Title : Clinical characteristics and prognostic factors of myocarditis associated with the mRNA COVID-19 vaccine

Authors and affiliations : Wongi Woo[1]†, Ah Young Kim[2,10]†, Dong Keon Yon[3]†, Seung Won Lee[4]†, Jimin Hwang[5], Louis Jacob[6,7], Ai Koyanagi[6,8], Min Seo Kim[9], Duk Hwan Moon[1], Jo Won Jung[2,10], Jae Young Choi[2,10], Se Yong Jung[2,10], Lucy Youngmin Eun[2,10], Sungsoo Lee[1]*, Jae Il Shin[10]*, Lee Smith[11]

1. Department of Thoracic and Cardiovascular surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul,Korea
2. Division of Pediatric Cardiology, Department of Pediatrics, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea
3. Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea
4. Department of Data Science, Sejong University College of Software Convergence, Seoul, South Korea
5. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
6. Parc Sanitari Sant Joan de Deu/CIBERSAM, Universitat de Barcelona, Fundacio Sant Joan de Deu, Sant Boi de Llobregat, Barcelona, Spain
7. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
8. ICREA, Pg. Lluis Companys 23, Barcelona, Spain
9. Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Samsung Medical Center, Seoul, Republic of Korea
10. Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea
11. Cambridge Centre for Health, Performance, and Wellbeing , Anglia Ruskin University, Cambridge, UK

† Co-first authors

Corresponding Authors:

Jae Il Shin, M.D., Ph.D.
Address: 50 Yonsei-ro, Seodaemun-gu, C.P.O. Box 8044, Department of Pediatrics, Yonsei University College of Medicine, Seoul 120-752, Republic of Korea
Tel: +82-2-2228-2050; Fax: +82-2-393-9118; E-mail: shinji@yuhs.ac

Sungsoo Lee, MD, Ph.D.
Address: 211 Eonju-ro, Gangnam-gu, Department of Thoracic and Cardiovascular Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea. 06273
Tel: +82-02-2019-3381, Fax: +82-02-3461-8282, E-mail: chestlee@yuhs.ac

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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The authors declare that they have no competing interests.

Ethics approval statement

Ethical approval was not required because this work was an pooled analysis of published articles.

Running title: Myocarditis associated with mRNA COVID-19 vaccine

Abstract

Objectives: To analyze the clinical presentation and outcomes of myocarditis after administration of the SARS-CoV-2 mRNA vaccine.

Methods: Nine case series and 15 case reports (74 patients) of myocarditis after administration of the BNT162b2 or mRNA-1273 vaccine were reviewed from PubMed, Scopus, Embase, and Web of Science. We analyzed clinical manifestations, diagnostic findings, and outcomes. In addition, we performed a pooled analysis and investigated risk factors leading to admission to ICU and recovery with conservative care.

Results: Most patients were male (94.6%), and the median age (range) was 17.6 (14-70) years. Patients who received the BNT162b2 (n=58, 78.4%) vaccine presented fewer systemic symptoms and left ventricular dysfunction than mRNA-1273 recipients. Although patients under 20 years experienced more fever and myalgia, they had better ejection fraction and less prominent myocardial inflammation in magnetic resonance imaging than older patients. The clinical course of all patients was favourable without mortality, and one-third of patients resolved with conservative care alone. Risk factor analyses revealed that patients with gastrointestinal symptoms required intensive care (OR:20.3, 95% CI 1.90-217, p=0.013).

Conclusion: The risk of fatality in myocarditis subjected to mRNA vaccination seems to be low. While patients with gastrointestinal symptoms received more intensive care, a significant proportion of patients recovered with conservative management.

Keywords: vaccine-induced myocarditis, BNT162b2, mRNA-1273, COVID-19 vaccine, myocarditis

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has resulted in a global health and economic crisis, causing a total of 228,541,752 confirmed cases and 4,691,866 deaths, as of September 20, 2021. Globally, vaccination against the virus, in order to achieve herd immunity, has become the most pressing issue for mitigating the global threat of the virus.[1] Currently, four vaccines have been approved either by the European Medicines Agency (EMA) or by the United States Food and Drug Administration (FDA), including two messenger RNA (mRNA)-based vaccines—BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)—and two recombinant adenoviral vector vaccines—ChAdOx1 nCoV-19 (Astra-Zeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen). These vaccines have been developed and distributed at an unprecedented pace, and they are highly effective in protecting against SARS-CoV-2 infection by neutralizing antibodies.[2–4] They have been proven safe in large scale trials in which adverse cardiovascular effects related to the vaccine were studied, wherein an incidence of <0.05% was reported, and myocarditis was not reported[3]. However, there have been emerging concerns regarding myocarditis as rare complications of mRNA-based COVID-19 vaccines, especially in young adults and adolescent males.[5]

According to the Advisory Committee on Immunization Practices from the Centers for Disease Control and Prevention (CDC), after over 365 million doses administered by August 26, 2021, there were 1903 reports of possible myopericarditis cases in the Vaccine Adverse Event Reporting System[6], of which 1839 (96.6%) were following the mRNA vaccine. Additional analyses by the CDC Vaccine Safety Datalink, with weekly monitoring performed using prespecified outcomes of interest, revealed an increased risk of myocarditis after the administration of COVID-19 mRNA vaccines, as compared with unvaccinated individuals or those who received non-mRNA vaccines during the same calendar days (rate ratio, 15.6 [95% CI, 6.1–47.2]; for individuals aged 12–39 years, during the 7-day risk interval after vaccination,

adjusted for site, age, sex, race/ethnicity, and calendar date). The estimated rate of myocarditis was 12.6 cases per million doses among individuals aged 12–39 years, receiving the second-dose of the COVID-19 mRNA vaccine. The Israeli Ministry of Health also reported 148 cases of myocarditis among 10.4 million vaccinated individuals, occurring within 30 days of receiving the mRNA vaccination. Among over 528 million doses of vaccines administered to people in the European Union and the European Economic Area, as of the beginning of September 2021, 392 million doses of BNT162b2 and 54.2 million doses of mRNA-1273 were administered. Of which, 2360 cases of myocarditis were reported among individuals who received BNT162b2 and 1050 cases were reported among those who received mRNA-1273. The estimated incidence of myocarditis after receiving the COVID-19 mRNA vaccine was 7.7 cases per million. Additionally, there were 54 deaths reported, suggesting that it is a very important issue that needs to be addressed and should not be overlooked.[7,8]

Thus far, case reports and case series of myocatditis related to mRNA vaccine are accumulating; however, owing to an insufficient sample size, it is difficult to draw consistent, significant conclusions regarding their clinical presentation and treatment. Moreover, no study has analysed the differential outcomes of COVID-19 vaccine-associated myocarditis, such as recovery with conservative care and ICU admission, along with associated risk factors. Given this background, the present systematic review aimed to study previously published case reports and case series associated with COVID-19 mRNA vaccine-related myocarditis, and investigate the risk factors related to clinical outcomes. Although our findings are limited in their generalizability, our study can provide clinicians a comprehensive understanding of this rare, adverse event, and also support people who require more information before getting vaccinated.

126 **Methods**

127 ***Search strategy and selection criteria***

128 This systematic review was performed in agreement with the Preferred Reporting Items for
129 Systematic Reviews and Meta-Analyses Protocols (PRISMA-P, Supplementary Table S1).[9] As
130 reports are being updated every day, a rapid review was conducted to summarize all published
131 cases of myocarditis related with mRNA vaccines.

132 The inclusion criteria of studies were as follows: (1) those that reported patients with a
133 history of COVID-19 vaccination with either the BNT162b2 or mRNA-1273 vaccine prior to
134 the presentation of myocarditis; and (2) if the patients were diagnosed with myocarditis with
135 no other identifiable causes based on clinical presentation, elevated levels of cardiac troponin,
136 electrocardiography findings, or cardiac magnetic resonance imaging (CMR); (3) case report
137 and case series to analyze at individual patient level with sufficient raw data. We excluded
138 cases if they had received any other type of COVID-19 vaccine or were diagnosed as having
139 pericarditis alone. We further excluded review articles, letters to the editors, abstracts, articles
140 that did not contain sufficient information on the patient characteristics or outcomes, and
141 duplicate cases.

142 We initially carried out a search on PubMed/Medline, EPub, Scopus, Embase, and Web of
143 Science databases, that include all articles available on patients with COVID-19 mRNA
144 vaccine-associated myocarditis published up to August 25, 2021. Our initial search yielded 63
145 articles. After reviewing individual abstracts and full texts of the articles, we identified 20
146 studies (12 case reports and eight case series) that met the inclusion criteria for this systematic
147 review.[10–29] In addition, we carried out an additional search in the same databases on September
148 10, 2021, and added one case series and three case reports.[30–33] The search terms used are
149 described in detail in Supplementary Table S2. The detailed selection process is depicted in
150 Supplementary Figure S1, and the characteristics of individual case studies are shown in
151 Supplementary Table S3–S4.

Three reviewers (J.I. Shin, W. Woo, A.Y. Kim) independently examined the studies, and any disagreement among the reviewers was resolved by consensus. For each eligible case report and case series, we extracted data on the demographic, clinical, and laboratory findings at presentation, types of treatment, clinical course, and outcome.

Data collection

We identified 24 studies on myocarditis related to immunization with BNT162b2 or mRNA-1273 COVID-19 vaccines, and collected data on demographic and clinical characteristics, including information on treatments, outcomes, age, sex, onset of symptoms, pre-existing conditions, laboratory results, immunologic assays, results of electrocardiography (ECG) and echocardiogram, as well as radiological findings of cardiac magnetic resonance (CMR) imaging, and finally, the length of hospitalization, length of intensive care unit (ICU) stay, and mortality.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25.0 (SPSS Inc., IBM Corporation, Chicago, Illinois, USA) and R version 4.0.4 (R Core Team, Vienna, Austria). Basic demographic and clinical information were presented as medians and range for continuous variables and percentage for categorical variables. Continuous variables were compared using the Mann-Whitney U-test and categorical variables were compared using Fisher's exact test. Spearman's correlation analysis was carried out to determine the relationships between continuous variables, and phi correlation coefficients were calculated to measure the strength of association between categorical variables. We included patients demographics, clinical presentation and diagnostic findings, then logistic regression analyses were used to identify independent risk factors for ICU admission, recovery with conservative care, and left ventricular dysfunction. Variables with a

p-value of <0.10 in the univariate analysis were entered into a multivariate analysis and a two-tailed p-value of < 0.05 was considered significant. Only significant variables in multivariate analyses were listed in the multivariate analyses.

Results

Demographics and clinical characteristics

In regard to age, the 74 patients with myocarditis were 14–70 years old (median age, 17.6) and approximately half of the patients (49.5%) were younger than 20 years. Almost all patients were male (n=70, 94.6%), and seven patients (9.5%) had underlying medical conditions such as hypertension, diabetes, hyperlipidemia, or endocrinologic disorder. Over two-thirds (78.3%) of patients received the BNT162b2 vaccine, and most (90.5%) patients presented with myocarditis after the second dose of the vaccine. Patients presented to the hospital from 6 hours to 16 days after vaccination, with a median time from vaccination of 3 days. The symptoms presented by these patients are shown in Supplementary Table S5. Most patients presented with chest pain (95.9%), accompanied with fever (33.8%), dyspnoea (21.6%), headache (14.9%), fatigue (10.8%), and chills (5.4%).

ECG findings of myocarditis patients are delineated in Table 1. Over two-thirds (87.8%) of patients had abnormal ECG findings: ST-segment (77.0%), T-wave (16.2%), and PR interval (14.9%). Echocardiography revealed that about a third (31.1%) of patients had left ventricular dysfunction (ejection fraction <55%) and 21 patients had regional wall motion abnormality. In regard to laboratory tests, all 74 patients showed elevated levels of cardiac enzymes, 64 (86.4%) patients had high levels of C-reactive protein, and 12 (16.2%) patients had high level of brain natriuretic peptides (BNP), pro-BNP, or NT-pro-BNP. Most patients (79.7%) underwent CMR imaging studies in hospitals, and 40 of 59 patients (67.8%) had CMR findings suggesting myocarditis, which met the original or modified Lake Louise criteria[34].

All patients recovered without significant complications. A third (35.1%) of the patients' symptoms resolved with conservative management. Among the remaining patients, more than half (54.0%) received anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, steroids, or intavenous immunoglobulin. In addition, 16.2% of them were treated with heart failure medications, including beta-blockers, angiotensin-

207 converting-enzyme (ACE) inhibitors/ angiotensin-receptor-blocker (ARB)s, diuretics, or
208 inotropics (Supplement Table S6). About 5% of patients (n=4) experienced complications,
209 including one major (multiorgan failure) and three minor cases (non-sustained ventricular
210 tachycardia). Twelve patients (16.2%) required ICU care, and about half (43.2%) of the patients
211 were discharged within 4 days.

212 ***Comparison between the BNT162b2 and mRNA-1273 vaccines***

213 Table 1 shows that mocarditis patients in individuals who received mRNA-1273 were older
214 than BNT162b2 recipients (median age, 27.0 vs 20.0, p=0.008). The number of patients with
215 underlying diseases were higher in the mRNA-1273 group (30.8% vs. 6.0%, p=0.036). More
216 patients reported chills as a symptom while visiting the hospital in the mRNA-1273 group (18.8%
217 vs. 1.7%, p<0.030). Patients who had received BNT162b2 less frequently showed PR interval
218 abnormality in the ECG (8.6% vs. 37.5%, p=0.010) and less frequent LV dysfunction (24.1%
219 vs. 56.2%, p=0.030). Other than these, there was no significant difference in terms of laboratory
220 and CMR findings between the groups. Treatment outcomes were also comparable; however,
221 more patients were discharged within 4 days in the mRNA-1273 group.

222 ***Comparison by age groups***

223 When we divided patients into two groups based on their age, i.e., at or over 20 and under 20
224 years (Table 2), patients under 20 years of age were more likely to present with systemic
225 symptoms such as fever (p=0.013) or myalgia (p=0.008). There were more patients with
226 preserved ejection fraction (p=0.025) and more patients with high levels of BNP (p=0.004).
227 CMR findings were less prominent in this age group (p=0.044), and they had fewer patients
228 who received treatment for heart failure (p=0.003). These were similarly observed in patients
229 who received the BNT162b2 vaccine.

230 ***Risk factor analysis for treatment outcome***

231 A third (35.1%) of the patients recovered without any medical treatment such as anti-

232 inflammatory agents or heart failure medications (Table 3). They had more preserved LV
233 function (p=0.015) and less significant CMR findings on T2 images (p=0.033). In the logistic
234 regression analyses for recovery with conservative care, previous COVID-19 infection, normal
235 ECG, preserved ejection fraction, and positive CMR findings were significant in the univariate
236 analyses. Finally, previous COVID-19 infection was found to be the only significant factor
237 (OR, 25.0; 95% CI, 1.82–343.0; p=0.016) in multivariate analysis (Table 4).

238 Gastrointestinal symptoms, such as anorexia (p=0.024), nausea (p=0.020), or vomiting
239 (p=0.012), were more prevalent in 12 patients (16.2%) who required intensive care. They
240 required additional medical treatments (p=0.006), and more patients stayed for over 6 days in
241 the hospital (p=0.019). In the multivariate logistic regression analyses, patients who
242 experienced vomiting as a symptom were significantly related to ICU care (OR, 20.3; 95% CI,
243 1.90–217.0; p=0.013) (Table 4).

244 ***Correlation among key clinical findings***

245 Several factors showed significant correlations when we analyzed the Phi coefficient among
246 the clinical findings (Figure 1). Positive correlations were found between the younger age
247 group and preserved ejection fraction among individuals who received the BNP162b2 vaccine.
248 ICU admission also showed positive correlations with elevated BNP levels and anti-
249 inflammatory treatment. On the contrary, significant negative relationships were found
250 between myalgia and CMR findings, COVID-19 history, and the second dose of the vaccine.
251 Other meaningful correlations among variables are also described in Figure 1.

252 ***COVID-19 myocarditis vs. vaccine-induced myocarditis***

253 Figure 2 describes the treatment and clinical outcomes between COVID-19-related myocarditis
254 and COVID-19 mRNA vaccine-related myocarditis patients. We reviewed the data of 42
255 COVID-19 related myocarditis patients from two systematic reviews[35,36] and compared the
256 outcomes with 74 patients in this review. There was no difference in the proportion of patients

who received steroid, colchicine, or IV immunoglobulin. However, the number of patients who experienced complications or required intensive care were significantly lower among the mRNA vaccine-related myocarditis patients. Furthermore, there was no mortality reported among the mRNA vaccine-related myocarditis patients, and more patients recovered without myocarditis-specific medical treatments.

263 **Discussion**

264 A case report on myocarditis linked to the COVID-19 mRNA vaccines was first published in
265 March 2021,[33] and ever since, it has been a challenge to understand this emerging new adverse
266 event of the mRNA vaccine owing to lack of incorporated data. To the best of our knowledge,
267 this systematic review is the first to analyze such a large sample and provides information for
268 understanding the clinical features of this rare adverse event. This systematic review
269 summarizes 74 cases of myocarditis that received the BNT162b2 or mRNA-1273 vaccines to
270 analyze the clinical manifestations, treatment modalities, outcomes, and prognostic factors
271 associated with adverse outcomes. Notably, our study compared clinical characteristics,
272 diagnostic findings, and outcomes based on the type of mRNA vaccines and the patients' age.
273 This review provides clinicians with a comprehensive understanding of this rare adverse event.

274 It is generally accepted that the acute onset of vaccine-associated myocarditis is attributable
275 to allergic/hypersensitivity reactions as observed in other vaccines[37,38]. For myocarditis after
276 COVID-19 vaccination, however, there have been additional plausible hypotheses. In previous
277 reports, these patients did not have eosinophilia or immune complex deposition in laboratory
278 studies[10,11,13,19,21,26,30,31,33,39], contrary to serum sickness or hypersensitivity reactions. Though
279 myocardial biopsies were performed in small patients, they also did not have eosinophilic
280 infiltration[19,28]. Several proposed mechanisms alternative to allergic/hypersensitivity reaction
281 for this rare adverse event are following: (1) elevated innate immune response against modified
282 nucleoside of vaccines in people with genetic predisposition[39–41]; (2) molecular mimicry
283 between self-antigen and spike protein formed by vaccines, which results in the dysregulated
284 activation of immunologic pathways[39,41,42].

285 Several studies have compared adverse events based on the type of vaccines. Meo *et al*.
286 reported a lower rate of adverse events after receiving BNT162b2 based on the patient's
287 symptoms and anaphylaxis reports, as compared to mRNA-1273.[43] Despite this, there has been
288 no study that compared myocarditis as an adverse event between the two mRNA-based

289 vaccines. In laboratory reports, IgG levels to the SARS-CoV-2 spike receptor-binding domain
290 were lower in recipients who received BNT162b2, compared with mRNA-1273, after the first
291 and second doses.[44] As it was stated earlier about the mechanism of myocarditis in the aspects
292 of molecular mimicry, higher antibody levels in mRNA-1273 recipients could be attributable
293 to more systemic symptoms and an advanced state of myocarditis-related immunologic
294 reaction. This laboratory result could support our finding that chills and LV dysfunction were
295 more prevalent in mRNA-1273 recipients.[45] However, due to the limited number of mRNA-
296 1273 myocarditis cases and the non-availability of laboratory data on the levels of antibodies,
297 it is currently challenging to make definitive conclusions regarding an association between
298 myocarditis and antibody levels. Also, contrary to clinical symptoms and echocardiography
299 findings, more patients who received mRNA-1273 were discharged within four days compared
300 to those who received BNT162b2. Further studies are necessary to draw conclusions and
301 understand the difference between the two vaccines regarding myocarditis as an adverse event.
302 In addition, young patients were more likely to experience systemic symptoms such as fever
303 and myalgia. Richards *et al*. evaluated humoral antibody levels after the primary immunization,
304 and the younger age group showed significantly higher antibody response than older
305 individuals.[45] A possible explanation could be a more potent immune response in younger
306 patients, which can also explain the higher rate of side effects to the vaccines in this age group.[46]
307 However, this age group (<20 years) reported fewer cases of LV dysfunction, and the number
308 of patients with prominent myocardial inflammation findings in the CMR was lower than that
309 observed in older patients in our review. Due to insufficient reports on adolescents who
310 received mRNA vaccines, further analyses for young individuals are necessary.
311 In agreement with previous reports on these patients' relatively favorable clinical courses,[5,47]
312 symptoms of all 74 patients in this review resolved, and nearly a third (31.0%) of them
313 recovered with conservative treatment. In contrast to these findings, several reports have
314 described fatal clinical courses in vaccine-related myocarditis patients in databases.[8,48–50] Thus,
315 patients with worse outcomes might not have been reported, and this study's bias in data

collection should also be considered. Additionally, this review does not represent the long-term prognosis of these patients. As general myocarditis patients experience fatal cardiac-related outcomes after recovering from the first event[51–53], clinicians should be cautious to determine any conclusion in terms of long-term prognosis.

Meanwhile, clinical presentations accompanied with vomiting were highly related to ICU admission in the risk factor analysis. Though the relationship between myocarditis and GI symptoms is unclear, it could be intuited from the significance of gastrointestinal symptoms in heart failure patients, which is cardiointestinal syndrome[54,55]. The gastrointestinal system roles as a venous reservoir[56] and a crucial immunologic barrier representing the largest mass of lymphoid tissue in the body[57]. As the ejection fraction reduces in myocarditis patients, the capacity of the splanchnic vein also decreases and shifts fluids out of the splanchnic system, thereby increasing the effective circulating volume. Due to hypoperfusion and edema of the gastrointestinal system, gut permeability increases and results in the translocation of bacterial or lipopolysaccharide[58]. Then, the elevated level of endotoxin and cytokines finally results in high immunologic reactions and a worse prognosis.[54,55,59] Additionally, several reports indicate that a history of gastrointestinal symptoms conferred a greater risk of mortality in pediatric myocarditis patients[60–62]. Therefore, these possible mechanisms could put myocarditis patients with gastrointestinal symptoms after mRNA vaccination at higher risk than others. Further immunologic studies and further clinical analysis would be necessary to find the causal relationship and the pathogenesis of gastrointestinal symptoms in these patients.

Many patients received anti-inflammatory agents such as NSAID, colchicine, steroid, and intravenous immunoglobulin. Though the reasons for selecting specific drugs were not described in the included studies, the use of drug regimens was in line with the current medical knowledge of general myocarditis,[63] in contrast to SARS-CoV-2 related myocarditis patients who received several experimental drugs.[35] Notably, symptoms of one-third (35.1%) of the patients resolved with conservative treatment, and previous SARS-CoV-2 infection was related to this favourable recovery process. Patients who recovered from earlier SARS-CoV-2

343 exposure may have an immune system that primed from it. Patients with previous exposure to
344 COVID-19 reported higher SARS-CoV-2 spike IgG titres, before and after the first and second
345 dose of an mRNA vaccine, compared to those without previous infection.[64] Also, the function
346 of B-cells specific to receptor binding domains remained unchanged at 6.2 months after
347 infection,[65] and the plasma neutralizing activity and relative numbers of receptor binding
348 domain-specific memory B cells of individuals who had recovered from natural infection was
349 higher and equivalent to those who were vaccinated.[44] Therefore, these immunologic
350 conditions in patients who had recovered from SARS-CoV-2 could more favourably facilitate
351 recovery from myocarditis after receiving an mRNA vaccine.

352 Meanwhile, myocarditis related to SARS-CoV-2 infection has been reported since the
353 beginning of the pandemic.[66–68] Multiple studies have reported the prevalence of cardiac
354 complications in adults after being diagnosed with COVID-19, which included heart failure
355 (23–33.3%), myocardial injury/myocarditis (8–27.8%), arrhythmia (16.7%), and
356 thromboembolism (31–40%). Among these, high mortality rates (51–97%) have been
357 described in several cases series.[35,69] Starekova *et al.* found that there was a low prevalence of
358 myocarditis (1.4%) among student-athletes recovering from COVID-19 with none, mild, to
359 moderate symptoms by CMR.[70] Recently published data from the health care organization in
360 Israel estimated the incidence of myocarditis due to COVID-19 infection as 11.0 cases per
361 100,000 persons (95% CI, 5.6–15.8), and the incidence of myocarditis following the
362 BNT1621b vaccine was 2.7 cases per 100,000 persons (95% CI, 1.0–4.6).[71] The systematic
363 reviews of 42 myocarditis cases related to COVID-19 infection revealed a high mortality rate
364 and severe complications,[35,36] compared to the present review's findings. Although the
365 incidence of myocarditis in the vaccinated population is higher than in unvaccinated
366 individuals, the risk of myocarditis due to COVID-19 and its fatal outcome is much lower
367 among vaccinated people. Moreover, infection with SARS-CoV-2 has more adverse events
368 beyond myocarditis, and thus, it is necessary to encourage the public to get vaccinated.

369 The present systematic review has several limitations. First, it is difficult to generalize the

study findings due to rapidly evolving medical knowledge about SARS-CoV-2 and its mRNA vaccines. This rare adverse event could be attributable to genetic predispositions of a specific population, as we mentioned the possible mechanism forehead. Furthermore, as we reviewed case reports, information about myocarditis related to mRNA vaccines has been updated continuously, and the eligibility of mRNA vaccination has also evolved. Cautious interpretation of our data is necessary based on this ever-changing medical environment. Second, the direct comparison of two mRNA vaccines should be carefully elucidated. Due to different vaccine eligibility criteria and the scarcity of myocarditis, we could not correct confounding factors such as demographic factors, locoregional policy in COVID-19 vaccination, and other accountable factors. Third, the data of case reports may have been incomplete. Due to insufficient data on continuous variables, many were classified as categorical variables, possibly limiting the strength of our statistical analysis. Third, information about clinical situations is widely varied. In terms of patient care, all cases did not specify the reason for medical decisions related to medications, ICU admission, and follow-up plans. Therefore, the risk of bias in data interpretation remains elevated. Further large-scale and multicenter studies addressing mRNA vaccine-associated myocarditis are necessary.

Conclusion

This systematic review summarizes clinical features, diagnostic findings, management, and myocarditis outcomes associated with mRNA vaccines. The risk of fatality in myocardial inflammation related to mRNA vaccines seems to be very low, and a significant proportion of patients recovered with conservative management. Previous SARS-CoV-2 infection was related to recovery with conservative care, and patients with nausea were more likely to require ICU admission. Otherwise, both BNT162b2 and mRNA-1273 vaccines do not demonstrate a difference in the clinical outcome of myocarditis patients. However, there are some variations concerning clinical manifestation and diagnostic findings. It is crucial to incorporate and analyze large-scale multicenter data to understand clinical characteristics of mRNA vaccine-

related myocarditis to efficiently educate the public.

Author contributions

WW, AYK, SWL, DKY, SS and JIS designed this study. WW, AYK and JIS collected the data, and WW, AYK, SWL, DKY, SS and JIS performed the statistical analysis. WW, AYK, SS, and JIS wrote the first draft of the manuscript. All authors had full access to all the study data. All authors reviewed, wrote and approved the final version. The corresponding authors had final responsibility for the decision to submit for publication.

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WW and AYK are spouses. However, both equally contributed in conceptualization, data curation, analysis, and writing the manuscript.

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Tables

Table 1. Characteristics and clinical findings of myocarditis patients after mRNA vaccinations

Variables	Total (n=74)	mRNA-1273 (n=16)	BNT162b2 (n=58)	P value
	Number of patients (%) or Median (range)	Number of patients (%) or Median (range)	Number of Patients (%) or Median (range)	
Demographic variables				
Age, years	17.6 [14.0, 70,0]	27.0 [20.0, 70.0]	20.0 [14.0, 56.0]	**0.008**
Male	70/74 (94.6)	13/16 (81.2)	57/58 (98.3)	**0.030**
Underlying medical history	8/74 (10.8)	4/16 (25.0)	3/55 (5.5)	**0.036**
COVID-19 related variables				
Negative COVID PCR test	73/73 (100.0)	15/15 (100.0)	58/58 (100.0)	NA
Previous COVID-19 infection	8/45 (17.8)	1/13 (7.7)	7/32 (21.9)	0.405
Presentation after 2nd dose	67/74 (90.5)	15/16 (93.8)	52/58 (89.7)	1.000
Clinical manifestations				
Interval after vaccination, days	3.00[0.25, 16.00]	3.00 [0.25, 10.00]	3.00 [0.25, 16.00]	0.496
Symptoms within 24h of vaccination¶	23/33 (69.7)	10/12 (83.3)	13/21 (61.9)	0.259
Symptoms leading to hospitalization				
Chest pain	71/74 (95.9)	14/16 (87.5)	57/58 (98.3)	0.116
Chilling	4/74 (5.4)	3/16 (18.8)	1/58 (1.7)	**0.030**
Fatigue	8/74 (10.8)	1/16 (6.2)	7/58 (12.1)	0.678
Fever	25/74 (33.8)	5/16 (31.2)	20/58 (34.5)	1.000
Headache	11/74 (14.9)	1/16 (6.2)	10/58 (17.2)	0.437
Dyspnea	16/74 (21.6)	5/16 (31.2)	11/58 (19.0)	0.315
Electrocardiography				
Abnormal ECG	65/74 (87.8)	13/16 (81.2)	52/58 (89.7)	0.396
Non-sinus rhythm	6/74 (8.1)	2/16 (12.5)	4/58 (6.9)	0.604
PR interval abnormality	11/74 (14.9)	6/16 (37.5)	5/58 (8.6)	**0.010**

ST changes	57/74 (77.0)	11/16 (68.8)	46/58 (79.3)	0.502
T wave abnormality	12/74 (16.2)	0/16 (0.0)	12/58 (20.7)	0.058
Echocardiography				
LVEF, %	55.0[27.0, 67.5]	52.0 [27.0, 61.0]	55.0 [37.5, 67.5]	**0.016**
LV dysfunction†	23/74 (31.1)	9/16 (56.2)	14/58 (24.1)	**0.030**
Pericardial effusion	7/30 (23.3)	1/5 (20.0)	6/25 (24.0)	1.000
RWMA	21/43 (48.8)	9/15 (60.0)	12/28 (42.9)	0.347
Laboratory findings				
Elevated BNP§	12/22 (54.5)	2/5 (40.0)	10/17 (58.8)	0.624
BNP, pg/ml	50.0 [22.0, 111.0]	57.2 [22.0, 97.0]	49.0 [42.0, 111.0]	0.905
Pro-BNP, pg/ml	428 [149, 43134]	978 [978, 978]	402 [149, 43134]	0.800
NT-pro-BNP, pg/ml	678.5 [571.0, 2862.0]	NA	678.5 [571.0, 2862.0]	0.800
Elevated CRP§	64/69 (92.8)	14/14 (100.0)	50/55 (90.9)	0.575
CRP, mg/dl	4.6[0.1, 18.1]	6.32 [0.69, 18.1]	3.78 [0.10, 15.5]	0.082
Leukocytosis§	11/32 (34.4)	2/7 (28.6)	9/25 (36.0)	1.000
WBC count, per mm^3	8,855[5,000, 17,860]	10,010 [8,280, 16,300]	8595 [5,000, 17,860]	0.196
Elevated Cardiac Enzymes†	74/74 (100.0)	16/16 (100.0)	58/58 (100.0)	NA
MRI findings				
Myocardial inflammation††	40/58 (69.0)	7/11 (63.6)	33/47 (70.2)	0.724
Late gadolinium enhancement	53/57 (93.0)	10/10 (100.0)	43/47 (91.5)	1.000
Hyperemia or scar/necrosis on T1	57/59 (96.6)	11/11 (100.0)	46/48 (95.8)	1.000
Myocardial edema on T2	40/54 (74.1)	7/7 (100.0)	33/47 (70.2)	0.171
Treatment				
Conservative care	26/74 (35.1)	6/15* (40.0)	20/58 (34.5)	0.766
Anti-inflammatory agents	40/74 (54.1)	5/16 (31.2)	35/58 (60.3)	**0.050**
NSAID	23/74 (31.1)	2/16 (12.5)	21/58 (36.2)	0.125
Colchicine	15/74 (20.3)	2/16 (12.5)	13/58 (22.4)	0.499
Steroid	17/74 (23.0)	3/16 (18.8)	14/58 (24.1)	0.750
IV immunoglobulin	12//74 (16.2)	0/16 (0.0)	12/58 (20.7)	0.058

Heart failure management[†††]	12/74 (16.2)	6/16 (42.9)	6/58 (10.7)	**0.011**
Supplemental oxygen	2/74 (2.7)	1/16 (7.1)	1/58 (1.8)	0.362
Outcome				
Complication[§§]	4/74 (5.4)	2/16 (12.5)	2/58 (3.4)	0.202
ICU admission	12/74 (16.2)	1/16 (6.2)	11/58 (19.0)	0.443
Hospital stay, days	4.0 [1.0, 21.0]	3.0 [2.0, 21.0]	4.0 [1.0, 8.0]	0.295
Hospital stay < 4 days	32/74 (43.2)	10/12 (83.3)	22/52 (42.3)	**0.022**

ECG, Electrocardiography; RWMA, regional wall motional abnormality; ICU, intensive care unit; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal-pro-BNP; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drugs; WBC, white blood cells

* One patient's medical treatment was not stated in detail.

[¶] Systemic symptoms(fever, chill, myalgia, generalized bod yache) within 24hrs after vaccine administration

[†] LVEF less than 55%

[†] CK, CK-MB, Troponin, Troponin-T, Hs-TnT, Hs-TnI

[††] Using either the original or updated Lake Louise Criteria[34]

[†††] Beta-blocker, diuretics, inotropic, angiotensin-converting enzyme(ACE) inhibitor, angiotensin-receptor blocker

[§§] Multiorgan failure(n=1) and cardiac arrhythmia(n=3) during hospitalization

[§] The normal ranges for selected variables are as follows : BNP <35 pg/mL, proBNP < 100pg/ml, NT-proBNP<125 pg/mL; CRP< 0.3mg/dL, white blood cell count < 11,000/mm3, CK <198 IU/L, CK-MB< 25 IU/L, Troponin<0.04ng/mL , Troponin-T < 14ng/L, troponin-I<0.04ng/ml, hs-TnT <14ng/L, hs-TnI <14ng/L,

Table 2. Clinical characteristics of mRNA vaccine-related myocarditis patients divided by age 20

	Total mRNA vaccines (n=74)			BNT162b2 (n=58) †		
	Age ≥ 20 (N=40)	Age < 20 (N=34)	P value	Age ≥ 20 (N=24)	Age < 20 (N=34)	P value
	Number of patients (%) or Median (range)	Number of Patients (%) or Median (range)		Number of patients (%) or Median (range)	Number of Patients (%) or Median (range)	
Demographic variables						
Male	37/40 (92.5)	33/34 (97.1)	0.620	24/24 (100.0)	33/34 (97.1)	1.000
Underlying medical history	6/40 (15.0)	1/34 (2.9)	0.223	2/24 (8.3)	1/24 (4.2)	0.564
COVID-19 related variables						
Previous COVID-19 infection	7/33 (21.2)	1/12 (8.3)	0.419	6/20 (30.0)	1/12 (8.3)	0.212
Presentation after 2nd dose	35/40 (87.5)	32/34 (94.1)	0.441	20/24 (83.3)	32/34 (94.1)	0.220
Type of vaccine			**<0.001**			
mRNA-1273	16/40 (40.0)	0/40 (0.0)				
BNT162b2	24/40 (60.0)	34/40 (100.0)				
Clinical manifestations						
Interval after vaccination, days	3.00 [0.25, 16.00]	2.00 [1.00, 6.00]	0.106	3.00 [0.25, 16.00]	2.00 [1.00, 6.00]	0.128
Symptoms within 24h of vaccination¶	19/24 (79.2)	4/9 (44.4)	0.090	9/12 (75.0)	4/9 (44.4)	0.203
Symptoms leading to hospitalization						
Chest pain	37/40 (92.5)	34/34 (100.0)	0.245	23/24 (95.8)	34/34 (100.0)	0.414
Fever	8/40 (20.0)	17/34 (50.0)	**0.013**	3/24 (12.5)	17/34 (50.0)	**0.005**
Myalgia	3/40 (7.5)	11/34 (32.4)	**0.008**	1/24 (4.2)	11/34 (32.4)	**0.010**
Electrocardiography						
Abnormal ECG	35/40 (87.5)	30/34 (88.2)	1.000	22/24 (91.7)	30/34 (88.2)	1.000
PR interval abnormality	11/40 (27.5)	0/34 (0.0)	**0.001**	5/24 (20.8)	0/34 (0.0)	**0.009**
Echocardiography						
LVEF, %	52.8 [27.0, 67.5]	56.8 [43.7, 64.7]	**0.026**	54.0 [37.5, 67.5]	56.8 [43.7, 64.7]	0.212
Pericardial effusion	4/10 (40.0)	3/20 (15.0)	0.181	3/5 (60.0)	3/20 (15.0)	0.070
RWMA	20/36 (55.6)	1/7 (14.3)	0.095	11/21 (52.4)	1/7 (14.3)	0.184
Laboratory findings						
Elevated BNP§	3/12 (25.0)	9/10 (90.0)	**0.004**	1/7 (14.3)	9/10 (90.0)	**0.004**
Elevated CRP	33/36 (91.7)	31/33 (93.9)	1.000	19/22 (86.4)	31/33 (93.9)	0.379

MRI findings						
Myocardial inflammation[††]	26/32 (81.3)	14/26 (53.8)	**0.044**	19/21 (90.5)	14/26 (53.8)	**0.010**
Late gadolinium enhancement	31/31 (100.0)	22/26 (84.6)	**0.038**	21/21 (100.0)	22/26 (84.6)	0.117
Hyperemia or scar/necrosis on T1	32/32 (100.0)	25/27 (92.6)	0.205	21/21 (100.0)	25/27 (92.6)	0.497
Myocardial edema on T2	26/28 (92.9)	14/26 (53.8)	**0.002**	19/21 (90.5)	14/26 (53.8)	**0.010**
Treatment						
Conservative care	12/39* (30.8)	14/34 (41.2)	0.463	6/24 (25.0)	14/34 (41.2)	0.266
Anti-inflammatory	21/40 (52.5)	19/34 (55.9)	0.818	16/24 (66.7)	19/34 (55.9)	0.431
Colchicine	12/40 (30.0)	3/34 (8.8)	**0.040**	10/24 (41.7)	3/34 (8.8)	**0.004**
IVIG	0/40 (0.0)	12/34 (35.3)	**<0.001**	0/24 (0.0)	12/34 (35.3)	**0.001**
Heart failure management	11/36 (30.6)	1/34 (2.9)	**0.003**	5/22 (22.7)	1/34 (2.9)	**0.030**
Supplement Oxygen	1/36 (2.8)	1/34 (2.9)	1.000	0/22 (0.0)	1/34 (2.9)	1.000
Outcome						
Complication[‡‡]	4/40 (10.0)	0/34 (0.0)	0.120	2/24 (8.3)	0/34 (0.0)	0.167
ICU admission	4/40 (10.0)	8/34 (23.5)	0.205	3/24 (12.5)	8/34 (23.5)	0.333
Hospital stay < 6 days	22/30 (73.3)	28/34 (82.4)	0.546	11/18 (61.1)	28/34 (82.4)	0.108

ECG, Electrocardiography; RWMA, regional wall motional abnormality; ICU, intensive care unit; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal-pro-BNP; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drugs; IVIG, intravenous immunoglobulin

[§] Included in this category if patient has elevated levels of BNP, proBNP, or NT-proBNP

[††] Using either the original or updated Lake Louise Criteria[34]

[¶] Systemic symptoms(fever, chill, myalgia, generalized body ache) within 24hrs after vaccine administration

[‡‡] Multiorgan failure(n=1) and cardiac arrhythmia(n=3) during hospitalization

[†]mRNA-1273 vaccine was not administered under age 20.

Table 3. Clinical characteristics of mRNA vaccine related myocarditis patients according to recovery course

	Total mRNA vaccines (n=74)			BNT162b2 (n=58)[†]		
	Medical treatment (n=47)	Conservative care[*,**] (n=26)	P value	Medical treatment (n=38)	Conservative care[*,**] (n=20)	P value
	Number of patients (%) or Median (range)	Number of Patients (%) or Median (range)		Number of patients (%) or Median (range)	Number of Patients (%) or Median (range)	
Demographic variables						
Age, years	22.0 [14.0, 67.0]	23.5 [16.2, 56.0]	0.668	20.0 [14.0, 45.0]	20.8 [16.2, 56.0]	0.587
Male	46/47 (97.9)	24/26 (92.3)	0.287	38/38 (100.0)	19/20 (95.0)	0.345
Underlying disease	6/46 (13.0)	0/16 (0.0)	0.325	3/37 (8.1)	0/13 (0.0)	0.558
COVID-19 related variables						
Previous COVID-19 infection	5/37 (13.5)	3/7 (42.9)	0.100	4/28 (14.3)	3/4 (75.0)	**0.025**
Presentation after 2nd dose	43/47 (91.5)	23/26 (88.5)	0.694	35/38 (92.1)	17/20 (85.0)	0.405
Type of vaccine			0.766			
mRNA-1273	9/47 (19.1)	6/26 (23.1)				
BNT162b2	38/47 (80.9)	20/26 (76.9)				
Clinical manifestations						
Interval after vaccination, days	3.00 [0.25, 16.00]	3.00 [1.00, 6.00]	0.834	2.00 [0.25, 16.00]	3.00 [1.00, 6.00]	0.609
Symptoms with 24h of vaccination[¶]	19/25 (76.0)	4/7 (57.1)	0.370	11/17 (64.7)	2/4 (50.0)	0.618
Chest pain	45/47 (95.7)	25/26 (96.2)	1.000	38/38 (100.0)	19/20 (95.0)	0.345
Fatigue	7/47 (14.9)	1/26 (3.8)	0.245	6/38 (15.8)	1/20 (5.0)	0.403
Fever	16/47 (34.0)	9/26 (34.6)	1.000	12/38 (31.6)	8/20 (40.0)	0.570
Nausea	7/47 (14.9)	1/26 (3.8)	0.245	5/38 (13.2)	1/20 (5.0)	0.653
Electrocardiography						
Abnormal ECG	44/47 (93.6)	20/26 (76.9)	0.061	37/38 (97.4)	15/20 (75.0)	0.016
Non-sinus rhythm	6/47 (12.8)	0/26 (0.0)	0.083	4/38 (10.5)	0/20 (0.0)	0.288
ST changes	38/47 (80.9)	18/26 (69.2)	0.386	33/38 (86.8)	13/20 (65.0)	0.086
Echocardiography						
LV dysfunction[‡]	19/47 (40.4)	3/26 (11.5)	**0.015**	14/38 (36.8)	0/20 (0.0)	**0.001**
RWMA	15/32 (46.9)	5/10 (50.0)	1.000	11/24 (45.8)	1/4 (25.0)	0.613
Laboratory findings						
Elevated BNP[§]	8/17 (47.1)	3/4 (75.0)	0.586	7/13 (53.8)	3/4 (75.0)	0.603
Elevated CRP	40/44 (90.9)	24/25 (96.0)	0.646	32/36 (88.9)	18/19 (94.7)	0.649
MRI findings						
Late gadolinium enhancement	40/41 (97.6)	12/15 (80.0)	0.055	34/35 (97.1)	9/12 (75.0)	**0.046**
Hyperemia or myocardial fibrosis on T1	42/43 (97.7)	14/15 (93.3)	0.454	35/36 (97.2)	11/12 (91.7)	0.441
Myocardial edema on T2	32/39 (82.1)	7/14 (50.0)	**0.033**	28/35 (80.0)	5/12 (41.7)	**0.025**

Outcome						
Complication[⁂]	3/47 (6.4)	1/26 (3.8)	1.000	2/38 (5.3)	0/20 (0.0)	0.540
ICU admission	12/47 (25.5)	0/26 (0.0)	**0.006**	11/38 (28.9)	0/20 (0.0)	**0.011**
Hospital stay < 4 days	17/40 (42.5)	14/23 (60.9)	0.196	12/33 (36.4)	10/19 (52.6)	0.382

ECG, Electrocardiography; RWMA, regional wall motional abnormality; ICU, intensive care unit; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal-pro-BNP; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drugs

[†]mRNA-1273 vaccine did not show any significant difference in parameters between spontaneous recovery and medical treatment groups.

[⁂] Patients who reovered without medical treatments such as anti-inflammatory agents or heart failure treatment.

[‡] LVEF less than 55%

[⁂] Multiorgan failure(n=1) and cardiac arrhythmia(n=3) during hospitalization

[§] Included in this category if patient has elevated levels of BNP, proBNP, or NT-proBNP

[¶] Systemic symptoms(fever, chill, myalgia, generalized body ache) within 24hrs after vaccine administration

Table 4. Risk factor analysis according to clinical presentation and outcome among mRNA vaccines related myocarditis patients

	Fisher's exact test			Univariate logistic regression		Multivariate logistic regression	
Factor	Event	Total	P-value	OR (95% CI)	P value	OR (95% CI)	P value
1. ICU admission							
Nausea	8	66	0.020*	7.25 (1.51-34.90)	0.013*		
No nausea	4	8		Ref.			
Vomiting	9	70	0.012*	20.30 (1.90-217.00)	0.013*	20.30 (1.90-217.00)	**0.013***
No vomiting	3	1		Ref.			
2. LV dysfunction‡							
Age < 20	6	34	0.025*	0.29 (0.10-0.86)	0.025*		
Age ≥ 20	17	40		Ref.			
BNT162b2 vaccine	14	44	0.030*	0.25 (0.08-0.79)	0.018*		
mRNA-1273 vaccine	9	7		Ref.			
No leukocytosis	5	21	0.123	0.26 (0.06-1.23)	0.090		
Leukocytosis	6	11		Ref.			
3. Recovery with conservative care*							
Previous COVID-19 history	3	8	0.100	4.80 (0.82-28.20)	0.082	25.00 (1.82-343.00)	**0.016***
No COVID-19 history	4	36		Ref.			
Normal ECG	6	9	0.061	4.40 (1.00-19.40)	0.050		
Abnormal ECG	20	64		Ref.			
Preserved LVEF	23	51	0.015*	5.20 (1.37-19.80)	0.016*		
Low LVEF	3	22		Ref.			
Myocardial edema in T2MR	7	39	0.033*	0.219 (0.058-0.826)	0.025*		
No Myocardial edema in T2MR	7	14		Ref.			

ECG, Electrocardiography; ICU, intensive care unit; COVID-19, coronavirus disease 2019; LV, left ventricle; LVEF, left ventricular ejection fraction; T2MR : T2 image on cardiac magnetic resonance imaging

[*] $p<0.05$
[‡] LVEF less than 55%
[**] Patients who reovered without medical treatments such as anti-inflammatory agents or heart failure treatment.

Figure Legends

Figure 1. Correlation among key clinical characteristics and diagnostic findings with Phi(Φ) coefficient

Tx, treatment; EF, ejection fraction; Hx, history;BNP, B-type natriuretic peptide; HOD, hospital stay

* Cardiac MRI findings satisfying original or modified Lake Louise criteria[34]

§ Conservative care: patients who recovered without administration of anti-inflammatory agents or cardiovascular medications

‡ Treatment including colchicine, non-steroidal anti-inflammatory drugs, steroid, or intravenous immunoglobulin

Figure 2. Treatment outcome of myocarditis patients between COVID-19 induced and COVID vaccine related

*p<0.05, **p<0.001

†It accounts for cases that needed intubation, mechanical ventilation, or ECMO support.
††It included patients who did not receive anti-inflammatory agents, steroids, IV immunoglobulin, cardiovascular medications

We compared the pooled data of 42 patients in two systematic reviews[34,35] of case reports about myocarditis due to COVID-19 infection and our data of myocarditis patients who developed after mRNA vaccinations.

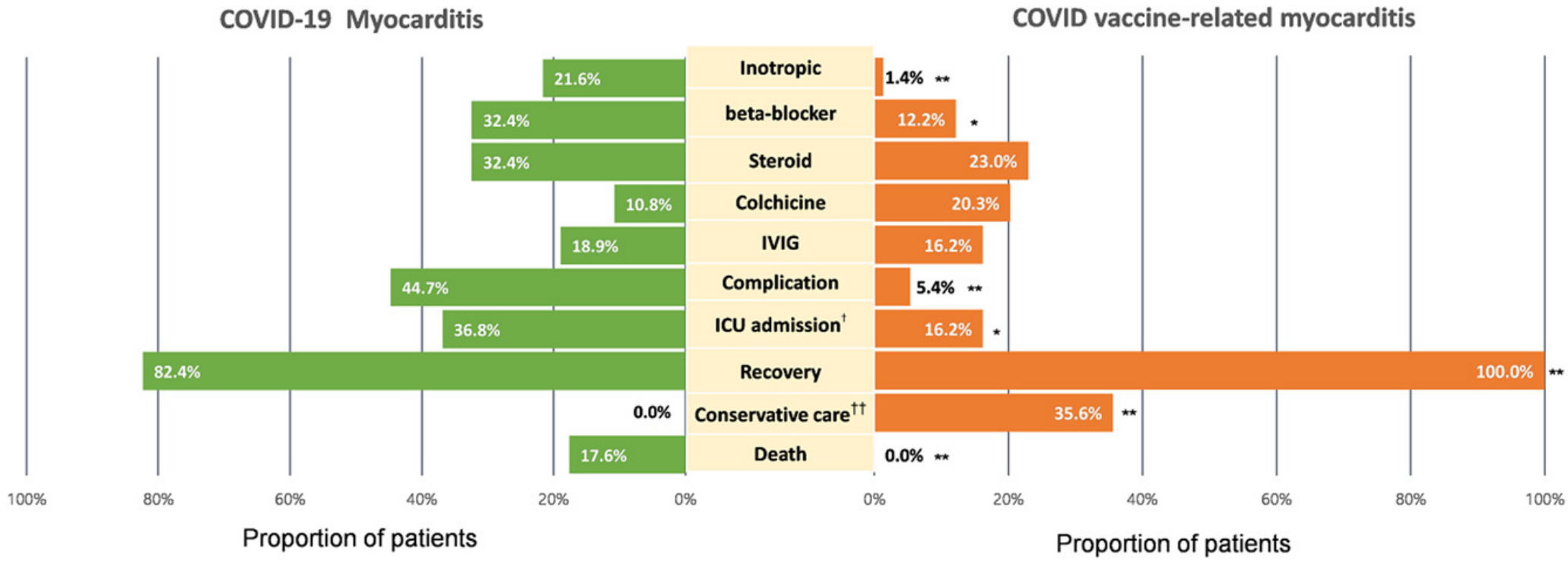
1 **Figure 1**

p-value	*Φ*
<0.001	(+1)
<0.01	
<0.05	
non significant	
<0.05	
<0.01	
<0.001	(-1)

Phi coefficient		Patients' characteristics							Diagnostic evaluation				Symptoms				Treatment and outcome				
		Age<20	Age<30	2nd dose	Male	Medical Hx	COVID Hx	BNT162b2	ST changes	Normal EF	Elevated BNP	MRI(+)*	Chill	Myalgia	Nausea	Vomiting	Conservative care§	Anti-inflammatory Tx#	HF Tx	ICU	HOD<4
Patients' characteristics	Age<20							0.484		0.268	0.650	-0.295		0.316					-0.366		
	Age<30			-0.395		-0.395			-0.337					0.254							
	2nd dose		-0.395				-0.390														
	Male					-0.390		0.310													
	Medical Hx		-0.395		-0.390			-0.319													
	COVID Hx			-0.390																	
	BNT162b2	0.484			0.310	-0.319				0.286			-0.310					0.240	-0.341		-0.320
Diagnostic evaluation	ST changes		-0.337													0.296		-0.270			
	Normal EF	0.268						0.286									0.301				
	Elevated BNP	0.650																		0.559	
	MRI(+)*	-0.295												-0.533							-0.421
Symptoms	Chill							-0.310													
	Myalgia	0.316	0.254									-0.533									
	Nausea															0.494				0.319	
	Vomiting								0.296						0.494					0.381	
Treatment and outcome	Conservative care§									0.301											
	Anti-inflammatory Tx#							0.240	-0.270											0.406	
	HF Tx	-0.366						-0.341													
	ICU										0.559				0.319	0.381		0.406			-0.315
	HOD<4							-0.320				-0.421								-0.315	

2

1 **Figure 2**



2

3 Treatment outcome of myocarditis patients between COVID-19 induced and COVID vaccine related $*p < 0.05$, $**p < 0.001$. †It accounts for cases that needed intubation,
4 mechanical ventilation, or ECMO support. ††It included patients who did not receive anti-inflammatory agents, steroids, IV immunoglobulin, cardiovascular medications We
5 compared the pooled data of 42 patients in two systematic reviews[34, 35] of case reports about myocarditis due to COVID-19 infection and our data of myocarditis patients who
6 developed after mRNA vaccinations