was reported by 26.62% (115), decreased appetite by 13.19% (57), diarrhea by 7.87% (34), abdominal pain by 5.56% (24), heartburn by

TABLE 3 Event rate classified based on review of organ systems

Symptoms after the first dose and or the second dose of vaccine	Percent reported	Number of HCWs reported
Generalized symptoms		
Generalized weakness/fatigue	65.74%	284
Headache	59.26%	256
Chills	52.78%	228
Fever	35.65%	154
Sweating	18.52%	80
Dizziness	14.58%	63
Flushing	9.03%	39
Localized symptoms		
Sore arm/pain	94.21%	407
Swelling	15.05%	65
Itching	14.58%	63
**Rash	13.43%	58
Residual skin discoloration	3.47%	15
Bleeding	0.46%	2
Neurological symptoms		
Brain fogging	9.95%	43
Vertigo like symptoms	3.47%	15
Tingling	3.24%	14
Numbness	1.39%	6
Tremor	0.93%	4
Incoordination	0.93%	4
Fainting	0.69%	3
Extremity weakness	0.69%	3
Seizures	0.23%	1
Musculoskeletal symptoms		
Muscle pain	54.17%	234
Arthritis/joint pains	24.77%	107
Muscle stiffness/spasm	11.11%	48
Gastrointestinal symptoms		
Nausea	26.62%	115
Diarrhea	7.87%	34
Abdominal pain	5.56%	24
Heartburn	3.24%	14
Vomiting	3.01%	13
Constipation	1.62%	7
Food intolerance	1.62%	7
Problems swallowing	0.23%	1

TABLE 3 (Continued)

Symptoms after the first dose and or the second dose of vaccine	Percent reported	Number of HCWs reported
Allergic/anaphylaxis symptoms		
**Rash	13.43%	58
Hives	1.62%	7
Atopic eczema	0.93%	4
Hay fever	0.69%	3
Swelling in mouth/throat	0.46%	2
Asthma exacerbation	0.46%	2
Swelling of lips or tongue	0.23%	1
Anaphylaxis	0.23%	1
Respiratory symptoms		
Cough	3.47%	15
Shortness of breath	2.31%	10
Cardiac-related symptoms		
Palpitations	8.10%	35
Blood pressure changes	2.08%	9
Chest pain	1.85%	8
Syncope	0.93%	4
Head/eyes/ears/nose/mouth/throat		
Nasal stuffiness	6.48%	28
Sore throat	6.02%	26
Eye pain	3.47%	15
Runny nose	2.78%	12
Ringing sensation in ears	2.31%	10
Ear pain	1.62%	7
Blurring of vision	0.93%	4
Flashing lights	0.69%	3
Change in hearing	0.46%	2
Double vision	0.23%	1
Nose bleeds	0.23%	1
Bleeding gums	0.23%	1
Hoarseness	0.23%	1
Urinary symptoms		
Urgent need to urinate	1.16%	5
Pain or burning on urination	0.69%	3
Frequent urination at night	0.69%	3
Blood in urine	0.46%	2
Incontinence of urine	0.23%	1
Decreased urine stream	0.23%	1
Endocrine symptoms		
Decreased appetite	13.19%	57
Heat/cold intolerance	8.56%	37
Increased thirst	3.24%	14
Increased appetite	1.62%	7
Increased urine production	1.62%	7
Psychologic or psychiatric symptoms		
Decreased sleep quality	10.65%	46
Anxiety	4.86%	21
Increase in sleep	4.86%	21
Feelings of joy/relief/gratitude	4.86%	21
Decrease in memory	1.62%	7
Depression	1.39%	6
Manic/hyper manic mood changes	0.93%	4
Psychological stress	0.69%	3
Behavioral changes	0.46%	2

**Rash reported as both localized side effect and allergic side effect.

3.24% (14), vomiting by 3.01% (13), constipation by 1.62% (7), food intolerance by 1.62% (7), and trouble swallowing by 0.23% (1) of the recipients (432).

3.5 | Psychological or psychiatric symptoms

Decreased sleep quality was reported by 10.65% (46), feelings of joy/relief/gratitude by 4.86% (21), anxiety by 4.86% (21), increased sleep by 4.86% (21), decrease in memory by 1.62% (7), depression by 1.39% (6), manic/hyper manic mood changes by 0.93% (4), psychological stress by 0.69% (3), and behavioral changes by 0.46% (2) of the recipients (432).

3.6 | Neurological symptoms

Brain fogging or confusion was reported by 9.95% (43), vertigo-like symptoms by 3.47% (15), tingling of the extremity with injection site by 3.24% (14), numbness by 1.39% (6), tremor by 0.93% (4), incoordination by 0.93% (4), extremity weakness by 0.69% (3), fainting by 0.69% (3), and seizures by 0.23% (1) of the recipients (432). Of note, one HCW reported reactivation of herpes or shingle-like lesions after receiving the vaccine.

3.7 | Head/eyes/ears/nose/mouth/throat symptoms

Nasal stuffiness was reported by 6.48% (28), sore throat by 6.02% (26), eye pain by 3.47% (15), runny nose by 2.78% (12), ringing

sensation in the ears reported by 2.31% (10), ear pain by 1.62% (7), blurred vision by 0.93% (4), flashing lights by 0.69% (3), changes in hearing by 0.46% (2), double vision by 0.23% (1), nose bleed by 0.23% (1), bleeding gums by 0.23% (1), and hoarseness by 0.23% (1) of the recipients (432).

3.8 | Endocrine symptoms

Decreased appetite*** was reported by 13.19% (57), heat or cold intolerance by 8.56% (37), increased thirst by 3.24% (14), increased appetite by 1.62% (7), and increased urine production by 1.62% (7) of the recipients (432).

3.9 | Cardiovascular symptoms

Palpitations/racing heart was reported by 8.1% (35), blood pressure changes by 1.85% (8), chest pain by 1.85% (8), and syncope by 0.93% (4) of the recipients (432).

3.10 | Respiratory symptoms

Shortness of breath was reported by 2.31% (10), and cough by 3.47% (15) of the recipients (432).

3.11 | Allergic/skin symptoms (except for rash**)

Among the 432 recipients, 1.62% (7) reported hives, 0.93% (4) reported atopic eczema, 0.69% (3) reported hay fever, 0.46% (2) reported swelling in the mouth/throat, 0.46% (2) reported asthma exacerbation, 0.23% (1) swelling of the lips, and 0.23% (1) reported anaphylaxis.

3.12 | Urinary symptoms

Urgent urination was reported by 1.16% (5), burning with urination by 0.69% (3), frequent urination by 0.69% (3), blood in urine by 0.46% (2), and urinary incontinence by 0.23% (1) of the recipients (432).

We obtained information on chronic medical problems among the study participants (Table 4). We evaluated the extent of the impact of these symptoms on the vaccine recipients: During the immediate postvaccination period, 254/432 (58.8%) had no issues and were able to continue their daily routine activities, 108/432 (25%) temporarily had trouble to perform regular daily activities, and 120/432 (27.78%) required temporary time off from work. Only 17/432 (3.94%) required seeking help from an outpatient provider, 1/632 (0.23%) required seeking help from emergency department providers, and none of the participants required hospitalization (Table 1).

TABLE 4 Chronic medical problems reported

Chronic medical problems	Percent reported (*n*)
Thyroid condition	15.28% (66)
Hypertension	12.73% (55)
Chronic lung disease/asthma/COPD	9.95% (43)
Gastrointestinal issues	8.8% (38)
Osteoarthritis	6.48% (28)
Mental illness	4.17% (18)
History of autoimmune[a] disease	3.94% (17)
Diabetes mellitus	3.47% (15)
Blood disorders	2.78% (12)
Heart disease	1.85% (8)
Cancer/tumor	1.85% (8)
Rheumatoid arthritis	1.85% (8)
Chronic alcohol intake	1.62% (7)
Chronic smoking (or quit within last 5 years)	1.39% (6)
Fibromyalgia	0.93% (4)
Liver disease	0.69% (3)
Stroke	0.46% (2)
Migraine	0.46% (2)
Epilepsy/seizures	0.46% (2)
Tuberculosis/HIV/Immunocompromised infectious condition	0.23% (1)

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency viruses.

[a]autoimmune conditions reported include: Crohns' disease, celiac disease, multiple sclerosis, Grave's disease, selective IgA deficiency, psoriasis, lichen planus, and reactive arthritis.

3.13 | Non-COVID-19-related benefit after vaccination

A total of 2.08% (9) participants reported improvement or resolution of symptoms from their chronic medical problems after receiving the vaccination.

4 | DISCUSSION

The present study aimed to analyze the safety and more detailed side effect profile of the mRNA-1273 vaccine among HCWs in the United States. Based on the above results, vaccine recipients can primarily expect the following symptoms during the early phase of the postvaccination period: Among all the symptoms reported, sore arm or localized pain, generalized weakness or fatigue, headache, myalgia or muscle pain, chills, fever, nausea, joint pain, sweating, localized swelling at the injection site, dizziness, itching, rash,

decreased appetite, muscle stiffness or spasm, decreased sleep quality, and brain fogging are the most commonly reported symptoms (in descending order of occurrence), followed by flushing, heat or cold intolerance, palpitations, diarrhea, nasal stuffiness, sore throat as other predominant symptoms. Of note, 97.02% of mRNA-1273 vaccine recipients did not intend to skip the second dose of the vaccine irrespective of side effects, their conflicting schedules, and personal apprehensions. Moreover, a total of 81.71% had already received the second dose of the vaccine by the time they responded to this survey.

At this point, the etiology of side effects or reactions to the mRNA-1273 vaccine is still unclear. The CDC estimates suggest that anaphylaxis (signs of trouble breathing, swelling of the face and throat, rash, and low blood pressure) occurs soon after vaccination in 2.5 cases per million doses among people receiving the mRNA-1273 vaccine.[19] Based on the "Morbidity and Mortality Weekly Report" from first month of COVID-19 vaccine safety monitoring by VAERS, a total of 113 deaths were reported including 78 among LTCF residents and 35 reports of death among non-LTCF residents. The number of deaths reported among these non-LTCF residents after administration of the mRNA-1273 vaccine was 19/35 (54.3%).[20] The investigations are in progress, but the underlying chronic conditions such as heart disease, cancer, stroke, probable pulmonary embolism, and otherwise frail health were thought to be the causes of death. The common adverse reactions to the mRNA vaccines, such as fever, nausea, and diarrhea, may have contributed to fatal outcomes in some of the frail patients.[20] However, in our study; since the response data was first hand (directly from the vaccine recipients), no data on deaths were collected which was reflected as if there were no reports of deaths from the mRNA-1273 vaccine in our study.

Therefore, we recommend following the CDC guidelines that everyone who is vaccinated should be observed for at least 15 minutes after receiving the vaccine, with epinephrine available at the vaccination site in case it is needed. It is the inactive ingredient or the excipient (including egg protein, gelatin, formaldehyde, thimerosal, or neomycin), but not the active ingredients, that are attributable for the allergic reactions. Avoidance of both mRNA COVID-19 vaccines in individuals with a history of anaphylaxis to polyethylene glycol (PEG), PEG derivatives, or polysorbate is recommended by the CDC.[17] Excipients (used in the vaccine to stimulate a stronger immune response, prevent bacterial contamination, and stabilize the potency of the vaccine during transportation and storage) are the major contributors to specific IgE-mediated and immediate reactions associated with vaccines.[21]

In our study, only two HCWs (0.46%) reported that they tested positive for COVID-19 infection during the period between the first and second doses of mRNA-1273 vaccine. There were concerns about whether COVID-19 can be caused by the vaccine, which might be impossible because these mRNA vaccines did not use live SARS-CoV-2 virus in their development. If COVID-19 infection is observed soon after vaccination, it is improbable that it is caused by the vaccine; instead, the infection might be caused by the failure of the vaccine (studies on this are in progress), pre-existing infection before vaccine administration, or infection at the time of vaccination.

We recommend monitoring for further reports from CDC about the side effects as the vaccination program continues with its subsequent phases. Less than 3% of respondents chose a rationale to skip their second dose. This can be considered as a positive sign. At best, most of the vaccine recipients among HCWs took the challenge to end the deadly pandemic, irrespective of side effects. Nevertheless, the vaccine recipients need to outweigh the risks of possible adverse events versus the potential benefit (before receiving the mRNA vaccine that helps protecting from a deadly virus that caused millions of deaths worldwide within 1 year).

5 | STUDY LIMITATIONS

This study has several limitations. Since this was an independent study investigating detailed self-reported symptoms through anonymous responses using a web-based survey, the receipt of vaccine by the study participants and their self-reported symptoms were not verified or confirmed and were not recorded or documented clinically or officially by the study investigators. Most of our study participants were females (89.35%) and also data from African American and other minority groups are minimal. According to the U.S. Census Bureau's American Community Survey, women have driven 80% of the overall growth in the booming health care field since the turn of the century and they account for nearly 75% of full-time, year-round HCWs.[22] This explains and reflects the predominance of females in our study sample. Most of the symptoms reported above were only in the early postvaccination phase of the vaccine. We did not study the latent effects of these vaccines. No specific data about the initial timing of the onset of symptoms after vaccine administration or the duration of symptoms were obtained in this study. Several HCWs attributed certain symptoms like bleeding, change in hearing, tremor, and many others directly to the vaccine soon after vaccination, although symptoms of their pre-existing chronic medical problems may have contributed to these side effects, or they could be an unfortunate coincidence from new underlying medical problems that are not related to the vaccine. Chronic medical problems, such as heart attacks, blood disorders, cancer, stroke, and other rare illnesses, have occurred before the pandemic and will continue to occur. Although, we did not gather information on prior history of allergies except for asthma, about 18% of vaccine recipients experienced mild to moderate allergic reactions and there was only one case of anaphylaxis reported during our study. These allergies are expected to be from the immune-mediated reactions triggered after the injecting the vaccine. Acute issues may be triggered from underlying chronic condition after vaccine administration, as shown in this study, where one respondent reported reactivation of herpes or shingle-like infection. The vaccine could be to blame if a thorough investigation is performed and if certain health problems occur at a higher-than-normal rate. If not, it is more likely to be an unfortunate coincidence that these effects are related to the vaccine (other

examples including rare cases of Bell's palsy and other neurologic disease that were reported after COVID vaccination; however, so far, there is no clear suggestion that the vaccine played any role).[23] We reviewed the symptomatology from the original trial conducted by Moderna which was released by FDA in its briefing document before the approval of COVID-19 mRNA-1273 vaccine.[24] Though, the percentages of several high-frequent symptoms in both the trial group and our study are almost similar, their reported list of symptomatology is certainly narrower in comparison to our detailed complete review of the organ systems (Tables 2 and 3). The side effects after the second dose of vaccine can be severe based on what CDC announced recently. Although 25% of the vaccine recipients temporarily had trouble to perform daily regular activities and a near percentage (27.78%) of the vaccine recipients needed to take off from work temporarily, it is important to realize that these responses were collected during early post vaccination phase and so the side effects may be severe enough for a transient period of time. Additionally, the sensitivity of symptoms perceived might be high in HCWs with their higher level of education (Table 1) and experience in healthcare field. Our questionnaire with the extended number of questions has covered a wide range of organ systems (with a long list of symptomatology) than any other study or the original vaccine trial. Hence, we tried to avoid the response fatigue from our survey respondents and limited or avoided the questions focusing on the severity level of every adverse effect. Therefore, the severity of each symptom was not gauged quantitatively in the study. The first-dose efficacy of 92.1% was reported for the mRNA-1273 vaccine.[24] Having such a highly protective first dose, the benefits derived from a scarce supply of vaccine could be maximized by deferring second doses until all priority group members are offered at least one dose.[25] Thereby, choosing alternative dosing regimens may also prevent the side effects associated with second dose of the vaccine. Our findings about side effects with BNT162b2 mRNA vaccine were reported in a parallel sub-study.[26]

6 | CONCLUSIONS

A more detailed review of organ systems on HCWs in this study after receipt of the mRNA-1273 vaccine in comparison to what the CDC is collecting through the VAERS showed that sore arm or localized pain, generalized weakness or fatigue, headache, myalgia or muscle pain, chills, fever, nausea, joint pain, sweating, localized swelling at the injection site, dizziness, itching, rash, decreased appetite, muscle stiffness or spasm, decreased sleep quality, and brain fogging are the most commonly reported symptoms (in the descending order of occurrence), followed by flushing, heat or cold intolerance, palpitations, diarrhea, nasal stuffiness, and sore throat as other predominant symptoms. Most of the symptoms reported during the early phase of post-vaccination period were non-life threatening. The high acceptance rate towards the second dose of vaccine is a positive sign and can be encouraging for future vaccine recipients to end the deadly pandemic, irrespective of side effects. The acceptability or tolerance of symptoms perceived might be higher in HCWs with their higher level of education (Table 1) and experience in the healthcare field. There is no available objective data to compare and analyze the tolerance rate for HCWs, but this can certainly be considered as a question for future or subsequent studies among nonhealthcare worker population using a similar questionnaire. Having a highly protective first-dose efficacy of 92.1% with the mRNA-1273 vaccine, vaccine researchers may consider to perform studies on alternative dosing regimen which may also help prevent several side effects associated with second dose of the vaccine.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Folarin for the timely COVID-19 updates and preparedness meetings at our health system, Dr. Ramu G. Sudhagoni for significant contributions with suggestions on the statistical analysis and critical reading of the manuscript, and to Sailaja Kadali (a student from Richard Montgomery High School, Maryland) for her assistance with sorting data obtained from secured Survey Monkey web source, percentage calculations of the obtained data, and her excellent secretarial assistance.

CONFLICT OF INTERESTS

The authors declare that they are no conflict of interests. The views in this article are those of the authors and not of their institutions, pharmaceutical companies, vaccine manufacturing companies, or the CDC, NIAID, NIH, and DHHS.

AUTHOR CONTRIBUTION STATEMENT

All authors contributed significantly to this study. *Conceptualization and proposal writing*: Renuka A. K. Kadali and Ravali Janagama. *Supervised data collection*: Ravali Janagama and Renuka A. K. Kadali. *Data management and analysis*: Renuka A. K. Kadali, Ravali Janagama, and Sharanya Peruru. *Contributed to the writing of the manuscript*: Renuka A. K. Kadali, Ravali Janagama, Sharanya Peruru, Viswanath Gajula, Rajasekhar R. Madathala, Nikhita Chennaiahgari, and Srikrishna V. Malayala. All authors have read and approved the manuscript.

ETHICS STATEMENT

The exempt approval for this web-based survey study was obtained from the Institutional Review Board at Cape Fear Valley Health System, 1638 Owen Drive, Fayetteville, NC 28304.

ORCID

Renuka Ananth Kalyan Kadali https://orcid.org/0000-0003-4105-7743

Ravali Janagama https://orcid.org/0000-0002-7601-7648

REFERENCES

1. Latinne A, Hu B, Olival KJ, et al. Origin and cross-species transmission of bat coronaviruses in China. *Nat Commun*. 2020;11(1):4235. https://doi.org/10.1038/s41467-020-17687-3
2. Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill*. 2020;25(17):2000257. https://doi.org/10.2807/1560-7917.ES.2020.25.17.2000257

3. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis [published correction appears in Lancet Gastroenterol Hepatol. 2020 Jul;5(7):e6]. *Lancet Gastroenterol Hepatol*. 2020;5(7):667-678. https://doi.org/10.1016/S2468-1253(20)30126-6
4. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7(6):e438-e440. https://doi.org/10.1016/S2352-3026(20)30145-9
5. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med*. 2020;38(7):1504-1507. https://doi.org/10.1016/j.ajem.2020.04.048
6. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. https://doi.org/10.1001/jamaneurol.2020.1127
7. Middeldorp S, Coppens M, vanHaaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1995-2002. https://doi.org/10.1111/jth.14888
8. Chen YT, Shao SC, Hsu CK, Wu IW, Hung MJ, Chen YC. Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. *Crit Care*. 2020;24(1):346. https://doi.org/10.1186/s13054-020-03009-y
9. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623. https://doi.org/10.1016/j.tmaid.2020.101623
10. Sadeghmousavi S, Rezaei N. COVID-19 infection and stroke risk. *Rev Neurosci*. 2020;32(3):341–349. https://doi.org/10.1515/revneuro-2020-0066
11. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. *Eur Respir J*. 2020;56(4):2003006 https://doi.org/10.1183/13993003.03006-2020
12. Rathore V, Galhotra A, Pal R, Sahu KK. COVID-19 pandemic and children: a review. *J Pediatr Pharmacol Ther*. 2020;25(7):574-585. https://doi.org/10.5863/1551-6776-25.7.574
13. COVID Data Tracker. United States at a Glance, Centers for Disease Control and Prevention. 2021. https://covid.cdc.gov/covid-data-tracker/#datatracker-home
14. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. https://doi.org/10.1056/NEJMoa2034577
15. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(50):1922-1924. https://doi.org/10.15585/mmwr.mm6950e2
16. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. https://doi.org/10.1056/NEJMoa2035389
17. COVID-19 Vaccination; Clinical Care. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States. Centers for Disease Control and Prevention website. 2021. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
18. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868-878. https://doi.org/10.1016/j.jaci.2015.07.048
19. CDC COVID-19 Response Team, Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine—United States, December 21, 2020–January 10, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(4):125-129. https://doi.org/10.15585/mmwr.mm7004e1
20. Gee J, Marquez P, Su J, et al. First month of COVID-19 vaccine safety monitoring—United States, December 14, 2020–January 13, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:283-288. https://doi.org/10.15585/mmwr.mm7008e3
21. Banerji A, Wickner PG, Saff R. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach [published online ahead of print, December 31, 2020]. *J Allergy Clin Immunol Pract*. 2020;S2213-2198(20):31411-31412. https://doi.org/10.1016/j.jaip.2020.12.047
22. U.S. Census Bureau. 2000 Census and 2017 American Community Survey 1-year estimates. https://www.census.gov/library/stories/2019/08/your-health-care-in-womens-hands.html
23. Robert HSCOVID-19 vaccines: safety, side effects and coincidence. Harvard Health Blog. 2021. https://www.health.harvard.edu/blog/covid-19-vaccines-safety-side-effects-and-coincidence-2021020821906
24. FDA Briefing Document: Moderna COVID-19 vaccine. Vaccines and Related Biological Products Advisory Committee Meeting. 2020. https://www.fda.gov/media/144434/download
25. Skowronski DM, De Serres G. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine [published online ahead of print, February 17, 2021]. *N Engl J Med*. 2021;384(11). https://doi.org/10.1056/NEJMc2036242
26. Kadali RAK, Janagama R, Peruru S, Malayala SV. Side effects of BNT162b2 mRNA COVID-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers [published online ahead of print, 2021 Apr 15]. *Int J Infect Dis*. 2021;S1201-9712(21)00358-1. https://doi.org/10.1016/j.ijid.2021.04.047

How to cite this article: Kadali RAK, Janagama R, Peruru S, et al. Non-life-threatening adverse effects with COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms. *J Med Virol*. 2021;93:4420–4429. https://doi.org/10.1002/jmv.26996