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Original article

Comparative safety analysis of mRNA and adenoviral vector COVID-19 vaccines: a nationwide cohort study using an emulated target trial approach

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ABSTRACT

Objective: This nationwide cohort study compared the incidence of adverse events of special interest (AESIs) between adenoviral vector-based (ChAdOx1) and mRNA-based (BNT162b2 or mRNA-1273) coronavirus disease 2019 (COVID-19) vaccines.

Methods: A targeted trial emulation study was conducted using data from the National Health Insurance Service database. Vaccinees aged 18–85 years who had received at least one dose of ChAdOx1 or an mRNA-based vaccine were identified. The 42-day risks of AESIs were calculated.

Results: A total of 1 767 539 ChAdOx1 vaccinees were matched exactly with mRNA vaccinees according to their risk factors. The 42-day risks of adverse events were low (~0 to 176 events per 100 000 persons in both vaccine groups), and the incidence rates of AESIs were comparable between the two platforms, except for a higher occurrence of acute cardiac injury (incidence rate ratio [IRR], 1.22; 95% CI, 1.10–1.35), myocarditis or pericarditis (IRR, 2.14; 95% CI, 1.14–4.04), and arrhythmia (IRR, 1.46; 95% CI, 1.24–1.71) in mRNA vaccinees. The incidence of Guillain–Barré syndrome (IRR, 0.20; 95% CI, 0.06–0.69), vasovagal syncope (IRR, 0.77; 95% CI, 0.62–0.97), radiculopathy (IRR = 0.59, 95% CI, 0.41–0.84), and aseptic arthritis (IRR, 0.81; 95% CI, 0.70–0.93) was significantly lower in mRNA-based vaccinees compared with ChAdOx1 vaccinees.

Discussion: A remarkable platform-dependent difference was observed in the safety profiles of COVID-19 vaccines, particularly for myocarditis or pericarditis and Guillain–Barré syndrome. However, the overall risk of AESIs was low for both vaccine platforms. **Min Joo Choi, Clin Microbiol Infect 2024;30:646**

Introduction

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, various SARS-CoV-2 vaccines with different platforms have been developed [1]. In South Korea, six COVID-19 vaccines have been approved; 96% of the population received the viral vector-based (ChAdOx1) or mRNA-based (BNT162b2 or mRNA-

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1273) vaccines for the primary series, and 99% of them received mRNA-based vaccines for the booster dose [2]. Considering the emergence of new variants and waning vaccine immunity, periodic booster vaccinations will be necessary in the future, most likely using mRNA-based vaccines [3]; however, vaccine hesitancy owing to fear of adverse events has hindered large-scale vaccine uptake [4].

Gene-based vaccines, such as mRNA-based or viral vector-based vaccines are theoretically considered safe because of their short manufacturing time, the lack of infectious materials in mRNA-based vaccines, and virulence genes in viral vector vaccines [5,6]. However, as this is one of the first instances of their widespread use in humans, vigilant monitoring is necessary. Although early randomized trials have revealed a low incidence of adverse events for viral vector-based and mRNA-based vaccines [7–9], post-approval monitoring is crucial considering the intrinsic limitations of clinical trials in detecting rare adverse events.

Despite the detection of several safety signals of rare serious adverse events in post-marketing observational studies, overwhelming evidence currently supports the overall safety of these vaccines, as the risk of COVID-19 infection far outweighs those that may occur secondary to vaccination [10]. However, most safety studies have relied on analyses, such as observed-to-expected rates [11–13], case-control studies [14], self-controlled case series [15], and cohort studies comparing vaccinated and unvaccinated individuals [16], raising concerns regarding the underestimation of adverse events because of confounding by indication. Although comparing vaccinated individuals could reduce bias, limited data are available.

Therefore, we aimed to compare the safety profiles of mRNA-based and viral vector-based vaccines using data from the National Healthcare Insurance Database, which is the largest integrated health care system in South Korea. To minimize potential selection bias, we applied a trial emulation technique [17], which mimicked the design of randomized trials.

Methods

Study design and database

We retrospectively evaluated data from the Korean National Health Insurance database [18]. This study was approved by the institutional review board of Korea University Guro Hospital (No. 2021GR0304) and was conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived by the ethics committee because of the deidentified nature of the data.

Eligibility criteria

All individuals aged 18–85 years who were vaccinated with at least one dose of ChAdOx1 or mRNA-based vaccines (BNT162b2 or mRNA-1273) between 1 April 2021 and 30 September 2021 were included. Patients with a previously documented SARS-CoV-2 infection, a history of adverse events of special interest (AESIs), a history of emergency department visits or hospital admissions within the past 3 or 6 months, previously documented hepatitis B or C, a history of anaphylaxis, or incorrect vaccination records and those who were foreign nationals or beneficiaries of medical aid were excluded [19]. The simulated studies are summarized in Supplementary Table S1.

AESIs definition

The definitions and lists of AESIs are summarized in the Supplementary Material and in Table S2.

Statistical analyses

The overall cohort and subgroups (18–59, 60–74, and 75–85 years) were emulated. We selected individuals who received either the ChAdOx1 or mRNA-based vaccines on the same vaccination date and exactly matched the two vaccine groups in a 1:1 ratio according to the following data: age, sex, medical utilization, number of concurrent drugs, and coexisting diseases (Table S2). After matching, the number of new cases of AESIs and the incidence rate (%) were calculated to compare the ChAdOx1 and mRNA-based vaccines. For each eligible individual, follow-up started on the day of the first dose of the vaccine (index date, within the study period) and ended on the day of the outcome of interest or 42 days after the index date, whichever occurred first. In addition, we calculated the incidence rate ratio (IRR) of the mRNA-based vaccine group to that in the ChAdOx1 vaccine group and presented the difference in incidence rates between the two vaccine groups as the incidence risk difference.

To assess the potential interference of the second vaccination dose, we examined the number of events that occurred after the second vaccination among the total reported cases and conducted separate analyses by censoring at the date of the second dose if the event occurred within 42 days. All analyses included sub-analyses stratified by sex. Individuals were permitted to contribute to more than one AESI. Details of the statistical methods are provided in the Supplementary Material.

Results

Study population

Of the eligible 6 455 848 and 19 415 539 participants who received ChAdOx1-based and mRNA-based vaccinees (BNT162b2 or mRNA-1273 vaccine), respectively, 1 767 539 ChAdOx1 vaccinees were matched 1:1 with mRNA-based vaccinees (Table 1). The mean age was 48.3 years (SD 10.3 years), and 51.3% of the participants were male. The two vaccine groups demonstrated identical distributions of all the variables used for exact matching. The baseline characteristics of the matched populations in the age-defined subgroups are shown in Tables S3–S5. All subgroups exhibited identical distributions of the measured variables after matching.

In the early stages of vaccination, ChAdOx1 vaccines were primarily administered to individuals aged ≥60 years, making it difficult to obtain enough individuals to match mRNA-based vaccines in this age group (Table S6). Hence, the number of participants in the older age groups is less. In the 18–59, 60–74, and 75–85 years age group, 1 464 412, 296 826 and 6301 individuals were matched, respectively.

Comparative safety

The 42-day risk of adverse events was low (~0–176 events per 100 000 persons in both vaccine groups). The IRR for mRNA-based vaccine recipients compared with ChAdOx1 vaccine recipients was 1.22 (95% CI, 1.10–1.34) for acute cardiac injury (myocarditis or pericarditis, heart failure, cardiomyopathy, coronary artery disease, and arrhythmia), 2.14 (95% CI, 1.14–4.04) for myocarditis/pericarditis, and 1.30 (95% CI, 1.14–1.49) for arrhythmia. Meanwhile, the IRR was 0.20 (95% CI, 0.06–0.69) for Guillain–Barré syndrome (GBS), 0.77 (95% CI, 0.62–0.97) for vasovagal syncope, 0.59 (95% CI, 0.41–0.84) for radiculopathy, and 0.81 (95% CI, 0.70–0.93) for aseptic arthritis, all of which were significantly lower in mRNA-based vaccinees compared with ChAdOx1 vaccinees (Fig. 1).

The overall adult age estimates were largely similar to those observed in the 18–59 years age subgroup, with only minor

Table 1
Baseline characteristics of matched individuals in the target trial emulation (all individuals were aged ≥18 years)

	Whole population		Emulated trial	
	ChAdOx1 (n = 6 455 848), n (%)	BNT162b2 or mRNA-1273 (n = 19 415 539), n (%)	ChAdOx1 (n = 1 767 539), n (%)	BNT162b2 or mRNA-1273 (n = 1 767 539), n (%)
Sex				
Male	3 153 147 (48.8)	9 480 293 (48.8)	907 333 (51.3)	907 333 (51.3)
Female	3 302 701 (51.2)	9 935 246 (51.2)	860 206 (48.7)	860 206 (48.7)
Age, mean ± SD	60.75 ± 10.2	42·41 ± 15.8	48·28 ± 10.3	48·28 ± 10.3
18-59 y, n (%)	1 606 328 (24.9)	17 802 032 (91.7)	1 464 412 (82.8)	1 464 412 (82.8)
60-74 y, n (%)	4 842 733 (75.0)	308 746 (1.6)	296 826 (16.8)	296 826 (16.8)
75-64 y, n (%)	6787 (0.1)	1 304 761 (6.7)	6301 (0.4)	6301 (0.4)
Comorbidity				
Cardiovascular disease	2 567 420 (39.8)	3 037 114 (15.6)	334 666 (18.9)	334 666 (18.9)
Endocrinopathy	2 152 453 (33.3)	2 694 711 (13.9)	292 140 (16.5)	292 140 (16.5)
Chronic respiratory disease	2 155 291 (33.4)	5 768 643 (29.7)	562 269 (31.8)	562 269 (31.8)
Chronic renal disease	280 314 (4.3)	442 614 (2.3)	39 539 (2.2)	39 539 (2.2)
Chronic liver disease	646 952 (10.0)	976 024 (5.0)	110 613 (6.3)	110 613 (6.3)
Chronic neurologic disease	695 581 (10.8)	860 009 (4.4)	71 640 (4.1)	71 640 (4.1)
Malignancy	251 085 (3.9)	375 203 (1.9)	34 340 (1.9)	34 340 (1.9)
Autoimmune disease	185 879 (2.9)	323 225 (1.7)	28 066 (1.6)	28 066 (1.6)
Haematologic disease	45 950 (0.7)	92 758 (0.5)	4848 (0.3)	4848 (0.3)
Mental and behavioural disorders	903 320 (14.0)	1 747 510 (9.0)	164 604 (9.3)	164 604 (9.3)
Immune deficiency	3614 (0.1)	9675 (0.1)	239 (0.0)	239 (0.0)
History of Influenza vaccination in the past 2 years	3 759 898 (58.2)	6 316 154 (32.5)	666 458 (37.7)	666 458 (37.7)
No. of outpatient visits in the past year				
0	503 547 (7.8)	2 954 045 (15.2)	212 311 (12.0)	212 311 (12.0)
1–5	1 482 837 (23.0)	7 469 579 (38.5)	624 342 (35.3)	624 342 (35.3)
6–10	1 328 839 (20.6)	3 818 151 (19.7)	377 706 (21.4)	377 706 (21.4)
11–15	1 047 214 (16.2)	2 118 490 (10.9)	223 960 (12.7)	223 960 (12.7)
>16	2 093 411 (32.4)	3 055 274 (15.7)	329 220 (18.6)	329 220 (18.6)
No. of comedications prescribed based on the index date				
0	2 668 419 (41.3)	13 980 000 (72.0)	1 140 131 (64.5)	1 140 131 (64.5)
1–2	1 426 115 (22.1)	2 296 270 (11.8)	295 449 (16.7)	295 449 (16.7)
3–4	1 076 884 (16.7)	1 645 726 (8.5)	178 838 (10.1)	178 838 (10.1)
>5	1 284 430 (19.9)	1 496 916 (7.7)	153 121 (8.7)	153 121 (8.7)
No. of hospitalisation in the past 6 months, mean ± SD	0.07 ± 0.3	0·05 ± 0.3	0·04 ± 0.2	0·04 ± 0.2
No. of ER visits in the past 7–90 days, mean ± SD	0.03 ± 0.2	0.02 ± 0.2	0·02 ± 0.1	0·02 ± 0.1

mRNA, messenger ribonucleic acid; SD, standard deviation; ER, emergency room; No, number.

differences in risk ratios (Fig. 2, Table S7). In the 60–74 years age subgroup, acute cardiac injury and arrhythmias occurred more frequently in the mRNA-based vaccinees compared with the ChAdOx1 vaccinees (IRRs 1.22 and 1.56, respectively) (Table S8). In the 75–84 years age subgroup, heart failure or cardiomyopathy was observed more frequently in the ChAdOx1 vaccinees than in the mRNA vaccinees (IRR 0.41; 95% CI, 0.17–0.99) (Table S9).

In the sub-analysis stratified by sex, platform-specific features observed in the overall analysis were predominantly identified in the male subgroup; post-mRNA vaccine myocarditis or pericarditis was more frequent in males, especially in younger age groups (3.4 times in the overall population; eight times in the 18–59 years age group), whereas the incidence of GBS was significantly lower in mRNA vaccine recipients (0.2 times in the overall population and 0.13 times in the 18–59 years age group) than ChAdOx1 vaccine recipients (Table S10–S13).

Events occurring after the second dose, within the total occurrences, were predominantly observed in the mRNA vaccine recipients, generally constituting <20% (Table S14). A separate analysis conducted by censoring the second dose yielded consistent results (Table S15–S19).

Discussion

In this nationwide cohort study, we used a target trial emulation method for a head-to-head comparison of mRNA-based (BNT162b2 or mRNA-1273) and viral vector-based (ChAdOx1) vaccine safety. Target trial emulation, while adopting a retrospective cohort structure, intensifies comparability through more stringent procedural methods, especially when clinical trials are impracticable. This approach is critically relevant for assessing vaccine adverse reactions, where inherent biases between vaccinated and unvaccinated groups present a major challenge. These biases stem from health behaviours that influence vaccination decisions and health screening conducted at the time of vaccination. Consequently, comparing the frequency of adverse reactions within the vaccinated groups across different platforms can minimize these biases. Therefore, this study has a unique significance, aiming to minimize confounding factors and serve as a valuable complement to the current literature comparing vaccinated individuals to unvaccinated controls.

We noted a few differences in the risk of adverse events within 42 days of the first dose of either the ChAdOx1-based or mRNA-based vaccines; however, the mRNA-based vaccines demonstrated a higher risk of acute cardiac injury, myocarditis or pericarditis, and arrhythmia than the ChAdOx1 vaccines. By contrast, ChAdOx1 vaccines were associated with a higher risk of GBS, vasovagal syncope, radiculopathy, and aseptic arthritis.

Compared with the previously reported baseline incidence rate in South Korea [20], the incidence of AESIs observed in both groups in this study was generally lower. For example, the occurrence of vasovagal syncope or radiculopathy was more frequent in ChAdOx1

Events	No. of events (/100,000 persons) BNT162b2 or mRNA-1273	ChAdOx1	Absolute risk difference, per 100,000 persons	Incidence rate ratio (95% CI)
Any event	6817 (329.10)	5889 (333.18)	4.07	0.99 (0.95-1.02)
Vasovagal syncope	141 (7.98)	182 (10.30)	2.32	0.77 (0.62-0.97)
Anaphylaxis (narrow)	59 (3.34)	68 (3.85)	0.51	0.87 (0.61-1.23)
Anaphylaxis (broad)	340 (19.24)	379 (21.44)	2.21	0.90 (0.77-1.04)
Radiculopathy	48 (2.72)	82 (4.64)	1.92	0.59 (0.41-0.84)
ADEM (narrow)	2 (0.11)	0 (0.00)	0.11	-
ADEM (broad)	2 (0.11)	0 (0.00)	0.11	-
Bell's palsy	65 (3.68)	67 (3.79)	0.11	0.97 (0.69-1.36)
Guillain-Barre syndrome	3 (0.17)	15 (0.85)	0.68	0.20 (0.06-0.69)
Encephalopathy	14 (0.79)	9 (0.51)	0.28	1.56 (0.67-3.59)
Optic neuritis	2 (0.11)	9 (0.51)	0.40	0.22 (0.05-1.03)
Multiple sclerosis including optic neuritis	2 (0.11)	9 (0.51)	0.40	0.22 (0.05-1.03)
Transverse myelitis	6 (0.34)	9 (0.51)	0.17	0.67 (0.24-1.87)
ITP	5 (0.28)	9 (0.51)	0.23	0.56 (0.19-1.66)
SLE	13 (0.74)	15 (0.85)	0.11	0.87 (0.41-1.82)
Narcolepsy	2 (0.11)	0 (0.00)	0.11	-
Thromboembolism	72 (4.07)	90 (5.09)	0.85	0.79 (0.56-1.12)
CVST	3 (0.17)	7 (0.40)	0.23	0.43 (0.11-1.66)
ARDS	18 (1.02)	19 (1.07)	0.06	0.95 (0.50-1.81)
Acute cardiac injury	875 (49.50)	719 (40.68)	8.94	1.22 (1.10-1.35)
AMI	98 (5.44)	94 (5.32)	0.23	1.03 (0.78-1.37)
Myocarditis/pericarditis	30 (1.70)	14 (0.79)	0.91	2.14 (1.14-4.04)
HF, CMP	396 (22.40)	347 (19.63)	2.77	1.14 (0.99-1.32)
Arrhythmia	481 (27.21)	370 (20.93)	6.34	1.46 (1.24-1.71)
Coagulation disorder	668 (37.79)	670 (37.91)	0.11	1.00 (0.90-1.11)
Anosmia/ageusia	12 (0.68)	12 (0.68)	0.00	1.00 (0.45-2.23)
Erythema multiforme	3 (0.17)	3 (0.17)	0.00	1.00 (0.20-4.96)
Single organ cutaneous vasculitis	1 (0.06)	3 (0.17)	0.11	0.33 (0.03-3.20)
Acute liver injury	25 (1.41)	23 (1.30)	0.11	1.09 (0.62-1.91)
Acute kidney injury	3 (0.17)	2 (0.11)	0.06	0.67 (0.11-3.99)
Acute pancreatitis	5 (0.28)	7 (0.40)	0.11	0.71 (0.23-2.25)
Rhabdomyolysis	24 (1.36)	28 (1.58)	0.23	0.86 (0.50-1.48)
Subacute thyroiditis	36 (2.04)	48 (2.72)	0.68	0.75 (0.49-1.16)
Thrombocytopenia	5 (0.28)	9 (0.51)	0.23	0.56 (0.19-1.66)
Generalized convulsion	178 (10.07)	162 (9.17)	0.91	1.10 (0.89-1.36)
Aseptic meningitis (narrow)	10 (0.57)	14 (0.79)	0.23	0.71 (0.32-1.61)
Aseptic meningitis (broad)	12 (0.68)	18 (1.02)	0.34	0.67 (0.32-1.38)
Aseptic arthritis	374 (21.16)	463 (26.19)	5.04	0.81 (0.70-0.93)
Sensorineural hearing loss	17 (0.96)	16 (0.91)	0.06	1.06 (0.54-2.10)
Non-haemorrhagic stroke	140 (7.92)	131 (7.41)	0.51	1.07 (0.84-1.36)
Haemorrhagic stroke	56 (3.14)	50 (2.83)	0.34	1.12 (0.76-1.64)
Type 1 DM	13 (0.74)	13 (0.74)	0.00	1.00 (0.46-2.16)
Tinnitus	45 (2.55)	49 (2.77)	0.23	0.92 (0.61-1.38)
Herpes zoster	3109 (175.89)	3109 (175.89)	0.00	1.00 (0.95-1.05)
Glomerulonephritis	26 (1.47)	31 (1.75)	0.28	1.19 (0.71-2.01)
Retinal vein and artery occlusion	11 (0.62)	9 (0.51)	0.11	1.22 (0.51-2.95)

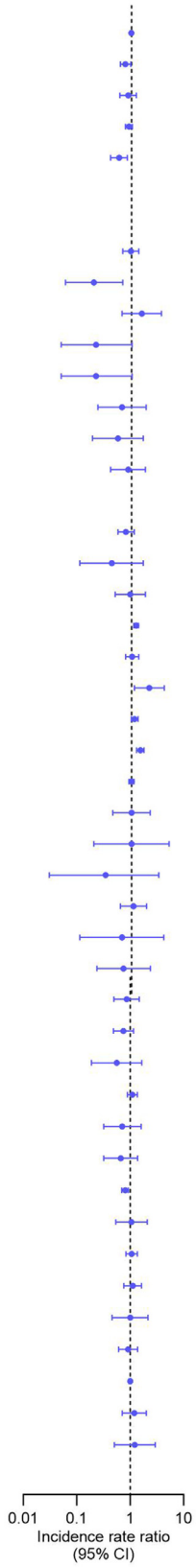

Fig. 1. Estimated comparative safety of the mRNA-based vaccines versus ChAdOx1 (all individuals aged ≥18 years). Incidence rate ratio represents the results of Poisson regression analysis, accounting for person-time in the follow-up period. ADEM, acute disseminated encephalomyelitis; ITP, immune thrombocytopenia; SLE, systemic lupus erythematosus; CVST, cerebral venous sinus thrombosis; ARDS, acute respiratory distress syndrome; AMI, acute myocardial infarction; HF, heart failure; CMP, cardiomyopathy; DM, diabetes mellitus, No, number.

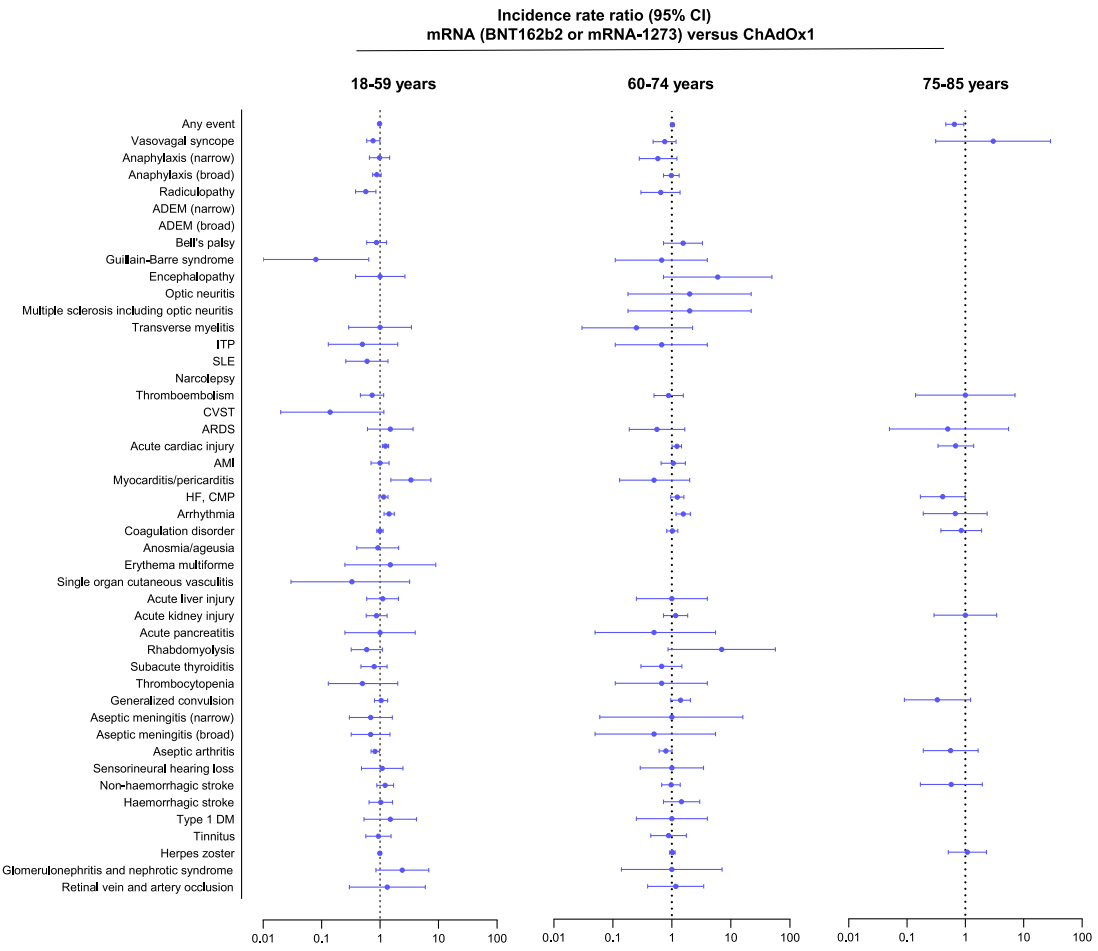

Fig. 2. Estimated comparative safety of mRNA vaccines versus ChAdOx1, stratified by age group. Incidence rate ratio represents the results of Poisson regression analysis, accounting for person-time in the follow-up period. ADEM, acute disseminated encephalomyelitis; ITP, immune thrombocytopenia; SLE, systemic lupus erythematosus; CVST, cerebral venous sinus thrombosis; ARDS, acute respiratory distress syndrome; AMI, acute myocardial infarction; HF, heart failure; CMP, cardiomyopathy; DM, diabetes mellitus.

vaccinees (10.30 and 4.64 per 100 000 persons, respectively), but lower than the baseline incidence rates (33.45 and 80.67 per 100 000 persons, respectively). Despite using similar International Classification of Diseases, 10th Revision (ICD-10) codes from the same data source, the exclusion of outpatient cases in our study may have contributed to the relatively low frequency. Although direct comparisons may be challenging, severe AESIs requiring hospitalization or emergency room visits appeared to be rare. Despite this strict definition, the occurrence of GBS in ChAdOx1 vaccinees showed a significantly higher incidence than the previously reported baseline rates and the mRNA vaccinees, adding further significance to the findings.

Guillain–Barré syndrome occurred five times more frequently in ChAdOx1-based vaccinees than in mRNA-based vaccinees, which was ~2.5 times higher than the predicted incidence reported in a previous study [20]. In a US study, GBS occurred after Ad26.COV2.S vaccine 4.18 and 9–12 times more frequently than the expected rate and after mRNA-based vaccination, respectively, suggesting that GBS occurrence is an adverse reaction related to adenovirus-based vaccines [13,21]. Although the mechanism remains unknown, human adenoviruses can potentially induce GBS, suggesting the possibility that the simian adenovirus used as a vector could also be responsible for GBS [22]. Compared with classical GBS, patients with COVID-19 vaccination-related GBS have been reported to demonstrate a more severe presentation [21]. Hence, clinicians need to have a high index of suspicion to identify potential GBS after adenoviral vector-based COVID-19 vaccination.

In this study, the incidence of myocarditis or pericarditis was significantly higher with mRNA-based vaccines than with ChAdOx1 vaccines, and was particularly prominent among young adult males. These findings are consistent with those of previous observational studies conducted in Asia, Europe, the United States, and other regions [11,12,14,15]. However, this study is noteworthy because it emulates a randomized trial with a population of >3 million individuals, directly comparing different vaccine platforms. However, the underlying biological mechanisms are unclear, although several possible mechanisms have been suggested, such as mRNA-based immune reactivity, molecular mimicry between spike proteins and cardiac autoantigens, and hormonal differences [23]. In addition, a potential role of the vaccine-induced inflammatory response, rather than specific findings related to SARS-CoV-2 spike protein exposure, have been suggested because increased cases of myocarditis/pericarditis have been observed after non-COVID-19 vaccinations, such as smallpox or influenza vaccinations [24]. Moreover, owing to the lower threshold for investigating nonspecific chest pain after COVID-19 vaccination or the current robust vaccine surveillance system, diagnoses of myocarditis or pericarditis may be more frequent after COVID-19 vaccination. However, consistent with observations from European and US surveillance systems [25] and a previous nationwide Korean study

[26], our study demonstrated a very low frequency (less than 1/10 000) of myocarditis/pericarditis after COVID-19 vaccination, with a difference between the two COVID-19 vaccine platforms, particularly for the mRNA-based vaccines. Although the long-term outcomes of vaccine-associated myocarditis or pericarditis are unclear, the current knowledge of short-term clinical trajectories is reassuring [27].

In this study, a significant increase in acute cardiac injury and arrhythmia was observed with mRNA-based vaccines when compared with ChAdOx1-based vaccines. Because these analyses were based solely on ICD-10 codes and the observed differences in incidence were minimal, the increased awareness of cardiovascular risk in the population, especially regarding mRNA vaccines, may have lowered barriers to health care-seeking behaviours. Alternatively, diagnostic codes related to cardiovascular episodes may have been used to evaluate myocarditis or pericarditis after COVID-19 vaccination.

The risk of thrombosis after ChAdOx1 vaccination has been widely reported [10,28]. Although this study also indicated a higher frequency in thrombosis or cerebral venous sinus thrombosis among ChAdOx1 vaccine recipients, it was not statistically significant. This might be attributed to the fact that this study predominantly recruited healthy individuals comparable to those in clinical trials, resulting in a lower prevalence of underlying conditions, including potential risk factors for thrombosis when compared with the general population. Alternatively, the incidence of confirmed thrombosis with thrombocytopenia syndrome after ChAdOx1 vaccination in South Korea was much lower at 0.21 per 1 000 000 population when compared with other countries [29], potentially making it less noticeable in a broad analysis based on ICD codes.

However, this study had some limitations. First, despite matching for key factors, there is a possibility that the choice of vaccine platform may have been influenced by potential biases, such as vaccination timing, supply, and information exposure. Second, increased awareness of safety episodes in the population could have lowered barriers to health care-seeking behaviours, possibly contributing to surveillance bias. Third, discrepancies may have occurred between the diagnoses entered and the actual diseases of patients. To overcome this problem, more refined definitions were used for certain key adverse reactions considering factors such as medication. Fourth, the proportion of individuals receiving the second dose may have varied between the two groups; a small percentage (<3%) of ChAdOx1 vaccinees received the mRNA vaccine as their second dose. However, the results remained unchanged, even after excluding those who received a second dose. Fifth, this study mimicked the clinical trial registration criteria when selecting participants, resulting in the inclusion of mostly healthy individuals, and a substantial number of elderly participants were excluded during the matching process. Therefore, these results should be interpreted with caution. Sixth, as there were no data on the incidence rates among unvaccinated individuals in this study, it may be challenging to detect simultaneous decreases or increases in AESIs in recipients of the two vaccine platforms. Seventh, we assumed that BNT162b2 and mRNA-1273 would have similar safety profiles. Finally, it is challenging to eliminate the impact of unrecognized SARS-CoV-2 infection. (The overall details of these limitations are described in the Supplementary Material).

In conclusion, remarkable platform-dependent differences in the safety profiles of COVID-19 vaccines were identified. Although rare, the risk of myocarditis or pericarditis was higher with mRNA-based vaccines than with adenoviral vector vaccines, particularly in young individuals. By contrast, the risk of GBS was significantly higher after immunization with the adenoviral vector vaccine. However, the overall risk of AESIs was generally low for both COVID-19 vaccine platforms. Therefore, these new vaccine platforms may be applicable for diverse infectious diseases, although the safety of vaccines for other infectious diseases should also be evaluated beyond the mere repeated dose aspect.

Author's contributions

MJC, YN, JJ, and HJC conceived and designed the study. YN and JJ contributed to the formal analysis. All authors contributed to the data interpretation. JJ and HJC contributed to the funding acquisition. MJC and YN were responsible for the manuscript integrity and preparation. JYS, JJ, and HJC supervised the study. All the authors reviewed the manuscript for intellectual content and approved the final version for submission. MJC and YN contributed equally to this paper.

Transparency declaration

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.12.010.

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