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Journal of Infection and Chemotherapy 28 (2022) 1159–1164

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

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

Original Article

Analysis of older adults visiting the emergency department with fever as a suspected Covid-19 vaccine-related adverse reaction: A retrospective multicenter study

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ARTICLE INFO

Keywords:
COVID-19 vaccine
Older adults
Fever
Adverse reactions
Emergency department

ABSTRACT

Introduction: After COVID-19 vaccination was initiated, the number of patients visiting the emergency department (ED) with vaccine-related adverse reactions increased. We investigated the clinical features of older adults (aged 65 years and older) visiting the ED with self-reported COVID-19 postvaccination fever.

Methods: We conducted a retrospective observational study at three EDs between March 2021 and September 2021. Patients who reported adverse reactions, fever (≥37.5 °C) and/or febrile sensation or rigors following COVID-19 vaccination were included. The demographic and clinical data of these patients were collected by reviewing their medical records.

Results: A total of 562 patients were selected, and 396 (70.5%) were female. The older adult group included 155 (27.6%) patients, and the median age was 75 (69–79 years). The older adults less frequently had a fever (≥37.5 °C) upon ED presentation (75.5% vs. 85.7%, respectively), used more emergency medical services (43.9% vs. 18.7%, respectively), and visited an ED more frequently during early hours (00:00–06:00) (31% vs. 20.1%, respectively) compared to the younger adults ($p = 0.004$, $p < 0.001$ and $p = 0.036$). Fewer older adults visited an ED within 2 days of fever onset (73.5% vs. 84%) ($p = 0.012$), and more older adults were admitted for medical conditions other than vaccine-related adverse reactions (32.9% vs. 4.2%) ($p < 0.001$). Older adults received more thorough testing (laboratory and imaging tests). Among the older adults, the admission rate was associated with age ($p = 0.003$).

Conclusion: Older adults presenting with fever as an adverse reaction following COVID-19 vaccination less frequently had a fever upon visiting the ED, required more ED testing, and had higher admission rates for non-vaccination-related medical conditions.

1. Introduction

COVID-19 vaccinations were initiated in February 2021 in the Republic of Korea. As of November 2021, nationwide vaccination rates had reached 76.9%, with the vaccination rate of adults over 18 years of age reaching 89.4% [1]. As a result, the number of patients visiting an emergency department (ED) with vaccine-related adverse reactions has increased. Throughout the COVID-19 pandemic, older adults have been at increased risk for severe COVID-19-associated illness and death. The government prioritized COVID-19 vaccinations for vulnerable groups, such as residents of long-term care facilities and nursing homes and older adults with frailty or comorbidities. However, data on the safety and efficacy of COVID-19 vaccines in these vulnerable groups are limited because such groups have been excluded from most clinical trials [2–4].

Frailty is characterized by a decline in function across multiple physiological systems, accompanied by an increased vulnerability to stressors. Frailty places a person at increased risk of adverse outcomes,

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https://doi.org/10.1016/j.jiac.2022.04.022
Received 3 February 2022; Received in revised form 31 March 2022; Accepted 22 April 2022
Available online 2 May 2022

including falls, hospitalization, and mortality. All older adults are at risk of developing frailty [5]. Immunosenescence is a broad term used to encompass declining immunity with age [6], and it may be the reason why certain clinical trials have reported reduced antibody responses and fewer adverse effects in older adults compared to their younger counterparts [2,3]. Additionally, some researchers have reported that vaccines may be somewhat less effective in older adults due to immunosenescence [7].

As noted above, although older adults may exhibit fewer adverse effects than younger adults, older adults, especially those with frailty or comorbidities, could have serious vaccine-related adverse reactions that are not serious to younger adults. In addition, older adults with frailty are more likely to show atypical clinical features, making it difficult for clinicians to distinguish vaccine-related adverse reactions from other medical conditions. For these reasons, we investigated the clinical characteristics of older adults with self-reported COVID-19 post-vaccination fever and/or febrile sensation or rigors.

2. Methods

2.1. Study design and data collection

We conducted a retrospective observational study in three hospitals, whose EDs serve as regional emergency centers in South Korea. These EDs had averages of approximately 70,000, 60,000, and 30,000 annual visits, respectively, prior to the COVID-19 pandemic. Patients who visited the EDs of these three hospitals with self-reported adverse reactions after COVID-19 vaccination between March 2021 and September 2021 were selected for this study. Patients with suspected adverse reactions that were reported to the national COVID-19 Immunization Registry System were selected. The types of COVID-19 vaccines included Oxford/AstraZeneca (AZD1222), Pfizer BioNTech (BNT162b2) and Moderna (mRNA-1273). The exclusion criteria were as follows: Patients under the age of 18 years; patients with symptoms occurring prior to vaccination; patients with symptoms occurring more than 14 days after vaccination; and patients with incomplete data. Subjects for this study were confined to patients who presented with fever (≥37.5 °C) and/or febrile sensation or rigors following COVID-19 vaccination.

We collected data on each patient's sex, age, use of emergency medical services (EMS), date of vaccination, type of administered vaccine, vaccine dose (first or second), outcomes (discharge or admission), ED length of stay, comorbidities, time of arrival to the ED, parenteral medication prescribed during their ED stay, and final diagnosis. Patients between the ages of 19 and 64 years were termed younger adults, while patients over the age of 65 years were termed older adults. The Institutional Review Board of the Catholic Medical Center approved this study. Informed consent was waived because of the retrospective nature of this study.

2.2. Statistical analysis

Data were analyzed by absolute frequency, percentage, median, and interquartile range, according to each patient's sex, age, type of vaccine, vaccine dose, laboratory findings, discharge outcomes, and diagnosis. The Kolmogorov–Smirnov test was applied to continuous variables to test for a normal distribution. For the data that were not normally distributed, the results are presented as the medians and interquartile ranges; these data were analyzed using the Mann–Whitney *U* test. Noncontinuous variables were analyzed using the chi-square test and are expressed as frequencies and percentages. A P value of 0.05 or less was considered a statistically significant difference. All statistical analyses were analyzed using SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Among the 3,948 patients who visited the EDs with self-reported adverse reactions after COVID-19 vaccination, 562 reported fever (≥37.5 °C) and/or febrile sensation or rigors (Fig. 1). Among these 562 patients, 155 (27.6%) were older adults. There were 396 females (70.5%), and most patients were in their 20s (Fig. 2). The median age of the older adults was 75 (69–79 years), and more Pfizer/BioNTech and AstraZeneca vaccines were administered to older adults, while the Moderna vaccine was more frequently given to younger adults (Table 1). Both older adults and younger adults visited the ED more often following the first vaccine dose (63.9% vs. 69.5%, respectively). The younger adults had more fevers (≥37.5 °C) upon initial ED presentation than the older adults (85.7% vs. 75.5%, respectively) ($p = 0.004$). The older adults more frequently used EMS (43.9% vs. 18.7%, $p < 0.001$) and most frequently visited the ED between 00:00 and 06:00 (31.0%, $p = 0.036$) (Table 1).

Postvaccination fever symptoms most commonly occurred on Days 0 and 1. A total of 73.5% of the older adults and 77.1% of the younger adults had symptoms within 2 days of vaccination. There was no significant difference between the two groups in the days of symptom onset after vaccination (Fig. 3A, Supplementary Table 1), but actual ED visits were significantly delayed in the older adult group compared to the younger adult group ($p = 0.403$, $p = 0.004$, respectively) (Fig. 3B and C).

ED management was similar between the two groups, but antimicrobials were more frequently received by the older adults ($p < 0.001$) (Table 2). More tests (laboratory and imaging tests) were needed for the older adults. The total admission rates (32.9% vs. 4.2%) and intensive care unit (ICU) admission rates (7.1% vs. 1.0%) were higher in the older adult group ($p < 0.001$). The ED length of stay was longer in the older adult group ($p < 0.001$).

3.2. Clinical features of the admitted febrile older adults

Among the 154 older adults, except for one transferred patient, 51 (33.1%) were admitted to the hospital. The common final diagnoses for the admitted older adults were as follows: 14 patients had a urinary tract infection (27.5%), 12 had pneumonia (23.5%), 8 had a hepatobiliary infection (15.7%), and 7 had a gastrointestinal infection (13.7%)

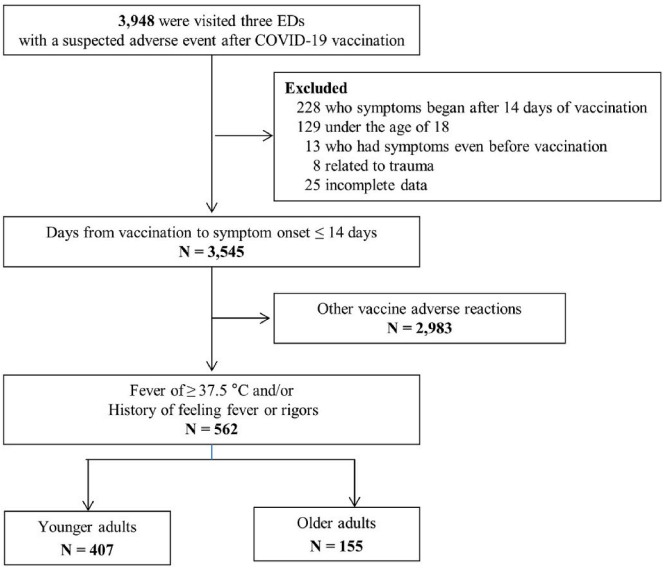

Fig. 1. Study population.

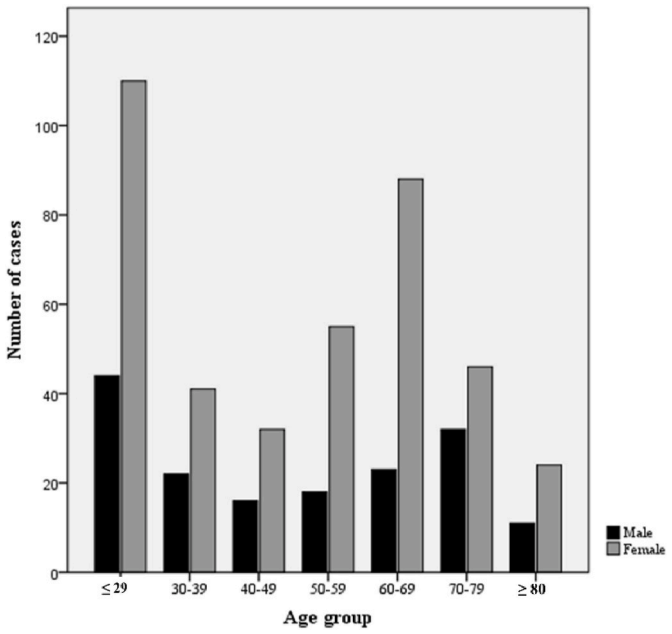

Fig. 2. Distribution of age groups according to sex
Among the 562 patients, 166 (29.5%) were males, and 396 (70.5%) were females. A greater number of females visited the ED in all age groups. Regardless of sex, patients in their 20s (154, 27.4%) visited the ED most frequently, followed by patients in their 60s (111, 19.8%) and 70s (98, 17.4%).

Table 1
Demographic and clinical characteristics.

Variables, n (%)	Total (n = 562)	Older adults (n = 155)	Younger adults (n = 407)	p value
Male	166 (29.5)	53 (34.2)	113 (27.8)	0.135
Age, Median (IQR)	52 (28–67)	75 (69–79)	38 (26–56)	<0.001
Vaccine type				
Pfizer/BioNTech	264 (47.0)	82 (52.9)	182(44.7)	
AstraZeneca	225(40.0)	71 (45.9)	154 (37.8)	<0.001
Moderna	73 (13.0)	2 (1.3)	71 (17.4)	
Vaccine dose				
First dose	382 (68.0)	99 (63.9)	283 (69.5)	0.199
Second dose	180 (32.0)	56 (36.1)	124 (30.5)	
Initial BT ≥ 37.5 °C	466 (82.9)	117 (75.5)	349 (85.7)	0.004
EMS visit to the ED	144 (25.6)	68 (43.9)	76 (18.7)	<0.001
Time of ED arrival				
00:00–06:00	130 (23.1)	48 (31.0)	82 (20.1)	0.036
06:00–12:00	161 (28.6)	44 (28.4)	117 (28.7)	
12:00–18:00	189 (33.6)	42 (27.1)	147 (36.1)	
18:00–00:00	82 (14.6)	21 (13.5)	61 (15.0)	
Comorbidities				
Hypertension	71 (12.6)	39 (25.2)	32 (7.9)	<0.001
Cardiovascular disease	42 (7.5)	29 (18.7)	13 (3.2)	<0.001
Diabetes mellitus	37 (6.6)	24 (15.5)	13 (3.2)	<0.001
Malignancy	24 (4.3)	16 (10.3)	8 (2.0)	<0.001
Respiratory disease	10 (1.8)	7 (4.5)	3 (0.7)	0.006
Cerebrovascular disease	7 (1.2)	5 (3.2)	2 (0.5)	0.019

Values are presented as median (IQR) or numbers (%). Pfizer/BioNTech; BNT162b2, AstraZeneca; AZD1222, Moderna; mRNA-1273. BT; body temperature, ED; emergency department, EMS; emergency medical services.

(Table 3). The older adults did not require admission to the general ward or ICU due to vaccine-related adverse reactions as the final diagnosis.

A total of 39.2% of the admitted older adults and 20.4% of the discharged older adults experienced fever symptoms after 3 days of vaccination (p = 0.023) (Supplementary Table 2), and the time from symptom onset to the ED visit was not different between the two groups. Compared to 58.3% of the discharged older adults, only 25.5% of the admitted older adults visited the ED within 2 days after vaccination (p < 0.001).

The increased admission rates were associated with age: 65–74 years (33.3%) and 75–84 years (52.9%) (p = 0.003). The number of patients with fever upon ED presentation and usage rates of EMS were higher among the admitted older adults than among the discharged older adults (p = 0.009, p = 0.001, respectively). Among the older adults, 86 (83.5%) patients were discharged from the ED with COVID-19 vaccine-related adverse reactions as the final diagnosis (p < 0.001) (Table 4).

4. Discussion

Despite being one of the most vulnerable groups for COVID-19 infection, older adults, particularly extremely old adults and those with frailty or comorbidities, have generally been excluded from most clinical trials investigating the safety and efficacy of COVID-19 vaccines [2,3]. Currently, the South Korean government is retrospectively monitoring the safety and efficacy of COVID-19 vaccines in these groups through the Adverse Event Reporting System. Randomized controlled trials in these vulnerable groups are necessary; however, in reality, such studies are rarely reported due to their many limitations. Thus, in this study, investigating the epidemiological and clinical characteristics of older adults reporting postvaccination adverse events can prove to be valuable. This multicenter study showed that the number of patients who visited the ED with fever as a suspected COVID-19 vaccine-related adverse reaction was lower for older adults than for younger adults. Although older adults did not require admission to the hospital due to vaccine-related adverse reactions, they had higher rates of admission for infections and other diseases in the ED than younger adults.

As of September 30, 2021, Pfizer/BioNTech was the most widely administered COVID-19 vaccine in South Korea, representing 54.0% of the total vaccine doses, followed by the AstraZeneca (33.1%), Moderna (10.5%), and Janssen (2.4%) vaccines [8]. This study showed a similar distribution of administered vaccines: Pfizer/BioNTech (47%), AstraZeneca (40%), and Moderna (13%). In a clinical trial regarding the Pfizer/BioNTech COVID-19 vaccine, fever was reported after the second dose by 16% of the younger vaccine recipients and by 11% of the older recipients [2], and in a study of the AstraZeneca vaccine, fever was reported by 7% of all vaccine recipients [9]. In this study, among the 3,545 individuals who visited the ED with adverse reactions within 14 days after COVID-19 vaccination, 562 (15.8%) reported fever (≥37.5 °C) and/or febrile sensation or rigors. In this study, 70.5% of the patients were female. Similarly, female sex was the main covariable in the study of vaccine adverse reactions, although a clear explanation of such an observation has yet to be provided [10].

Compared to younger adults, older adults more commonly used EMS, more frequently visited the ED between 00:00 and 06:00, received more thorough testing in the ED, had longer stays in the ED. This implies that the older adults had more severe medical conditions and therefore required more time and resources for diagnosis and management. Although the older adults less frequently had a fever (≥37.5 °C) upon initial ED presentation compared to the younger adults, their total admission rates and ICU admission rates were higher. This may be attributed to atypical clinical features of diseases in older adults due to declines in functioning across multiple physiological systems. On the other hand, such observations may simply be due to a lower frequency of vaccine-related adverse reactions in older adults, as has been reported in other studies [11].

Older adults were more likely to be delayed ED visits after postvaccination symptom onset than younger adults. Older adults may take postvaccination symptoms lightly, leading to a delayed hospital presentation and an unfavorable prognosis. Therefore, more detailed guidelines and observations should be provided after vaccination in

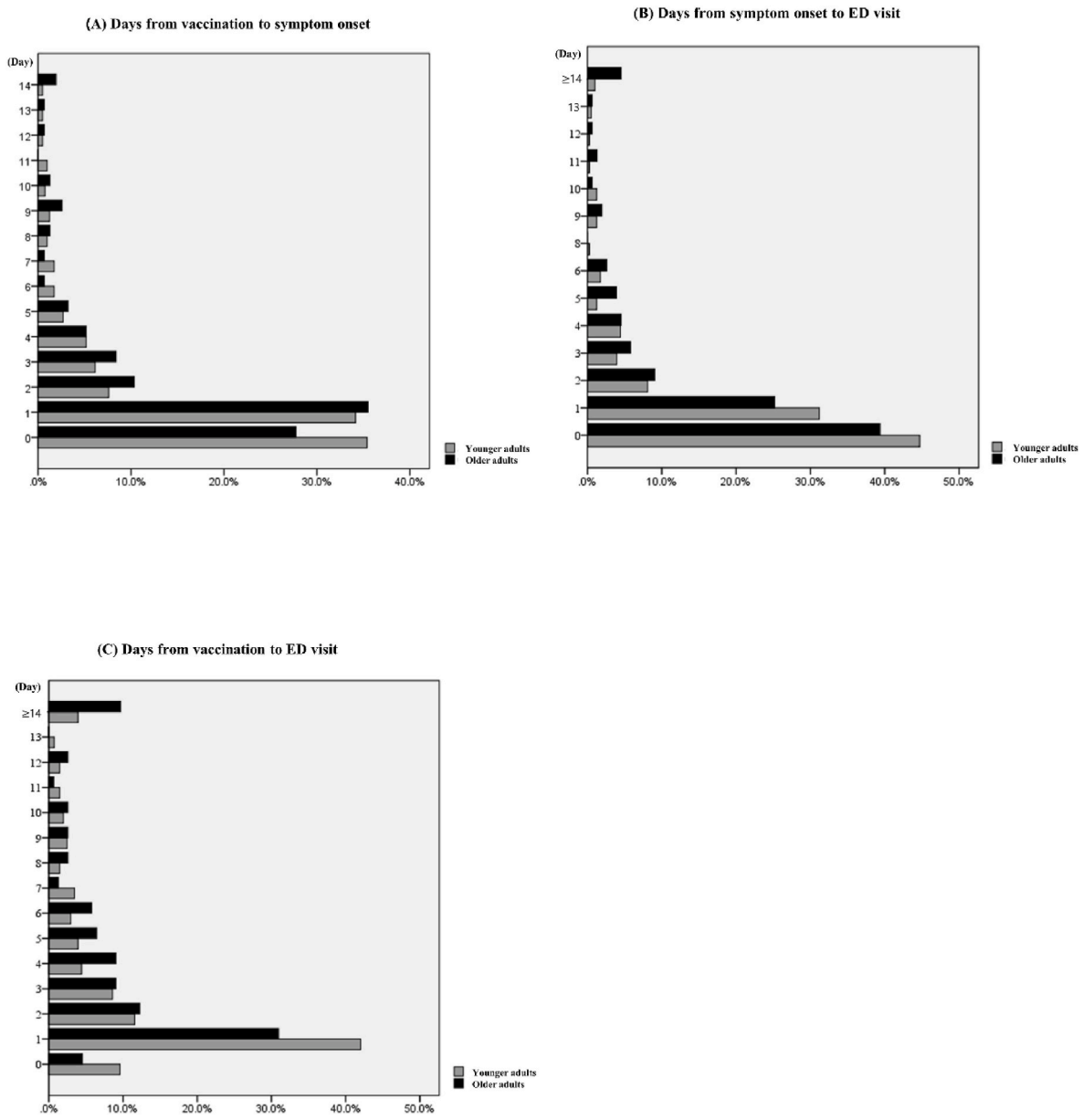

Fig. 3. Symptom onset days and ED visit days since vaccination.
(A) Fever occurred most commonly on the day of vaccination (0 days) and one day later (1 day). (B) A total of 39.4% of the older adults and 44.7% of the younger adults visited the ED on the day that they had a fever (0 days); 73.5% vs. 84%, respectively, visited ≤2 days since fever onset; 16.8% vs. 11.3%, respectively, visited within 3–7 days; and 9.7% vs. 4.7%, respectively, visited ≥8 days since fever onset ($p = 0.024$). (C) Patients most frequently visited the ED on the day after vaccination (1 day) due to suspicion of an adverse reaction after vaccination. Compared to 63.1% of the younger adults, only 47.7% of the older adults visited the ED within 2 days of vaccination ($p < 0.001$).

older adults. In this study, the patients most frequently visited the ED for suspected postvaccination adverse events on the day after vaccination. However, compared to 63.1% of the younger adults, only 47.7% of the older adults visited the ED within 2 days of vaccination. A total of 39.2% of the admitted older adults visited the ED after 3 days of vaccination. Therefore, clinicians must consider not only postvaccination adverse events but also other medical conditions in older adults reporting fever following COVID-19 vaccination, especially those with delayed fever onset after 3 days of vaccination.

COVID-19 vaccines have been shown to have more side effects than seasonal influenza vaccines, and numerous infection specialists have advocated for an annual COVID-19 booster, as immunity may wane over time and the virus mutates. In addition, other studies have shown a greater decline in COVID-19 morbidity and mortality in older adults with the highest vaccination rates [12–14]. Therefore, it is expected that older adults reporting COVID-19 vaccine-related adverse reactions will continuously present to the ED for the foreseeable future, which is why additional study will be needed.

Although this was a multicenter study, several limitations exist, including its retrospective nature and small sample size. This study was performed in three EDs; therefore, selection bias might have occurred. Second, the results for vaccine types should be interpreted carefully, as the vaccination rates and administered vaccine types in each age group varied during our study period. Third, this study focused on febrile patients who self-reported postvaccination adverse effects within 14 days upon vaccine administration, and the lack of long-term follow-up creates the potential for missed critical adverse events. Finally, this study was a retrospective study, and it was not possible to prove causality and

Table 2
Therapeutics and disposition of febrile patients.

Variables, n (%)	Total (n = 562)	Older adults (n = 155)	Younger adults (n = 407)	p value
Parenteral management in the ED				
IV hydration	520 (92.5)	145 (93.5)	375 (92.1)	0.570
Antipyretics	345 (61.4)	93 (60.0)	252 (61.9)	0.677
Narcotic analgesics	93 (16.5)	30 (19.4)	63 (15.5)	0.269
Antiemetics	62 (11.0)	18 (11.6)	44 (10.8)	0.786
Antimicrobials	70 (12.5)	38 (24.5)	32 (7.9)	<0.001
Resources utilized in the ED				
Laboratory test	502 (89.3)	149 (96.1)	353 (86.7)	0.001
Chest X-ray		151 (97.4)	375 (92.1)	0.022
COVID-19 PCR	325 (57.8)	102 (65.8)	223 (54.8)	0.018
Brain CT	91 (16.2)	30 (19.4)	61 (15.0)	0.209
Chest CT	197 (35.1)	87 (56.1)	110 (27.0)	<0.001
Abdominal CT	81 (14.4)	48 (31.0)	33 (8.1)	<0.001
ED disposition				
Discharge	491 (87.4)	103 (66.5)	388 (95.3)	<0.001
Admission to general ward	53 (9.4)	40 (25.8)	13 (3.2)	
Admission to ICU	15 (2.7)	11 (7.1)	4 (1.0)	
Transfer	3 (0.5)	1 (0.6)	2 (0.5)	
ED length of stay, hrs	2.5 (2.0–4.0)	3.5 (2.0–7.0)	2.0 (2.0–3.0)	<0.001

Values are presented as number (%) or the median (IQR). IV; intravenous, PCR; polymerase chain reaction.

Table 3
Diagnoses of the admitted patients.

Diagnosis	Total (n = 68)	Older adults (n = 51)	Younger adults (n = 17)	p value
Urinary tract infection	19 (28.0)	14 (27.5)	5 (29.4)	0.734
Pneumonia	17 (25.0)	12 (23.5)	5 (29.4)	
Hepatobiliary infection	9 (13.2)	8 (15.7)	1 (5.9)	
Gastrointestinal infection	9 (13.2)	7 (13.7)	2 (11.8)	
Other infection	7 (10.3)	4 (7.8)	3 (17.6)	
Other disease	7 (10.3)	6 (11.8)	1 (5.9)	

Values are presented as numbers (%). The χ^2 test was used for statistical analysis.

effect between the final diagnosis and vaccine-related adverse reactions. However, there are no studies on older adults presenting to the ED with fever after receiving a COVID-19 vaccine, so our study is expected to guide the decision-making and disposition of older adults.

In conclusion, older adults less frequently had a fever upon ED presentation, required more ED testing, and had higher admission rates for non-vaccination-related medical conditions than adults. Emergency physicians should consider not only adverse reactions but also other infectious diseases in febrile older adults visiting the ED after COVID-19 vaccination.

Author contributions

WJJ, SJ and WJL performed data analysis and drafted the manuscript. SH, TO and DK 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.

Table 4
Characteristics of the admitted and discharged older adults.

	Total (n = 154)	Admission (n = 51)	Discharge (n = 103)	p value
Male	52 (33.8)	21 (41.2)	31 (30.1)	0.171
Age, Median				
65–74	76 (49.4)	17 (33.3)	59 (57.3)	0.003
75–84	68 (44.2)	27 (52.9)	41 (39.8)	
≥85	10 (6.5)	7 (13.7)	3 (2.9)	
Vaccine dose				
first dose	98 (63.6)	27 (52.9)	71 (68.9)	0.052
second dose	56 (36.4)	24 (47.1)	32 (31.1)	
Initial BT ≥ 37.5 °C	116 (75.3)	45 (88.2)	71 (68.9)	0.009
EMS visit to the ED	67 (43.5)	32 (62.7)	35 (34.0)	0.001
Time of ED arrival				
00:00–06:00	48 (31.2)	18 (35.3)	30 (29.1)	0.657
06:00–12:00	44 (28.6)	16 (31.4)	28 (27.2)	
12:00–18:00	42 (27.3)	12 (23.5)	30 (29.1)	
18:00–00:00	20 (13.0)	5 (9.8)	15 (14.6)	
Comorbidities				
Hypertension	38 (24.7)	14 (27.5)	24 (23.3)	0.574
Diabetes mellitus	23 (14.9)	8 (15.7)	15 (14.6)	0.854
Respiratory disease	7 (4.5)	2 (3.9)	5 (4.9)	0.794
Cardiovascular disease	29 (18.8)	10 (19.6)	19 (18.4)	0.862
Cerebrovascular disease	5 (3.2)	2 (3.9)	3 (2.9)	0.740
Malignancy	16 (10.4)	6 (11.8)	10 (9.7)	0.694
Final diagnosis				
Vaccine-related adverse reaction	86 (55.8)	0	86 (83.5)	<0.001
Infectious disease	49 (31.8)	45 (88.2)	4 (3.9)	
Other	19 (12.3)	6 (11.8)	13 (12.6)	

Values are presented as numbers (%).

Informed consent

Because the clinical measurements were part of routine patient management in the emergency department, 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 do not have any financial or other relationships that might cause any conflicts of interest.

Acknowledgments and Funding

No funding was received for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.04.022.

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