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

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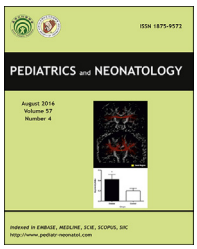

Original Article

BNT162b2 immunization-related myocarditis in adolescents and consequent hospitalization: Report from a medical center

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Key Words
adolescent;
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Background: To investigate Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine (BNT162b2) immunization-related myocarditis and describe the risk factors for consequent hospitalization in the pediatric intensive care unit (PICU) in children between 12 and 18 years.
Methods: Children and adolescents 12 years of age and older who presented with discomfort after BNT162b2 immunization (BNTI) and visited pediatric emergency room (PER) at Chang Gung Memorial Hospital from September 22, 2021 to March 21, 2022, were included for analysis.
Results: 681 children presented with discomfort after BNTI and visited our PER. The mean age was 15.1 ± 1.7 years. Three hundred and ninety-four (57.9%) and 287 (42.1%) events were after 1st and 2nd dose, respectively. 58.4% (n = 398) were male. The most common complaints were chest pain (46.7%) and chest tightness (27.0%). The median (interquartile range [IQR]) interval of discomfort after BNTI was 3.0 (1.0–12.0) days. BNTI-related pericarditis, myocarditis and myopericarditis were diagnosed in 15 (2.2%), 12 (1.8%) and 2 (0.3%) patients, respectively. Eleven (1.6%) needed hospitalization in PICU. The median (IQR) hospital stay was 4.0 (3.0

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−6.0) days. There was no mortality. More patients were diagnosed myocarditis ($p = 0.004$) after 2nd dose BNTI. PICU admission occurred more commonly after 2nd dose BNTI ($p = 0.007$). Risk factors associated with hospitalization in PICU were abnormal EKG findings ($p = 0.047$) and abnormal serum troponin levels ($p = 0.003$) at PER.

Conclusion: Myocarditis in children aged 12−18 years occurred more commonly following 2nd dose BNTI. Most cases were of mild or intermediate severity without death. Factors predicting BNTI-related myocarditis and consequent hospitalization in PICU were abnormal EKG findings and abnormal serum troponin levels at PER in this study.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), has spread across the globe since 2019, causing many people infection and death.[1−4] In the U.S.A., the American Academy of Pediatrics (AAP) recorded almost 13 million children that tested positive for COVID-19 since the onset of the pandemic according to available state reports.[5] AAP claimed any COVID-19 vaccine authorized through Emergency Use Authorization or approved by the US Food and Drug Administration and appropriate by age and health status could be vaccinated according to Centers for Disease Control and Prevention guidelines for children and adolescents in protecting individuals and populations against infectious diseases.[6]

Though heart complications are not common, occurrence of pericarditis and/or myocarditis in adolescents and young adults after mRNA COVID-19 vaccinations was sporadically reported from April 2021.[7−12]

The benefits of COVID-19 vaccination outweigh the reported known and potential risks in the current pandemic.[9,13] In Taiwan, the Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine (BNT162b2) was approved and utilized in pediatric patients aged 12−18 years old from September 2021.[14] Increasing cases of myocarditis were reported as BNT162b2 vaccinations were administered. Here, we aim to investigate factors associated with BNT162b2 immunization (BNTI)-related myocarditis and consequent hospitalization in a pediatric intensive care unit (PICU) in adolescents between 12 and 18 years.

2. Materials and methods

2.1. Participants and study design

This retrospective observational study was conducted at pediatric emergency departments (PERs) in Chang Gung Medical Hospital (CGMH) in Northern Taiwan from September 22, 2021, to March 21, 2022. Medical records for all pediatric patients aged 12−18 years old visiting our PERs were taken in detail. This study was approved by CGMH institutional review board (No. 202200782B0). All methods were carried out and followed in accordance with the approved guidelines and regulations for medical research.

In Taiwan, the Pfizer-BioNTech was approved on August 3, 2021. It was utilized for all children and adolescents 12 years of age and older without contraindications from September 22, 2021, at two doses per person.[14] According to the policy from Advisory Committee on Immunization Practices (ACIP) and the Ministry of Health and Welfare in Taiwan, the interval between the doses was at least 12 weeks in adolescents.[15] In our enrolled participants, those who suffered from uncomfortable symptoms and signs after BNTI were divided into Group A (after 1st dose BNTI) and Group B (after 2nd dose BNTI). Demographic information was obtained as follows: age, gender, interval of discomfort after BNTI, systolic and diastolic blood pressure (SBP and DBP) at PER, number of patients with abnormal Electrocardiogram (EKG) findings at PER, serum laboratories findings at PER, number of patients diagnosed with pericarditis, myocarditis and myopericarditis,[16−19] number of patients admitted and discharged home, and number of surviving patients. Abnormal EKG findings at PER indicated that previously healthy patients without any heart disease showed ST-segment elevation, incomplete right bundle branch block, T wave inversion, tachy- and bradyarrhythmia, and first-degree AV block in our study population.[16−19]

The diagnosis and the definition of COVID-19 vaccine-associated acute pericarditis and acute myocarditis were determined according to the ACIP about COVID-19 vaccine safety updates on June 23, 2021,[16−19] as shown in the Supplementary Figure.

Pediatric patients hospitalized due to BNTI-related acute pericarditis, myocarditis, and myopericarditis[16−19] were divided into Group C (admitted to ward) and Group D (admitted to PICU). The outcome comparison between these two groups was conducted; the difference of ejection fraction on heart echocardiogram, COVID-19 polymerase chain reaction result and hospital length of stay (LOS) were also recorded.

We compared the difference between junior high school age patients (aged 12−15 years) and high school age patients (aged 16−18 years) on clinical characteristics after 1st or 2nd dose of BNTI and hospitalization in the ward or PICU.

2.2. Statistical analysis

Descriptive statistics are presented to represent specific data (e.g., demographics). Univariate summaries are provided for continuous variables (e.g., mean ± standard deviation [SD] for age, SBP and DBP at PER; median and interquartile range [IQR] for serum troponin, CK-MB, NT-ProBNP, brain natriuretic peptide [BNP], C-reactive protein [CRP] level). In contrast, frequencies and percentages summarize categorical variables (e.g., gender, abnormal EKG findings at PER, number of patients who survived). All analyses were performed using SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA), and a p-value <0.05 was taken to indicate statistical significance. The Student's t-test and the $\chi 2$ test or Fisher's exact test was used for continuous and categorical variables, respectively. Multivariate logistic regression analyses were performed to determine the predictive factors for pediatric patients who needed admission to PICU. Variables were kept in the final model if the p-value was <0.05.

3. Results

In all, 681 pediatric patients aged 12–18 years old were enrolled in our study. Among them, three hundred ninety-four (57.9%) patients had discomfort after 1st dose of BNTI (Group A) and 287 (42.1%) after 2nd dose of BNTI (Group B). Their chief discomfort complaints were chest pain, chest tightness, palpitation, tachycardia, shortness of breath, dyspnea, dizziness, weakness, abdominal pain, and fever; the proportion of each symptom is shown in Fig. 1. Fig. 1 also presents the detailed percentage after 1st and 2nd dose of BNTI.

The mean age was 15.1 ± 1.7 years. Three hundred ninety-six (58.1%) were aged 12–15 years and 285 (48.9%) were aged 16–18 years. Over half (58.4%, n = 398) were male children. The median (IQR) interval of discomfort after BNTI was 3.0 (1.0–12.0) days. The mean SBP and DBP at PER were 127.4 ± 18.1 and 74.9 ± 12.1 mmHg, respectively. Eighteen (2.6%) patients had abnormal EKG findings at PER, including 9 with ST-segment elevation, 4 with incomplete right bundle branch block, 1 with T wave inversion, 1 with tachyarrhythmia, 2 with bradyarrhythmia and 1 with first-degree AV block. The serum laboratories findings at PER were as follows: mean white blood cell (WBC) count (1000/uL) 7.9 ± 4.5; mean hemoglobulin (Hb) (g/dL) 14.4 ± 7.0; mean platelet (PLT) count (1000/uL) 276.4 ± 63.9; median (IQR) troponin I level (ng/mL) 0.0 (0.0–0.0); median (IQR) troponin T level (ng/L) 3.1 (1.5–4.7); median (IQR) CK-MB level (ng/mL) 1.1 (0.8–1.6); median (IQR) NT-ProBNP level (pg/mL) 18.2 (10.9–31.8); median (IQR) BNP level (pg/mL) 5.1 (2.5–8.8); mean serum creatinine (SCr) level (mg/dL) 0.7 ± 0.3; and median (IQR) CRP level (mg/L) 0.9 (0.4–0.7). BNTI-related pericarditis, myocarditis and myopericarditis were diagnosed in 15 (2.2%), 12 (1.8%) and 2 (0.3%) patients, respectively. Six hundred forty-seven (95%) patients were discharged home and 34 (5.0%) needed admission, including 23 (3.4%) admitted to ward and 11 (1.6%) admitted to PICU. All patients survived (Table 1).

In Table 1, Group B seems to be older ($p < 0.001$), with more male patients ($p = 0.004$), shorter interval of discomfort after vaccination ($p < 0.001$), lower platelet count level ($p < 0.001$), higher CRP level ($p = 0.001$), more patients diagnosed with myocarditis ($p = 0.004$) and in need of PICU admission ($p = 0.007$). Group A only showed lower SBP at PER ($p = 0.007$). There was no statistical difference regarding DBP at PER, number of patients with abnormal EKG findings at PER, WBC count level, Hb level, troponin I level, troponin T level, CK-MB level, NT-ProBNP level, BNP level, SCr level, number of patients diagnosed with pericarditis and myopericarditis, number of patients in need of ward admission and number of patients discharged home.

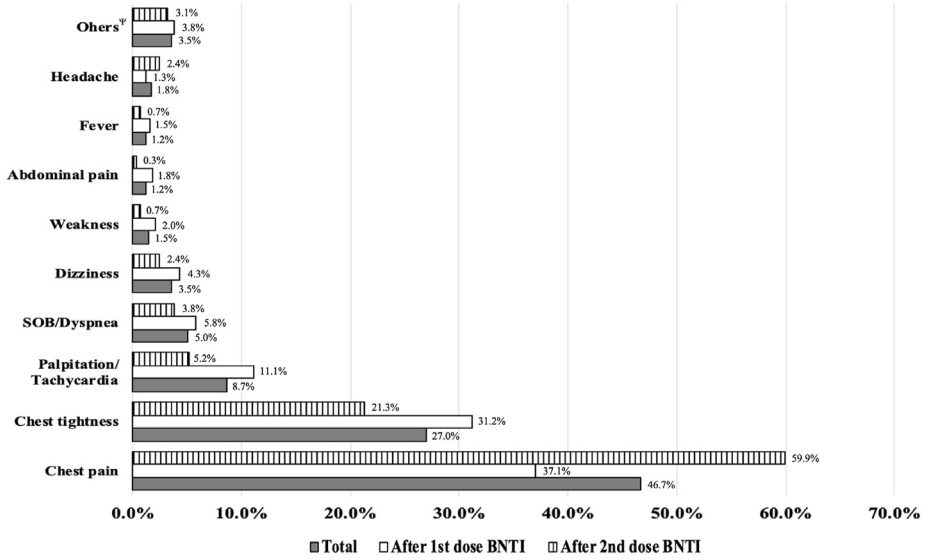

Figure 1 Chief discomfort complaints in adolescent visited our PERs after BNTI PERs: pediatric emergency rooms; BNTI: Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine immunization; SOB: shortness of breath, Ohers Ψ: including out-of-hospital cardiac arrest, numbness, tremor, skin rash, back pain, diarrhea, general sore pain, loss of consciousness, vomiting, flank pain, bradycardia and myalgia.

Table 1 Demographics of the patients visited our PERs with discomfort after 1st (Group A) or 2nd (Group B) dose BNTI.

	Total (n = 681, 100%)	Group A (n = 394, 57.9%)	Group B (n = 287, 42.1%)	*p* value
Age (years old)	15.1 ± 1.7	14.8 ± 1.8	15.4 ± 1.6	<0.001*
Junior high school age (12–15 yrs), n (%)	396 (58.1%)	242 (61.4%)	154 (53.7%)	0.043*
High school age (16–18 yrs), n (%)	285 (48.9%)	152 (38.6%)	133 (46.3%)	0.043*
Male gender, n (%)	398 (58.4%)	212 (53.8%)	186 (64.8%)	0.004*
Discomfort after BNTI (days), M (IQR)	3.0 (1.0–12.0)	4.0 (1.6–14.0)	2.0 (1.0–7.0)	<0.001*
Systolic blood pressure (mmHg) at PER	127.4 ± 18.1	125.8 ± 18.8	129.6 ± 17.0	0.007*
Diastolic blood pressure (mmHg) at PER	74.9 ± 12.1	74.6 ± 12.3	75.4 ± 11.8	0.350
Abnormal EKG findings at PER[a], n (%)	18 (2.6%)	9 (2.3%)	9 (3.1%)	0.495
Serum laboratories findings at PER				
White blood cell count (1000/uL)	7.9 ± 4.5	8.0 ± 5.0	7.7 ± 3.6	0.410
Hemoglobulin (g/dL)	14.4 ± 7.0	14.2 ± 5.8	14.7 ± 8.4	0.413
Platelet count (1000/uL)	276.4 ± 63.9	284.4 ± 63.1	264.7 ± 63.4	<0.001*
Troponin I (ng/mL), M (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.780
Troponin T (ng/L), M (IQR)	3.1 (1.5–4.7)	3.4 (1.5–4.7)	1.5 (1.5–4.6)	0.118
CK-MB (ng/mL), M (IQR)	1.1 (0.8–1.6)	1.0 (0.8–1.5)	1.1 (0.8–1.6)	0.640
NT-ProBNP (pg/mL), M (IQR)	18.2 (10.9–31.8)	18.4 (11.3–35.5)	18.1 (10.8–28.7)	0.234
BNP (pg/mL), M (IQR)	5.1 (2.5–8.8)	5.7 (2.5–10.1)	2.5 (2.5–6.9)	0.291
Serum Creatinine (mg/dL)	0.7 ± 0.3	0.7 ± 0.2	0.6 ± 0.1	0.801
C-reactive protein (mg/L), M (IQR)	0.9 (0.4–3.9)	0.5 (0.3–1.8)	2.9 (0.6–8.4)	0.001*
Diagnosis				
Pericarditis, n (%)	15 (2.2%)	11 (2.8%)	4 (1.4%)	0.220
Myocarditis, n (%)	12 (1.8%)	2 (0.5%)	10 (3.5%)	0.004*
Myopericarditis[b], n (%)	2 (0.3%)	0 (0%)	2 (0.7%)	0.097
Admission, n (%)	34 (5.0%)	15 (3.8%)	19 (6.6%)	0.096
Ward, n (%)	23 (3.4%)	13 (3.3%)	10 (3.5%)	0.895
PICU, n (%)	11 (1.6%)	2 (0.5%)	9 (3.1%)	0.007*
Discharge home, n (%)	647 (95.0%)	379 (96.2%)	268 (93.4%)	0.096
Survival, n (%)	681 (100%)	394 (100%)	287 (100%)	NA

PER: pediatric emergency room; BNTI: Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine immunization; yrs.: years old; M: median; IQR: interquartile range; EKG: Electrocardiogram; BNP = brain natriuretic peptide; PICU: pediatric intensive care unit.
NA: not applicable.
*$p < 0.05$.
[a] Including: ST-segment elevation, incomplete right bundle branch block, T wave inversion, tachy- and bradyarrhythmia, and first-degree AV block.
[b] Myopericarditis: according to Centers for Disease Control and Prevention Case Definitions for COVID-19 Vaccine-Associated acute myocarditis and pericarditis, this term may be used for patients who meet criteria for both myocarditis and pericarditis.[16–19]

In Table 2, patients admitted to PICU (Group D) were associated with 2nd dose BNTI ($p = 0.024$), lower SBP at PER ($p = 0.011$), lower DBP at PER ($p = 0.002$), more frequent of abnormal EKG findings at PER ($p = 0.041$), higher troponin I level ($p < 0.001$), higher CK-MB level ($p = 0.031$), higher CRP level ($p = 0.030$), more patients diagnosed with myocarditis ($p = 0.006$) and longer hospital LOS ($p < 0.001$). Patients admitted to ward (Group C) were associated with 1st dose BNTI ($p = 0.024$) and more pericarditis ($p < 0.001$) being diagnosed. There was no statistical difference regarding age, gender, triage classification, interval of discomfort after BNTI, patient's body height and body weight, WBC count level, Hb level, PLT level, prothrombin time, activated partial thromboplastin time, D-dimer level, troponin T level, NT-ProBNP level, BNP level, SCr level, lactate level, number of patients diagnosed with myopericarditis, or ejection fraction on heart echocardiogram.

A multivariate analysis of predictive factors for patients needing hospitalization in PICU due to BNTI-related pericarditis and myocarditis was conducted (Table 3) and indicated that abnormal EKG findings at PER (95% confidence interval [CI]: 0.036–0.976, $p = 0.047$) and abnormal serum troponin level at PER (95% CI: 0.002–0.296, $p = 0.003$) were statistically significant. After 1st or 2nd dose of BNTI, abnormal SBP and DBP at PER, abnormal serum CK-MB level at PER, and abnormal serum CRP level at PER were statistically significant in univariate analyses. Still, they were not retained in the final model of multivariate analyses.

4. Discussion

BNTI-related myocarditis in adolescents and subsequent hospitalization in PICU was a public safety concern and this study was the first original related observation report with novel finding in Taiwan. We observed that most chief discomfort complaints were chest pain, chest tightness or palpitation after 1st dose or 2nd dose of BNTI. More acute

Table 2 Comparison of adolescent admitted to ward (Group C) or PICU (Group D) due to BNTI-related myocarditis.

	Total (n = 29, 100%)	Group C (n = 18, 62.1%)	Group D (n = 11, 37.9%)	*p* value
Age (years old)	15.6 ± 1.5	15.3 ± 1.5	16.2 ± 1.5	0.128
Junior high school age (12–15 yrs), n (%)	12 (41.4%)	9 (50%)	3 (27.3%)	0.243
High school age (16–18 yrs), n (%)	17 (58.6%)	9 (50%)	8 (72.7%)	0.243
Male gender, n (%)	22 (75.9%)	14 (77.8%)	8 (72.7%)	0.768
Triage at PER				
Classification I, n (%)	1 (3.4%)	0 (0%)	1 (9.1%)	0.206
Classification II, n (%)	4 (13.8%)	1 (5.6%)	3 (27.3%)	0.107
Classification III, n (%)	24 (82.8%)	17 (94.4%)	7 (63.6%)	0.295
Discomfort after BNTI (days), M (IQR)	3.0 (2.0–15.0)	4.0 (2.3–15.0)	3.0 (2.5–10.5)	0.970
After 1st dose BNTI, n (%)	13 (44.8%)	11 (61.1%)	2 (18.2%)	0.024*
After 2nd dose BNTI, n (%)	16 (55.2%)	7 (38.9%)	9 (81.8%)	0.024*
Body Height (cm)	163.9 ± 6.8	164.6 ± 6.1	162.7 ± 8.0	0.479
Body Weight (kg)	57.0 ± 13.7	58.6 ± 15.8	54.2 ± 9.4	0.414
Systolic blood pressure (mmHg) at PER	123.8 ± 30.0	134.7 ± 16.3	116.6 ± 17.3	0.011*
Diastolic blood pressure (mmHg) at PER	74.3 ± 19.9	82.8 ± 10.2	66.5 ± 14.6	0.002*
Abnormal EKG findings at PER[a], n (%)	14 (41.4%)	6 (33.3%)	8 (72.7%)	0.041*
Serum laboratories findings at PER				
White blood cell count (1000/uL)	8.4 ± 2.2	8.3 ± 2.1	8.6 ± 2.4	0.674
Hemoglobulin (g/dL)	14.3 ± 1.9	14.5 ± 1.7	14.0 ± 2.2	0.448
Platelet count (1000/uL)	249.1 ± 52.6	252.8 ± 44.9	243.2 ± 65.1	0.642
Prothrombin time (s)	13.5 ± 3.7	12.5 ± 0.4	14.1 ± 4.6	0.414
aPTT (s)	30.7 ± 6.9	28.0 ± 0.7	31.9 ± 8.1	0.307
D-dimer (1000 ng/mL), M (IQR)	0.38 (0.23–0.64)	0.44 (0.38–0.63)	0.33 (0.20–0.95)	0.468
Troponin I (ng/mL), M (IQR)	0.2 (0.0–2.4)	0.0 (0.0–0.1)	4.9 (2.0–8.0)	<0.001*
Troponin T (ng/L), M (IQR)	5.6 (4.3–106.0)	4.9 (4.5–5.2)	106.0 (55.2–139.5)	0.252
CK-MB (ng/mL), M (IQR)	2.6 (1.3–16.0)	1.6 (1.2–2.7)	16.0 (8.4–47.0)	0.031*
NT-ProBNP (pg/mL), M(IQR)	38.3 (15.4–122.7)	27.0 (14.3–87.5)	98.5 (61.6–159.4)	0.943
BNP (pg/mL), M (IQR)	9.0 (5.5–19.3)	6.0 (5.5–7.5)	9.0 (5.0–19.5)	0.468
Serum Creatinine (mg/dL)	0.7 ± 0.3	0.7 ± 0.1	0.8 ± 0.5	0.627
C-reactive protein (mg/L), M (IQR)	4.9 (1.0–19.2)	3.0 (0.5–10.4)	16.3 (7.2–33.4)	0.030*
Lactate (mg/dL), M (IQR)	10.5 (9.2–11.5)	10.7 (10.6–13.5)	9.7 (9.1–11.4)	0.688
Diagnosis				
Pericarditis, n (%)	15 (51.7%)	14 (77.8%)	1 (9.1%)	<0.001*
Myocarditis, n (%)	12 (41.4%)	4 (22.2%)	8 (72.7%)	0.006*
Myopericarditis[b], n (%)	2 (6.9%)	0 (0%)	2 (18.2%)	0.064
EF on cardiac echocardiogram (%)	72.5 ± 10.6	75.3 ± 6.1	68.0 ± 14.6	0.069
COVID-19 PCR positive (NP), n (%)	0 (0%)	0 (0%)	0 (0%)	NA
Hospital LOS, M (IQR) (days)	4.0 (3.0–6.0)	3.0 (2.3–4.0)	7.0 (5.5–8.5)	<0.001*

PICU: pediatric intensive care unit; BNTI: Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine immunization; yrs.: years old; M: median; IQR: interquartile range; PER: pediatric emergency room; aPTT: Activated Partial Thromboplastin Time.
EKG: Electrocardiogram; BNP: brain natriuretic peptide; EF: Ejection fraction; COVID-19: coronavirus disease 2019.
NP: Nasopharyngeal; PCR: polymerase chain reaction; LOS: length of stay; NA: not applicable.
*$p < 0.05$.
[a] Including: ST-segment elevation, incomplete right bundle branch block, T wave inversion, tachy- and bradyarrhythmia and first-degree AV block.
[b] Myopericarditis: according to Centers for Disease Control and Prevention Case Definitions for COVID-19 Vaccine-Associated acute myocarditis and pericarditis, this term may be used for patients who meet criteria for both myocarditis and pericarditis.[16–19]

myocarditis and myopericarditis occurred in healthy adolescents after 2nd dose of BNTI; this result was similar to other reports from America, Europe, and Singapore.[7,8,20–24] Therefore, we considered that BNTI-related myocarditis might not have racial differences. More young male adolescents suffered from myocarditis after 2nd BNTI (myocarditis in 9 males and 1 female; pericarditis in 3 males and 1 female; myopericarditis in 2 male and 0 female patients) in our study, which was compatible with other studies in America, Europe, Korea, Hong Kong and Singapore.[8–10,20–26] All our patients with BNTI-related myocarditis had favorable outcomes without any mortality, so BNTI may be safe in most children and adolescents 12 years of age and older, which was the same as in other international reports.[8,23–29]

All our 681 enrolled participants were collected from PER, including 18 and 11 patients hospitalized to ward and PICU, respectively. The admission rate might have the

Table 3 Multivariable analyses of predictive factors for patients needing hospitalization in PICU due to BNTI-related myocarditis.

Parameters	95% CI	*p* value
After 1st or 2nd dose BNTI	0.028—1.219	0.079
Abnormal systolic blood pressure (mmHg) at PER	0.093—2.622	0.407
Abnormal diastolic blood pressure (mmHg) at PER	0.077—2.221	0.303
Abnormal EKG findings at PER[a]	0.036—0.976	0.047*
Abnormal serum troponin level at PER	0.002—0.296	0.003*
Abnormal serum CK-MB level at PER	0.029—7.211	0.577
Abnormal serum C-reactive protein level at PER	0.052—4.063	0.486

PICU: pediatric intensive care unit; BNTI: Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine immunization.
CI: confidence interval; PER: pediatric emergency room; EKG: Electrocardiogram.
*$p < 0.05$.
[a] Including: ST-segment elevation, incomplete right bundle branch block, T wave inversion, tachy- and bradyarrhythmia and first-degree AV block.

possibility of mild overestimation because not all patients with BNTI-related uncomfortable symptoms would visit PER; rather, they might be brought to pediatric outpatient department for milder complaints, where EKG and cardiac echocardiogram would be performed by the cardiology specialists. However, the epidemic prevention policy in our hospital during the pandemic of COVID-19 was that all patients needing admission must be referred to emergency room to complete COVID-19 polymerase chain reaction in order to achieve segregation of patients and flow control measures. Hence, admission numbers are be credible because those in need of ward or ICU hospitalization would be transferred to PER.[30]

In our study, the initial evaluation of BNTI-related myocarditis usually included measurement of serum WBC count, Hb level, PLT count, troponin level (troponin T or troponin I), CK-MB level, NT-ProBNP level, BNP level CRP level, SCr level, chest X rays and EKG, just like the initial evaluation for those under suspicion of typical myocarditis[8,31,32] at PER. There was only one fly in the ointment: some of our PERs check serum troponin I level, but others check serum troponin T level. Supportive care, medications for uncomfortable symptoms relief, and closely monitoring, including clinical manifestations and serum laboratories data, were mainstay strategies for those with mild or intermediate severity after BNTI[8,31,32]; intensive care would be arranged according to patients' clinical condition. Cardiac echocardiogram and cardiac magnetic resonance imaging (MRI) can also be used for the diagnostic and consequent prognosis evaluation of BNTI-related myocarditis.[8,12,27,33,34] Previous studies mentioned that cardiac MRI might be a potential differentiator in children and adolescents with multisystem inflammatory syndrome rather than myocarditis.[35] Cardiac MRI was performed in only four of our patients with BNTI-related myocarditis because their clinical symptoms were much more severe and persistent. The results were all compatible with recent myocarditis.

Though no obvious myocarditis was detected at PER initially in patients presenting with discomfort after 1st dose BNTI, some were still admitted to the ward (Group C) for observation and further examination on the following grounds: 1) the uncomfortable symptoms influenced their daily routine; and 2) physicians had no similar experience before and feared the poor progression of patients' clinical condition in reports regarding pericarditis and/or myocarditis occurrence in adolescents and young adults after BNTI.[7—12] These reasons might explain why Group C seems to be significantly related to 1st dose BNTI, rather than 2nd dose. Several possible mechanisms for mRNA-related myocarditis had been proposed, but these have not yet been elucidated clearly.[11,12] With increasing experience and research, the most hypothesized pathogenesis might be likely mediated through an autoimmune mechanism (autoantibody-mediated), causing increased prevalence of myocarditis after 2nd dose of mRNA COVID-19 vaccines,[11,12] which could account for why Group D was more significantly associated with 2nd dose BNTI.

Most of our patients admitted to ward or PICU were mild or intermediate severity without death. They were mainly healthy without history of hospitalization; only 6 patients had underlying diseases or had been hospitalized because of asthma with acute exacerbation, acute gastroenteritis caused by Norovirus, acute epididymitis and renal biopsy for Papillorenal syndrome with renal hypodysplasia. One case encountered serious and critical status due to fulminant myocarditis. She was a case of out-of-hospital cardiac arrest status under the cardiopulmonary resuscitation process in the ambulance during transfer. She was sent to our PICU for further intensive care management. Ventricular tachycardia with poor biventricular function and acute kidney injury were also noted subsequently. Veno-arterial extracorporeal membrane oxygenation for cardiogenic shock and continuous veno-venous hemofiltration program for acute kidney injury with unstable hemodynamic status were both been conducted for life support. She survived with mild residual sequelae due to intensive care and she gradually improved after following a tailored rehabilitation program.

Five patients had discomfort and were hospitalized in the ward post-BNTI, but they were not diagnosed with pericarditis or myocarditis. They were pneumothorax ($n = 3$), asthma with acute exacerbation ($n = 1$) and right hemisphere infarction related left side limbs weakness ($n = 1$). The serum laboratory findings in patient with right hemisphere infarction were all within the normal range. Still, she had the underlying disease of precursor B cell acute lymphoblastic leukemia in remission status. We could not be sure whether her right hemisphere infarction was associated with BNTI or her underlying disease.

Few previous reports presented the predictive factors for patients needing hospitalization in PICU compared to those in the ward because of COVID-19 vaccine or BNTI-related myocarditis. Multivariate analysis showed that abnormal EKG findings and serum troponin levels at PER could be two possible predictive factors. This could aid

physicians at PERs in early detection of patients at risk of critical conditions requiring intensive care.

According to the recommendations from the American Heart Association and the American College of Cardiology guidelines,[36] those who have suffered from myocarditis need to follow several precautions: 1) before returning to competitive sports, a resting cardiac echocardiogram and EKG should be performed 3—6 months after initial illness; 2) only when the ventricular systolic function returns to the normal range, and serum markers of myocardial injury have normalized, with absence of clinically relevant arrhythmias, can they then resume training and competition; and 3) those with probable or definite myocarditis should not participate in competitive sports while active inflammation is present.[36] Those who have had pericarditis must not participate in competitive sports during the acute phase regardless of its pathogenesis and they can only return to full activity when there is complete absence of pericardial effusion and serum markers of inflammation are within normal range.[36]

The long-term impact on children and adolescents of 12 years of age and older after COVID-19 mRNA vaccine-related myocarditis remains unknown. Further follow-up and surveillance of these patients will be required to assess health, cardiac function, and complications; and there may be an interval of at least 3—6 months after the initial illness before they can return to usual, competitive activity according to the American Heart Association and the American College of Cardiology guidelines.[36]

4.1. Limitations

This study had some limitations. First, it is possible that patients with mild or self-limited discomfort might not be reported, so our result may be underestimated. Second, as our cases came only from a single tertiary care hospital, the number of patients with BNTI-related myocarditis was relatively small. Additional multicenter studies of larger cohorts are required to identify the accurate incidence rate of myocarditis and to clarify the predictive factors for patients needing hospitalization in PICU compared to those in ward from PER. Third, there might exist a selection bias of total enrolled cases. We could not collect all adolescents visiting our hospital with discomfort after BNTI because some of them with milder complaints might have visited the pediatric outpatient department for EKG and cardiac echocardiogram examination instead of PER. Fourth, cardiac MRI was not applied in all of our patients with BNTI-related myocarditis. Standardized protocols may be considered for cardiac MRI acquisition. Last but not least, the information on long-term follow-up and surveillance for patients' cardiac function, serum markers of cardiac enzyme, and outcome after returning to usual competitive activity is lacking, and further evaluations may be needed.

5. Conclusions

BNTI-related myocarditis seems to be more common after 2nd dose of BNTI in patients aged 12—18 years according to our observational study. Most cases of pericarditis, myocarditis, or myopericarditis were of mild or intermediate severity without death, so that BNT162b2 may be safe in most children and adolescents 12 years of age and older. Abnormal EKG findings and abnormal serum troponin level at PER were noted to be two predictive factors associated with subsequent hospitalization in PICU in adolescents with BNTI-related myocarditis. However, this risk should still be considered in the context of the benefits from BNTI.

Availability of data and materials

The datasets analyzed during the current study are not publicly available because the data are part of the patients' medical record and are treated as confidential. A completely de-identified version of the data is available from the corresponding author on reasonable request, following approval of the institutional review board.

Ethics approval and consent to participate

All methods were carried out in accordance with the relevant guidelines and regulations in accordance with the Declaration of Helsinki. The need to obtain informed consent from participants was waived because this is a purely retrospective study that does not affect patient care. This waiver was approved by Ethics Committee on Human Studies at Chang Gung Memorial Hospital, in Taiwan, R.O.C. (202200782B0). The study was approved by the Ethics Committee on Human Studies at Chang Gung Memorial Hospital, in Taiwan, R.O.C.

Declaration of competing interest

All authors declare that they have no competing of interest.

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Abbreviations

COVID-19	coronavirus disease 2019
BNT162b2	Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine
BNTI	Pfizer-BioNTech 162b2 mRNA COVID-19 vaccine immunization
PICU	pediatric intensive care unit
PER	pediatric emergency room

Appendix A. Supplementary data

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