Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Chemotherapy 28 (2022) 1616–1622

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

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

Original Article

Factors related to the serious adverse events in patients visiting the emergency department after ChAdOx1 and mRNA COVID-19 vaccination

Won Jung Jeong [a], Byung Hak So [a], Hyung Min Kim [a], Kyungman Cha [a], Woon Jeong Lee [b], Sikyoung Jeong [c], Seung Pill Choi [d,1,*], Seon Hee Woo [b,1,**]

[a] Department of Emergency Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[b] Department of Emergency Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[c] Department of Emergency Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[d] Department of Emergency Medicine, Eunpyeong St. Mary Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

ARTICLE INFO

Keywords:
COVID-19
Vaccination
Adverse event
Emergency department

ABSTRACT

Introduction: We investigated the clinical characteristics, outcomes and factors related to the serious adverse events (AEs) of patients visiting the emergency department (ED) with various AEs after ChAdOx1 and mRNA COVID-19 vaccination.

Methods: Patients with AEs who visited the ED between March 2021 and September 2021 were selected from three EDs. The clinical data of these patients were collected by retrospectively reviewing medical records. Serious adverse events (AEs) were defined as any adverse medical events that led to hospital admission.

Results: A total of 3572 patients visited the ED with AEs; 69.6% were administered mRNA vaccines, and the median (IQR) age was 48 (31–63) years. Regarding chief complaints, chest pain/discomfort (43.7%) was most common in the mRNA vaccines group, while fever (15.8%) was more commonly presented in the ChAdOx1 group. Most patients (93.9%) were discharged from the ED. In multivariate analysis, age ≥70 years, days from vaccination to ED visit ≥8 days, fever and dyspnea as chief complaints were higher independent risk factors for serious AEs (OR 27.94, OR 2.55, OR 1.95 and OR 2.18: $p < 0.001$, $p < 0.001$, $p = 0.003$ and $p = 0.003$, respectively).

Conclusion: Most patients who visited the ED with AEs after vaccination were discharged from the ED regardless of the type of vaccine. Emergency physicians need to differentiate serious AEs and consider factors that may require admission to the ED.

1. Introduction

To overcome the coronavirus disease 2019 (COVID-19) pandemic, COVID-19 vaccines were authorized for emergency use in February 2021. In South Korea, two viral vector vaccines (ChAdOx1 [AstraZeneca] and Ad26.COV2. S[Janssen]) and two mRNA vaccines (BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]) initiated inoculation with high-risk patients and first-line healthcare workers and gradually expanded to the general public [1].

Several studies about the safety and effectiveness of COVID-19 vaccines have been reported before the emergency use authorization of these vaccines in each country [2–5]. However, the safety concerns of these vaccines due to a lack of sufficient clinical research period have been raised continuously. Some studies on adverse events (AEs) of COVID-19 vaccines showed that most of the AEs were general and mild adverse reactions, did not worsen to severe, and improved without any special treatment [6,7]. However, rare but severe AEs related to COVID-19 vaccines have also been reported, such as specific thrombotic events with thrombocytopenia, acute myocarditis and pericarditis depending on whether viral vector-based DNA vaccine or mRNA vaccine

* Corresponding author. Department of Emergency Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 1021, Tongil-ro, Eunpyeong-gu, Seoul, South Korea.
** Corresponding author. Department of Emergency Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 56, Dongsu-ro, Bupyeong-gu, Incheon, South Korea.
E-mail addresses: emvic98@catholic.ac.kr (S.P. Choi), drme@catholic.ac.kr (S.H. Woo).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jiac.2022.08.013
Received 15 April 2022; Received in revised form 8 June 2022; Accepted 11 August 2022
Available online 19 August 2022

was used [8–12]. Thus, serious adverse events (AEs) were defined as any untoward medical events that led to hospital admission or to death in a previous study [13–15]. The definition of adverse events following immunization (AEFI) is important to understand that the AEs reported are not necessarily direct side effects of the COVID-19 vaccination. The CDC mentioned that they are medical events that presented after the vaccination that may or may not be triggered by the immunization [14,15].

As COVID-19 vaccination was expanded to the general population, the number of patients visiting the ED with AEFI has increased recently. Many patients visited the ED for a short period of time with different chief complaints following viral vector-based DNA vaccines or mRNA vaccines. Additionally, among the various chief complaints of AEs, some of these (such as fever, chest pain, dyspnea, headache, etc.) may likely be regarded as mild AEs after vaccination in the overcrowded ED environment. However, they may be chief complaints of serious AEs that may require differential diagnosis for other critical diseases. This overcrowding and burden of work in the ED can cause delays in the treatment of other critically ill patients. To date, there have been no studies that have analyzed the clinical features of patients who visit the ED with AEs according to ChAdOx1 and mRNA vaccines in the ED.

Therefore, we investigated the detailed clinical characteristics and outcomes of patients visiting the ED with various AEs after ChAdOx1 and mRNA COVID-19 vaccination to help ED physicians make decisions when managing these patients. Second, we analyzed the demographic and clinical factors affecting serious AEs in patients who visited the ED with self-reported COVID-19 AEs.

2. Methods

2.1. Study design and population

This study was a multicenter retrospective study that was conducted by reviewing the electronic medical records of three hospitals, whose EDs serve as regional emergency centers in South Korea. These EDs had annual averages of approximately 70,000 visits, 60,000 visits, and 30,000 visits before the COVID-19 outbreaks.

The patients visiting the ED between March 2021 and September 2021, with self-reported AEs following COVID-19 vaccination were included in this study. AEs were defined as medical events that presented after the vaccination that may or may not be triggered by the immunization [13–15]. Patients with suspected AEs were reported to the national COVID-19 Immunization Registry System of South Korea. Patients over the age of 19 who visited the EDs with AEs after the first or second dose of the COVID-19 vaccination were included. The types of COVID-19 vaccines included ChAdOx1, BNT162b2 and mRNA-1273. The exclusion criteria were patients who were vaccinated with Ad26. COV2. S, patients under the age of 18, patients who had symptoms even before vaccination, patients who had symptoms beginning after 28 days of vaccination, trauma related patients, and patients who had incomplete data.

2.2. Data collection

We obtained the following demographic and clinical data from the medical records of the study participants: age, sex, date of vaccination, type of vaccine administered and vaccine dose. We reviewed the days from vaccination to symptom onset, days from vaccination to ED visit, emergency medical services (EMS) visit to the ED, chief complaint, comorbidity (hypertension, diabetes, respiratory disease, cardiovascular disease, cerebrovascular disease and malignancy status), diagnostic tests in the ED and ED treatments. Additionally, we collected patients' clinical outcomes (discharge, admission to the general ward [GW], admission to the intensive care unit [ICU], transfer to another hospital). Serious AEs were defined as any untoward medical events that led to hospital admission [13–15]. This analysis was divided into two groups: the group inoculated with ChAdOx1 and the group inoculated with mRNA vaccines (BNT162b2 and mRNA-1273).

2.3. Statistical analysis

SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis of the collected data. We explored demographic characteristics, clinical characteristics, ED management, and ED disposition to analyze the comparison of the ChAdOx1 vaccine and mRNA vaccines. The Kolmogorov–Smirnov test was applied to continuous variables to test whether they followed a normal distribution; for those that were not normally distributed, the results are presented as the medians and interquartile ranges, and the data were analyzed using the Mann–Whitney *U* test. Noncontinuous variables are expressed in terms of frequency and percentage and were analyzed using the chi-square test. Statistical significance was considered when the p value was less than 0.05. A multivariate logistic regression model was constructed to identify the independent risk factors for serious AEs. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

3. Results

3.1. Characteristics of the study population

A total of 3948 patients visited the ED with suspected AEs after COVID-19 vaccination during the study period. We excluded 140 patients who visited EDs after Ad26.COV2.S vaccination, 129 patients under the age of 18, 61 patients whose symptoms began after 28 days of vaccination, 13 patients who had symptoms even before vaccination, 8 trauma related patients, and 25 who had missing data in the ED. Thus, a total of 3572 patients were included in this study.

The baseline characteristics are shown in Table 1. A total of 2348 (65.7%) patients were female, and 22.6% were under 30 years of age, accounting for the largest group (Fig. 1). The median (IQR) age was 48 (31–63) years. Of all patients, 2487(69.6%) patients visited the ED due to AEs following the mRNA vaccines. A total of 30.6% patients in the mRNA group were under the age of 30, and the patients over the age of 60 in the ChAdOx1 group represented 57.0%. A total of 70.5% in the mRNA vaccines group and 80.5% in the ChAdOx1 group visited the ED

Table 1
Clinical characteristics stratified according to COVID-19 vaccinations.

Variables, n (%)	mRNA vaccines (n = 2487)	ChAdOx1 (n = 1085)	p value
Male sex	881 (35.4)	343 (31.6)	0.027
Age (years)			<0.001
Mean ± SD	43.1 ± 18.3	59.9 ± 12.4	
Median (IQR)	40 (28–54)	63 (59–67)	
Vaccine dose			<0.001
First dose	1754(70.5)	873 (80.5)	
Second dose	733 (29.5)	212 (19.5)	
Comorbidities, n (%)			
Hypertension	265 (10.7)	203 (18.7)	<0.001
Diabetes mellitus	90 (3.6)	87 (8.0)	<0.001
Respiratory disease	23 (0.9)	16 (1.5)	0.146
Cardiovascular disease	116 (4.7)	93 (8.6)	<0.001
Cerebrovascular disease	33 (1.3)	24 (2.2)	0.052
Malignancy	67 (2.7)	53 (4.9)	0.001
EMS visit to the ED, n (%)	345 (13.9)	228 (21.0)	<0.001
Top 6 chief complaints			
Chest pain/discomfort	1088 (43.7)	123 (11.3)	<0.001
Fever/chilling/myalgia	184 (7.4)	171 (15.8)	<0.001
Headache	189 (7.6)	153 (14.1)	<0.001
Allergy response	190 (7.6)	119 (11.0)	0.001
General weakness	130 (5.2)	115 (10.6)	<0.001
Dyspnea/Shortness of breath	167 (6.7)	47 (4.3)	0.006

Values are expressed as number (%) or the median (interquartile range). The χ^2 test and Mann–Whitney test were used for statistical analysis.
ED = emergency department, EMS = emergency medical services.

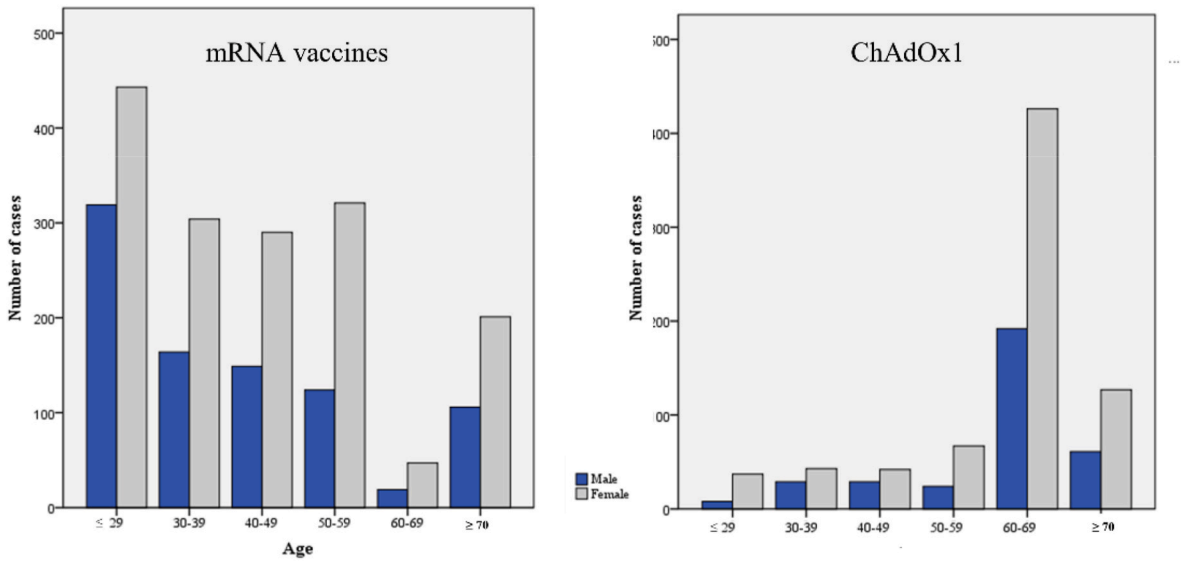

Fig. 1. Distribution of patients visiting the ED according to sex and age. ED = emergency department. A total of 2348 (65.7%) patients were female, and 22.6% were under 30 years of age, accounting for the largest group. The age and sex were significantly different between the ChAdOx1 and mRNA vaccines ($p = 0.027$, $p < 0.001$), and the rate of female patients was higher in all age groups of both groups.

after the first dose. When comparing clinical features according to the ChAdOx1 and mRNA vaccines, age and sex were significantly different between the two groups ($p < 0.001$, $p = 0.027$), and the rate of female patients was higher in all age groups of both groups (Fig. 1). A total of 56.5% of patients presented symptoms within 2 days of vaccination (Fig. 2A), and 69.8% of patients had ED visits within 7 days of vaccination (Fig. 2B); a significant difference was seen between the two groups ($p = 0.003$, $p < 0.001$) (Fig. 2).

The incidence of comorbidities (hypertension, diabetes mellitus, cardiovascular disease and malignancy) differed significantly between the two groups. EMS visits to the ED showed more frequent utilization in the ChAdOx1 group (21.0% vs. 13.9%) ($p < 0.001$). The chief complaints differed according to the two groups: fever/chilling/myalgia accounted for 15.8% in the ChAdOx1 group, and chest pain/discomfort accounted for 43.7% in the mRNA vaccines group ($p < 0.001$, $p < 0.001$) (Table 1). A total of 306 patients with allergic responses showed mild urticaria and angioedema, except for three patients with anaphylaxis reactions in the mRNA vaccines group. Additionally, arm pain, redness, bruising and swelling of the injection site were observed in 16 patients in the ChAdOx1 group and 18 patients in the mRNA vaccines group. Herpes zoster was present in two patients in the ChAdOx1 group and two patients in the mRNA vaccines group.

3.2. ED management and outcomes

ED management and resources for diagnosis differed according to the type of vaccines. In all patients, common ED management was IV hydration. The administration of antipyretics was significantly different between the two groups (8.8% vs. 17.1%) ($p < 0.001$). In the mRNA vaccines group, narcotic analgesics and nonnarcotic analgesics were used 24.8% and 5.9% of the time, respectively. In the two groups, there was a difference in the use of basic laboratory tests, cardiac enzymes, chest X-rays, ECG tests, and the reverse transcriptase polymerase chain reaction (RT–PCR) assay for COVID-19. The RT–PCR assay for COVID-

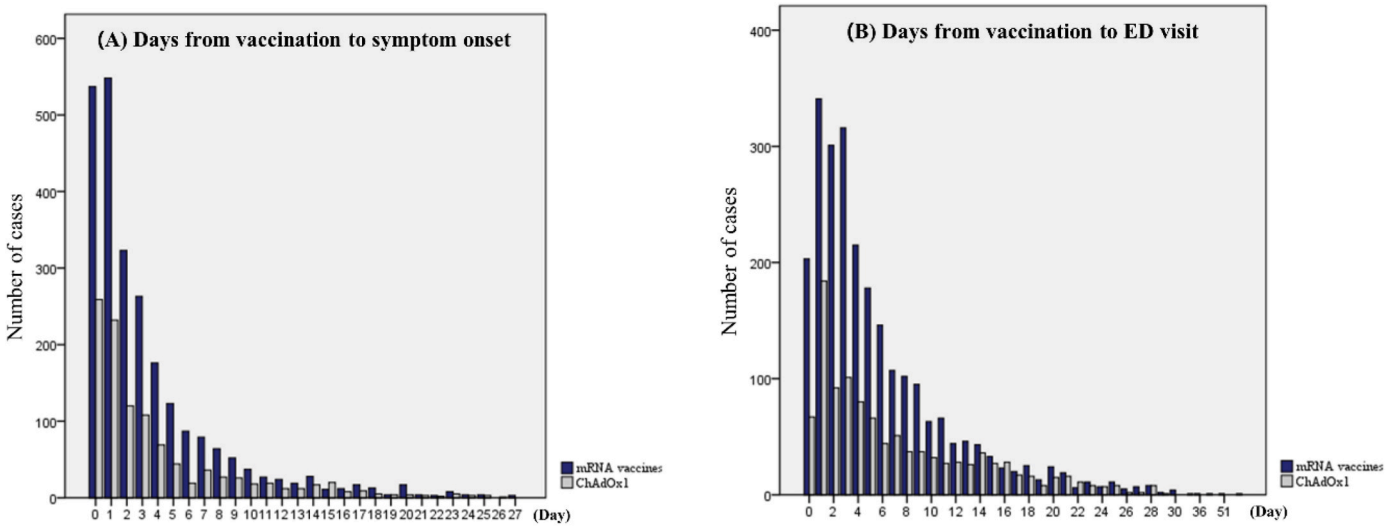

Fig. 2. (A) Days from vaccination to symptom onset and (B) ED visit according to COVID-19 vaccine. ED = emergency department. A total of 56.5% of patients showed symptoms within 2 days of vaccination, and 69.8% of patients had ED visits within 7 days of vaccination; a significant difference was seen between the two groups ($p = 0.003$, $p < 0.001$).

19 was tested in 23.2% of the ChAdOx1 group, and brain CT was examined in 33.6% of the ChAdOx1 group (Table 2).

Among all patients, 212 (5.9%) were admitted to the hospital. The median age of the patients who required admission was 70 (60–79) years, and the median age of the patients who were discharged from the ED was 46 (30–62) years ($p < 0.001$). The hospital admission rate was 8.2% for those aged 60 to 69 and 22.7% for those over 70 years according to age distribution. In both groups, 92.0% of the ChAdOx1 group and 94.7% of the mRNA vaccine group were discharged to home after ED treatment, and the admission rate was higher in the ChAdOx1 group ($p = 0.021$) (Fig. 3).

3.3. Prediction of serious AEs

In the multivariate logistic regression analysis, age, male sex, days from vaccination to symptom onset and ED visit, type of vaccines, comorbidity, and severe chief complaint (fever, chest pain, dyspnea and headache), known clinically important factors for the association of demographic and clinical factors with serious AEs, were set as variables. In all patients, age ≥70 years (OR 27.94; 95% CI 11.54–67.67; $p < 0.001$), days from vaccination to ED visit ≥8 days (OR 2.55; 95% CI 1.52–4.30 $p < 0.001$), fever (OR 1.95; 95% CI 1.26–3.00; $p = 0.003$) and dyspnea (OR 2.18; 95% CI 1.31–3.64; $p = 0.003$) showed higher odds ratios as independent risk factors for serious AEs (Table 3) (Fig. 4).

In the analysis of inpatients (admission to the GW or admission to the ICU), although there was no difference between the two groups in final diagnosis, infectious disease accounted for the highest rate at 104 (49.1%), followed by cardiovascular disease (myocarditis, unstable angina, myocardial infarction, heart failure, arrhythmia, etc.) with 39 (18.4%) (Table 4). Myocarditis was diagnosed in 2 patients in the mRNA vaccines group who required admission to GW.

Table 2
Common ED management and outcomes stratified according to COVID-19 vaccinations.

Variables, n (%)	mRNA vaccines (n = 2487)	ChAdOx1 (n = 1085)	p value
Parenteral management in ED			
IV hydration	1999 (80.4)	925 (85.3)	0.001
Antipyretics	218 (8.8)	185 (17.1)	<0.001
Narcotic analgesics	617 (24.8)	213 (19.6)	0.023
Nonnarcotic analgesics	146 (5.9)	37 (3.4)	0.002
Antihistamine	243 (9.8)	119 (11.0)	0.276
Steroid	181 (7.3)	93 (8.6)	0.182
Anti-emetics	302 (12.1)	206 (19.0)	<0.001
Nitroglycerin	97 (3.9)	20 (1.8)	0.001
Resource of utilization at ED			
Basic laboratory test	2296 (92,3)	956 (88.1)	<0.001
Troponin I, T/CK-MB	2100 (84.4)	802 (73.9)	<0.001
Chest X-ray	2297 (92.4)	975 (89.9)	0.013
ECG	2250 (90.5)	897 (82.7)	<0.001
RT–PCR assay for COVID-19	478 (19.2)	252 (23.2)	0.006
Brain CT	484 (19.5)	365 (33.6)	<0.001
Chest CT	317 (12.7)	147(13.5)	0.512
ED disposition			0.021
Discharge	2355 (94.7)	998 (92.0)	
Admission to general ward	103 (4.1)	68 (6.3)	
Admission to ICU	25 (1.0)	16 (1.5)	
Transfer	4 (0.2)	3 (0.3)	

Values are expressed as number (%) or the median (interquartile range). The χ^2 test and Mann–Whitney test were used for statistical analysis.
ED = emergency department, IV = intravenous, RT–PCR = reverse transcriptase polymerase chain reaction, CT = computed tomography, ICU = intensive care unit, OPD = outpatient department.

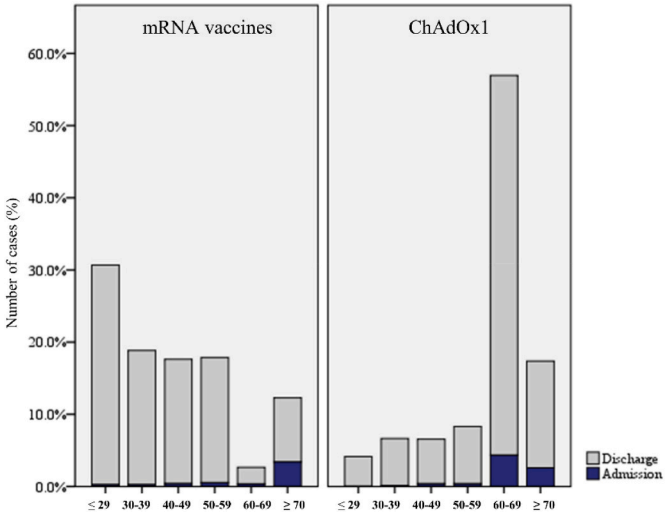

Fig. 3. Distribution according to age group and ED disposition (except transferred patients). ED = emergency department. In both groups, 92.0% of the ChAdOx1 group and 94.7% of the mRNA vaccines group were discharged to home after ED treatment ($p = 0.021$), and the admission rate was higher in the ChAdOx1 group.

Table 3
Multivariate logistic regression analysis for serious AEs.

	Multivariate analysis		
	Odds ratio	95% CI	p value
Age			
≤29	(reference)		
30-39	1.79	0.59–5.40	0.302
40-49	3.70	1.40–9.80	0.008
50-59	4.0	1.54–10.41	0.005
60-69	13.10	5.12–33.47	<0.001
≥70	27.94	11.54–67.67	<0.001
Sex	0.45	0.33–0.52	<0.001
Days from vaccination to symptom onset			
0-2	(reference)		
3-7	0.82	0.53–1.26	0.358
≥8	1.01	0.60–1.71	0.972
Days from vaccination to ED visit			
0-2	(reference)		
3-7	1.72	1.08–2.72	0.022
≥8	2.55	1.52–4.30	<0.001
Type of vaccines	0.63	0.42–0.93	0.019
EMS visit to the ED	0.31	0.22–0.43	<0.001
Hypertension	1.15	0.78–1.69	0.487
Diabetes mellitus	0.76	0.46–1.24	0.270
Cardiovascular disease	0.95	0.60–1.49	0.809
Fever	1.95	1.26–3.00	0.003
Chest pain	0.74	0.47–1.18	0.203
Dyspnea	2.18	1.31–3.64	0.003
Headache	0.17	0.06–0.47	0.001

Multiple logistic regression was used for statistical analysis.
ED = emergency department, EMS = emergency medical services.

4. Discussion

At the end of this study, October 1, 2021, in South Korea, the inoculation rate for those aged 18 years old and older was 89.1% for the first dose and 58.2% for the second dose, and BNT162b2 50.8%, ChAdOx1 35%, mRNA 1273 12.1%, and Ad26.COV2. S 2.1% were administered (COVID-19 domestic occurrence and vaccination status (October 1)) [1]. This study showed that 94% of patients who visited the ED with AEs after COVID-19 vaccination were discharged regardless of the type of vaccine. Although small in number, they may require admission, and higher independent risk factors for serious AEs in the ED were age ≥70

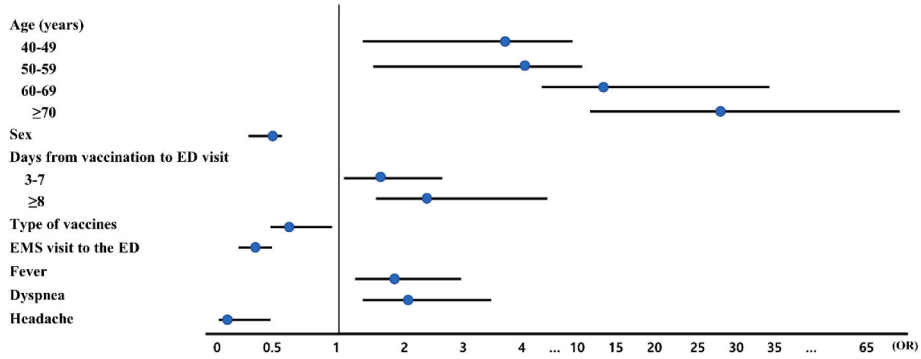

Fig. 4. Factors related to serious adverse events.

Table 4
Final diagnosis of admitted patients.

Diagnosis	Total (n = 212)	mRNA vaccines (n = 128)	ChAdOx1 (n = 84)
Infectious diseases	104 (49.1)	64 (50.0)	40 (47.6)
Pneumonia	30 (14.2)	22 (17.2)	8 (9.5)
Hepatobiliary infection	24 (11.3)	11 (8.6)	13 (15.5)
Gastrointestinal infection	18 (8.5)	18 (14.1)	8 (9.5)
Urinary tract infection	26 (12.3)	10 (7.8)	8 (9.5)
Other infection	6 (2.8)	3 (2.3)	3 (3.6)
Cardiovascular disease	39 (18.4)	22 (17.2)	22 (26.2)
Cerebrovascular disease	25 (11.8)	13 (10.2)	12 (14.3)
Others	44 (20.8)	29 (22.7)	10 (11.9)

Values are expressed as number (%) or the median (interquartile range).

years, days from vaccination to ED visit ≥8 days, patients presented with fever and dyspnea.

The present study showed that the proportion of patients under the age of 30 was high in the mRNA vaccines group, whereas in the ChAdOx1 group, the proportion of patients over the age of 60 was higher. As thrombosis with thrombocytopenia syndrome (TTS) was reported as a severe adverse reaction to the ChAdOx1 vaccine [9,10], the government restricted the ChAdOx1 vaccination to those over 30 years old in April 2021, raised it to over 50 years old in July 2021, and lowered it to over 30 years old again in August 2021. Due to these age restrictions, the ChAdOx1 vaccine was given in a higher age group than the mRNA vaccine, increasing the mean age of the ChAdOx1 group. Therefore, the distribution by age group and the mean age in this study should be interpreted carefully considering this background.

There was a difference between the previous study and this study in terms of the mean age and discharge rate of patients who visited the ED with AEs [13]. Among the 1842 patients who visited the ED after COVID-19 vaccination by Kewan et al., the mean age was 70 years, and the admission rate was 40.3%, higher than the 5.9% in this study [13]. The median age of this study was 48 years, and they were younger and had a lower admission rate than in the previous study. In South Korea, it is easy to access the ED due to the Korean National Insurance Coverage and cheaper medical costs, so the demographic characteristics and outcomes of these patients in South Korea may differ from those in other countries. However, approximately 89% of the total number of admitted patients in this study was over 60 years of age. The increased hospital admission was associated with old age group. A previous study in this country showed that older age was associated with an increased hospital admission rate in the ED for internal medicine management (65–74 years vs. 75–84 years vs. ≥ 85 years; 57.5% vs. 59.3% vs. 64.7%) [16]. Another study reported that the admission rate of elderly individuals in the general population (≥65 years) who visited the ED was 26.1% [17]. This study showed that the admission rate of elderly patients visiting the ED with AEs following COVID-19 vaccination was lower than the admission rate of the elderly general population in previous studies.

During the same period as this study, the most common adverse symptoms reported to the government through the Vaccine Adverse Event Reporting System were headache, myalgia, dizziness, nausea, allergic reactions, and fever [18–20]. In this study, the most common AEs of ED visits were chest pain/discomfort, fever, headache, allergic reaction, general weakness, and dyspnea. This study showed that these patients visiting the ED with AEs may complain of more severe chief complaints requiring differential diagnosis for critical disease than the general population of other studies. In vulnerable patients, these chief complaints (chest pain, dyspnea, fever and headache) of ED may need more tests and longer ED stay times to identify critical medical conditions. The present study showed that many patients began to visit the ED with different chief complaints according to the type of vaccine. These differences in chief complaints between the two groups also led to differences in treatments and tests conducted in the ED. The rate of antipyretic administration was high in the treatment of the ChAdOx1 vaccination group with symptoms of fever and headache. In the mRNA vaccine group, the rate of administration of nitroglycerin and narcotic analgesics was high due to the chief complaints of chest pain. Thus, more blood tests and cardiac enzyme, EKG, and chest X-ray analyses in the mRNA vaccine group were performed to differentiate other severe cardiovascular diseases in the ED. Furthermore, mRNA vaccines were reported to cause severe adverse reactions, although low, such as severe allergic reactions or anaphylaxis and myocarditis [21–24]. Although the incidence of myocarditis after the BNT162b2 mRNA vaccination was low, there were reports of myocarditis cases after the second dose among young males [23,24]. Myocarditis was diagnosed in 2 patients in the mRNA vaccine group, and 37 patients were admitted to the hospital for the management and treatment of other cardiovascular diseases in this study. Previous clinical trial studies reported thrombocytopenia or thrombosis in the ChAdOx1 group [8–11]. In this study, cases of multiple minor bruises and purplish spots were found, and no cases showed thrombotic thrombocytopenia after ChAdOx1 vaccination. Additionally, most patients with allergic responses showed mild urticaria and angioedema, and only three patients had severe anaphylaxis reactions in the mRNA vaccine group.

In elderly patients, the immediate adverse reactions caused by vaccination may appear weakly due to immune aging [25,26]. Some studies reported reduced antibody responses and fewer AEs in the elderly compared to their younger participants, and they explained that the reason may be due to immunosenescence of elderly individuals, with declining immunity with age [3,18,27,28]. Elderly individuals with frailty or comorbidities can show atypical clinical features of diseases [16,17], which may lead to delayed ED visits. Thus, elderly individuals may present more critical conditions requiring hospital admission when visiting the ED and need more ED tests for final diagnosis due to the difficulty of differential diagnosis. Additionally, the admitted patients of this study were diagnosed with a high proportion of infectious diseases,

such as pneumonia, which is thought to be associated with fever and dyspnea being factors related to serious AEs. The variable of days from COVID-19 vaccination to ED visit was independent factor related to serious AEs. This means that patients with more delayed ED visits after COVID-19 vaccination may be considered to differentiate other severe medical diseases rather than direct adverse reactions to COVID-19 vaccination, especially elderly or vulnerable patients with comorbidities.

There are several limitations to this study. First, although this was the result of a multicenter study, selection bias might have occurred. We included only patients who reported symptoms within 28 days of vaccination and did not follow up with discharged patients from the ED; this lack of long-term follow-up leaves potential for missed critical AEs. Second, since this study was analyzed through a retrospective medical chart review of self-reported AEs in the ED, it did not include all patients in the ED who received a COVID-19 vaccine within 28 days of vaccine administration. However, our study is the first multicenter study to analyze detailed clinical features and outcomes of patients who visited the ED with self-reported AEs following COVID-19 vaccination. Therefore, this study can provide a guide for decision-making and patient disposition within the ED for patients with various AEs by different types of COVID-19 vaccination.

In conclusion, most patients were discharged from the ED after symptomatic treatment among the patients who visited the ED with AEs after COVID-19 vaccination regardless of the type of vaccine. Although small in number, serious AEs have occurred, and factors of old age, delayed ED visits from vaccination, fever, and dyspnea related to serious AEs should be considered when accessing these patients in the ED.

Funding

No funding.

Author Contributions

WJL, SJ and WJJ performed data analysis and drafted the manuscript. BHS, HMK, KC and SPC acquired the data and critically revised the manuscript. SJ and SHW managed the data and revised the manuscript. All authors read and approved the final manuscript.

Statement of human and animal rights

All procedures performed in studies involving patients were in accordance with the ethical standards of the institution and/or national research. The protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital.

Informed consent

The data were reviewed and approved by the Institutional Review Board of this hospital (approval No. XC21RIDI0141). As the clinical measurements collected were routine due to the retrospective nature of the study.

Informed consent was unnecessary, which was confirmed by the Institutional Review Board.

Data availability

All data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors have no potential conflicts of interest to disclose.

Acknowledgments and Funding

No funding was received for this study. The results of the interim analysis were presented as a poster in the 2022 ESICM's annual congress.

References

[1] Korea Disease Control and Prevention Agency. https://ncv.kdca.go.kr/menu.es?mid=a10117010000. [Accessed 2 December 2021]. Accessed.
[2] Krammer F. SARS-CoV-2 vaccines in development. Nature 2020 Oct;586(7830):516–27.
[3] Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2021;396(10267):1979–93.
[4] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397(10269):99–111.
[5] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603–15.
[6] Park MJ, Choi YJ, Choi S, Park MJ, et al. Emergency department utilization by in-hospital healthcare workers after COVID-19 vaccination. J Kor Med Sci 2021;36(27):e196.
[7] Kim SH, Wi YM, Yun SY, Ryu JS, Shin JM, Lee EH, et al. Adverse events in healthcare workers after the first dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 vaccination: a single center experience. J Kor Med Sci 2021;36(14):e107.
[8] Sørvoll IH, Horvei KD, Ernstsen SL, Laegreid IJ, Lund S, Grønli RH, et al. An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination. J Thromb Haemostasis 2021;19(7):1813–8.
[9] Tobaiqy M, Elkout H, MacLure K. Analysis of thrombotic adverse reactions of COVID-19 Astrazeneca vaccine reported to EudraVigilance database. Vaccines (Basel) 2021;9(4):393.
[10] Krzywicka K, Heldner MR, Sánchez van Kammen M, van Haaps T, Hiltunen S, Silvis SM, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency. Eur J Neurol 2021;28(11):3656–62.
[11] Abbattista M, Martinelli I, Peyvandi F. Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: thrombosis at unusual sites. J Thromb Haemostasis 2021;19(10):2554–8.
[12] Nevet A. Acute myocarditis associated with anti-COVID-19 vaccination. Clin Exp Vaccine Res 2021;10(2):196–7.
[13] Kewan T, Flores M, Mushtaq K, Alwakeel M, Burton R, Campbell J, et al. Characteristics and outcomes of adverse events after COVID-19 vaccination. J Am Coll Emerg Physicians Open 2021;2(5):e12565.
[14] Understanding the vaccine adverse event reporting System (VAERS). CDC; 2013.
[15] World Health Organization. COVID-19 vaccines: safety surveillance manual. World Health Organization; 2021.
[16] Lee SB, Oh JH, Park JH, Choi SP, Wee JH. Differences in youngest-old, middle-old, and oldest-old patients who visit the emergency department. Clin Exp Emerg Med 2018;5(4):249–55.
[17] Ross MA, Compton S, Richardson D, Jones R, Nittis T, Wilson A. The use and effectiveness of an emergency department observation unit for elderly patients. Ann Emerg Med 2003;41(5):668–77.
[18] Skowronski DM, De Serres G. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2021;384(16):1576–7.
[19] Korea Disease Control and Prevention Agency. https://ncv.kdca.go.kr/menu.es?mid=a10118070000. [Accessed 6 August 2021]. Accessed.
[20] Korea Disease Control and Prevention Agency. https://ncv.kdca.go.kr/menu.es?mid=a10118060000. [Accessed 6 August 2021]. Accessed.
[21] Banerji A, Wickner PG, Saff R, Stone Jr CA, Robinson LB, Long AA, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. J Allergy Clin Immunol Pract 2021;9(4):1423–37.
[22] Blumenthal KG, Robinson LB, Camargo Jr CA, Shenoy ES, Banerji A, Landman AB, et al. Acute allergic reactions to mRNA COVID-19 vaccines. JAMA 2021;325(15):1562–5.
[23] Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA vaccine against covid-19 in Israel. N Engl J Med 2021;385(23):2140–9.
[24] Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after covid-19 vaccination in a large health care organization. N Engl J Med 2021;385(23):2132–9.
[25] Yuan P, Ai P, Liu Y, Ai Z, Wang Y, Cao W, et al. Safety, tolerability, and immunogenicity of COVID-19 vaccines: a systematic review and meta-analysis. medRxiv [Preprint] 2020. Nov 4:2020.11.03.20224998.

[26] Aemro A, Amare NS, Shetie B, Chekol B, Wassie M. Determinants of COVID-19 vaccine hesitancy among health care workers in Amhara region referral hospitals, Northwest Ethiopia: a cross-sectional study. Epidemiol Infect 2021;149:e225.

[27] Gustafson CE, Kim C, Weyand CM, Goronzy JJ. Influence of immune aging on vaccine responses. J Allergy Clin Immunol 2020;145(5):1309–21.

[28] Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing 2021;50(2):279–83.