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RESEARCH

Changes of ECG parameters after BNT162b2 vaccine in the senior high school students

Shuenn-Nan Chiu[1] · Yih-Sharng Chen[2] · Chia-Chen Hsu[4,5,6] · Yu-Chuan Hua[7] · Wei-Chieh Tseng[1,3] · Chun-Wei Lu[1] · Ming-Tai Lin[1] · Chun-An Chen[1] · Mei-Hwan Wu[1] · Yu-Ting Chen[8] · Ting-Chou Hung Chien[8] · Chien-Lun Tseng[8] · Jou-Kou Wang[1]

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Abstract

The purpose of this study is to determine the ECG parameter change and the efficacy of ECG screening for cardiac adverse effect after the second dose of BNT162b2 vaccine in young population. In December 2021, in cooperation with the school vaccination system of Taipei City government, we performed a ECG screening study during the second dose of BNT162b2 vaccines. Serial comparisons of ECGs and questionnaire survey were performed before and after vaccine in four male-predominant senior high schools. Among 7934 eligible students, 4928 (62.1%) were included in the study. The male/female ratio was 4576/352. In total, 763 students (17.1%) had at least one cardiac symptom after the second vaccine dose, mostly chest pain and palpitations. The depolarization and repolarization parameters (QRS duration and QT interval) decreased significantly after the vaccine with increasing heart rate. Abnormal ECGs were obtained in 51 (1.0%) of the students, of which 1 was diagnosed with mild myocarditis and another 4 were judged to have significant arrhythmia. None of the patients needed to be admitted to hospital and all of these symptoms improved spontaneously. Using these five students as a positive outcome, the sensitivity and specificity of this screening method were 100% and 99.1%, respectively.

Conclusion: Cardiac symptoms are common after the second dose of BNT162b2 vaccine, but the incidences of significant arrhythmias and myocarditis are only 0.1%. The serial ECG screening method has high sensitivity and specificity for significant cardiac adverse effect but cost effect needs further discussed.

What is Known:

- *The incidence of cardiac adverse effects was reported to be as high as 1.5 per 10 000 persons after the second dose BNT162b2 COVID-19 vaccine in the young male population based on the reporting system.*

What is New:

- *Through this mass ECG screening study after the second dose of BNT162b2 vaccine we found: (1) The depolarization and repolarization parameters (QRS duration and QT interval) decreased significantly after the vaccine with increasing heart rate; (2) the incidence of post-vaccine myocarditis and significant arrhythmia are 0.02% and 0.08%; (3) The serial ECG screening method has high sensitivity and specificity for significant cardiac adverse effect.*

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✉ Jou-Kou Wang
jkww@ntuh.gov.tw

[1] Department of Pediatrics, National Taiwan University Hospital and Medical College, National Taiwan University, No. 7, Chung-Shan South Road, Taipei 100, Taiwan

[2] Department of Surgery, National Taiwan University Hospital and Medical College, National Taiwan University, Taipei, Taiwan

[3] Department of Emergency Medicine, National Taiwan University Hospital and Medical College, National Taiwan University, Taipei, Taiwan

[4] Graduate Institute of Gerontology and Health Care Management, Chang Gung University of Science and Technology, Taoyuan, Taiwan

[5] Department of Otorhinolaryngology, Taipei City Hospital, Taipei, Taiwan

[6] Department of Exercise and Health Sciences, University of Taipei, Taipei, Taiwan

[7] Cardiac Children's Foundation Taiwan, Taipei, Taiwan

[8] QT Medical, Incorporated, Taipei, Taiwan

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Abbreviations

COVID-19	Coronavirus disease 2019
ECG	Electrocardiogram

Introduction

Since the initial outbreak of COVID-19 in Wuhan, China, in early 2020, the COVID-19 pandemic has become the main health issue worldwide [1]. Although general protection and personal hygiene are important, there are many in the medical community who believe that a vaccine is the ultimate solution for preventing COVID-19. Several types of vaccine have been proposed, but only mRNA vaccines (BNT162b2 and mRNA-1273-Moderna) have been approved for use in adolescents [2, 3]. However, mRNA vaccines can cause adverse cardiovascular effects, such as peri- and myocarditis, especially in the young [4, 5]. Although the incidence of myocarditis is low, there was still concern about subclinical myocarditis and arrhythmia events in these patients [6, 7].

In Taiwan, through strict public health quarantine and mask policy, the incidence of COVID-19 is low (0.1% of total population till Mar 31, 2022) [8]. High school students began to receive mass vaccination with BNT162b2 in September 2021. The second dose was given 12 weeks after the first. The Taiwanese Severe Infectious Pneumonia Central Command Center decided on this delay vaccination with the second dose considering both the shortage of vaccines and recipients' safety [8]. Here, we performed a study of ECG screening for the detection of BNT126b2-related cardiac adverse effects in senior high school students in Taipei City, Taiwan. We investigated the ECG parameters changes and the incidence of cardiac adverse effect after the second dose of BNT162b2 vaccination.

Methods

Participants

In Taiwan, BNT162b2 vaccine was administered to school-aged students (aged 12 to 18) through a school-based system. All students in the same high school who were willing to receive BNT162b2 vaccine received it on the same day in the school, which was supported by Taipei City Hospital. In the present study, in cooperation with the school vaccination system of Taipei City government, we performed mass ECG screening of students willing to receive a second dose of BNT162b2 vaccine in December 2021. We enrolled students at four male-predominant senior high schools (Taipei Municipal Jianguo High School, Taipei Municipal Chenggong High School, Taipei Municipal Da-An Vocational High School, and Taipei Municipal Nangang Vocational High School) as a study population. A flow chart of the participant selection is presented in Fig. 1. The study was approved by the Ethical Committee and Institutional Review Board of the National Taiwan University Hospital (202109018RINA). For all participants, written informed consent was obtained from the students and their parents before the study. The participants received a pre-vaccine questionnaire (Supplementary) about their symptoms after the first dose of BNT162b2 and underlying comorbidities. Standard 12-lead ECGs were obtained 1 to 10 days before the second dose of BNT162b2. Two days after the second dose of BNT162b2, 12-lead ECGs and post-vaccine questionnaire were again obtained for all participants.

ECG screening and data analysis

The ECG screening was performed in the sports halls of these high schools. We performed three sets of standard 12 leads ECGs at sitting position in each student, and the ECG with the best quality was selected for evaluation. The ECG data were transferred wirelessly to the cloud (QT Cloud; QT Medical Inc.) and analyzed using an ECG diagnostic system (QTM-DX; QT Medical, Inc.). In addition, the pre- and post-vaccine ECGs were compared using the serial comparison function of QTM-DX (Supplementary Fig. 1, online). The criteria of significant change were listed in Supplementary Table 1 and any ECG fulfilled the criteria was checked by a pediatric cardiologist immediately through the cloud dashboard. If a case was judged as possibly involving myocarditis or significant arrhythmia, the students were informed immediately and referred to a hospital for further analysis. We contacted these students or school nurses for information on their disease progression, hospitalization, and final diagnosis. The detailed information of vaccination and post-vaccine cardiac adverse effects of all other students were collected from the school nurses and school vaccination reporting system of the Health Bureau of Taipei City government 1 month after vaccine.

The definition of myocarditis is based on a CDC working definition with some modification [9]. According to the definition, the diagnosis of probable myocarditis require at least 1 cardiovascular symptoms or signs, including chest pain, chest tightness, palpitation, or dyspnea, accompanied with at least 1 abnormal test, including elevated cardiac troponin T, abnormal ECG finding, decreased function on echocardiography, or cardiac magnetic resonance (CMR) which shows positive finding. In confirmed myocarditis, the patient should have cardiovascular symptoms and signs, with

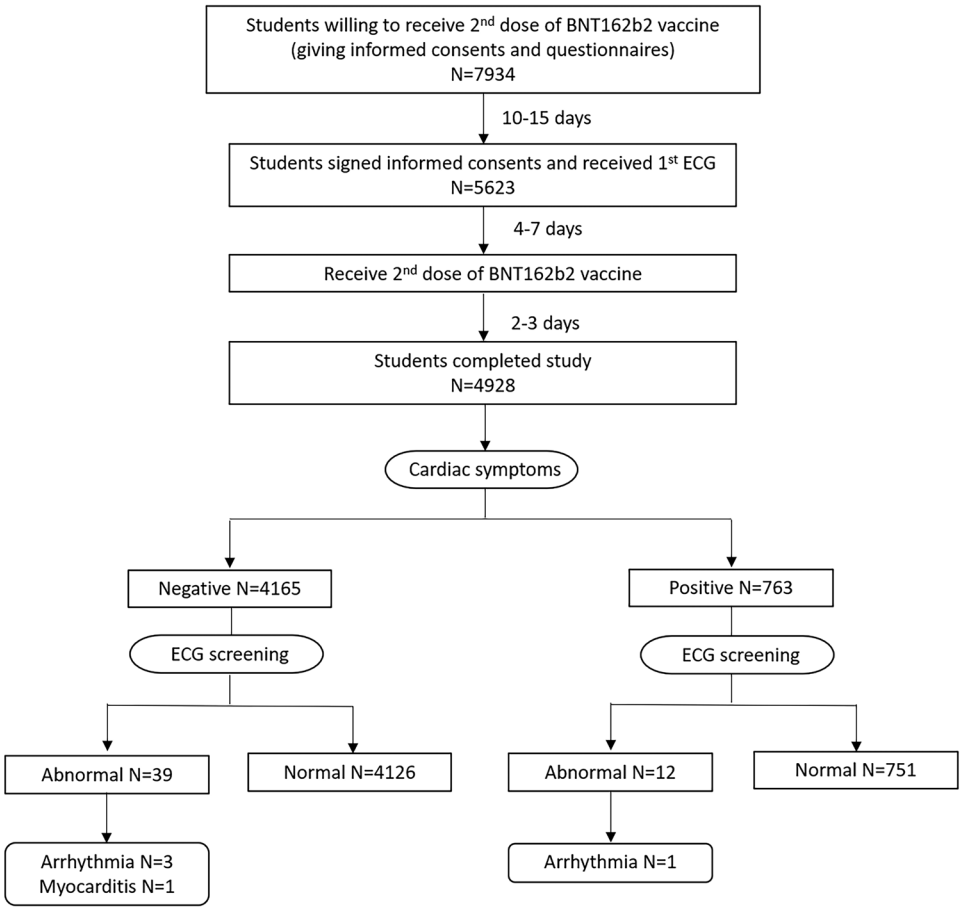

Fig. 1 Flow chart of the mass ECG screening and the case numbers. Overall, 70.8% of those willing to receive a second dose of BNT162b2 vaccine provided written informed consent and underwent pre-vaccine ECG. Among them, 87.6% (4928 students) underwent second ECG and completed the study. Because the students could request sick leave for the first 2 days after vaccination based on government policy, some of the students did not go to school and missed the second ECG screening. This flow chart also showed the brief outcome result in this study

the confirmation of diagnosis by endomyocardial biopsy or elevated cardiac troponin T plus CMR confirmation.

Data collection and statistics

All ECG parameters and depolarization and repolarization changes were analyzed initially by QTM-DX, and then double-checked by pediatric cardiologists.

Data are expressed as mean (standard errors). Paired Student's *t*-test was used for the numerical data analysis, and chi-squared or Fisher's exact test was used for the categorical data analysis. A *P*-value < 0.05 was considered significant.

Results

Cardiac symptoms and incidence of cardiac adverse events after BNT162b2 vaccine

Among 7934 eligible students, 4928 (62.1%) completed the pre- and post-vaccine ECGs. The male/female ratio was 4576/352. The mean age was 16.7 (0.9) years. Underlying disease was present in 109 (2.2%) of the patients, with simple congenital heart disease in 33, mitral valve prolapses in 36, arrhythmia in 36, Kawasaki disease in 11, and previous myocarditis in 2. Among the subjects, 9 had more than one underlying disease.

From the questionnaire, the incidence of cardiac-related symptoms after the second dose BNT162b2 vaccine was 17.1%, which was significantly higher than that of the first dose (5.7%, Table 1). The individual items of cardiac-related symptoms as chest pain, palpitations, and dizziness or syncope were significantly higher after the second dose of BNT162b2 vaccine ($p < 0.001$).

After comparisons of the pre- and post-vaccine ECGs by pediatric cardiologists, 51 (1.03%) students were judged to have

Table 1 The incidence of cardiac related symptoms after the 1st and 2nd dose of BNT162b2 vaccine in our cohort

	After 1st dose	After 2nd dose	*P* value
Palpitation	62 (1.3%)	373 (8.5%)	<.001
Chest pain	102 (2.1%)	394 (8.9%)	<.001
Dyspnea	51 (1.0%)	17 (0.4%)	<.001
Dizziness or syncope	109 (2.2%)	151 (3.4%)	<.001
Any of the cardiac symptoms	280 (5.7%)	763 (17.1%)	<.001

Table 2 The significant ECG change comparing the pre- and post-vaccine ECG in 4928 students

	Number (%)	Incidence
ST-T change (elevation ≥ 2 mm or new T wave inversion)	37 (72.5%)	0.75%
Arrhythmia	7 (13.7%)	0.14%
Premature ventricular contractions (all new onset)	4 (7.8%)	0.08%
Sinus bradycardia	2 (3.9%)	0.04%
Atrial tachycardia	1 (2.0%)	0.02%
BBB (all new incomplete right bundle branch block)	3 (5.9%)	0.06%
Abnormal QRS (QRS axis change > 45 degrees or sum of chest leads' (R + S) decreased by > 30%)	2 (3.9%)	0.04%
Prolong QT (QT interval increase > 20 ms)	2 (3.9%)	0.04%
Total	51 (100%)	1.03%

significant ECG change after vaccination. The distribution of ECG change is shown in Table 2. Among these 51 students, 12 had cardiac-related symptoms and 31 students were asymptomatic. Thirty-three students sought medical help after positive screening findings. After referral to hospital, with serial examinations including troponin T, C-reactive protein, and follow-up ECG in all, and echocardiography in selected patients, only one (0.02%) asymptomatic boy (patient No 1, Table 3) with new-onset premature ventricular contractions (PVCs) was found to have mildly elevated troponin T. He was followed at an outpatient clinic due to probable myocarditis (Supplementary Fig. 1A). The laboratory data normalized 10 days after vaccine. Ten subjects (23.2%) were suspected of having pericarditis due to ST-T change and increased C-reactive protein, with or without chest pain symptoms, but echocardiography provided negative results in all cases (Supplementary Fig. 1B). Another 4 boys with arrhythmias (patient No 2–5 in Table 3: 2 with sinus bradycardia, 1 with PVCs, and 1 with atrial tachycardia) were judged as significant arrhythmia by pediatric cardiologists (Supplementary Fig. 1C). Three of them who sought medical help showed normal troponin level and normal cardiac function. These 3 patients improved upon follow-up at an outpatient

Table 3 The clinical characteristics and ECG finding in 5 patients with significant cardiovascular adverse events

No.	Age (yeas)	Sex	Pre-vaccine ECG		symptoms		Post-vaccine ECG	Referral examination	Outcome
			Heart rate	Other abnormal finding		Heart rate	Other abnormal finding		
1	17	M	70	None	None	88	new onset PVC	Troponin T elevated to 19 ng/L 6 days after the vaccine. CMR normal 20 days after the vaccine	Troponin T normalized at 10 days
2	18	M	62	None	None	77	new onset PVC	Troponin T, CRP, and echocardiography all normal. Holter showed 4% PVC	No symptoms complained
3	15	M	72	None	Chest pain	51	sinus bradycardia	Troponin T, CRP, and echocardiography all normal	Follow-up heart rate normal
4	16	M	71	None	None	44	sinus bradycardia	Troponin T, CRP, and echocardiography all normal	Follow-up heart rate normal
5	17	M	81	None	None	163	atrial tachycardia	Refuse referral due to no symptoms. Subjective normal heart rate by telephone contact 3 days and 1 month later	

PVC premature ventricular complex, *ECG* electrocardiogram

clinic. In these 5 students with significant arrhythmia or myocarditis, only 1 had a cardiac-related symptom. After 1 month of follow-up, no other students enrolled in the present study were diagnosed with myocarditis or other serious cardiac events based on the school reporting system. We also tracked the clinical courses in 18 of the 51 students, who did not adhere to the recommendation of referral, and all showed no symptoms during 1-month follow-up.

ECG parameters change

The ECG parameter change before and after vaccination is shown in Table 4. The heart rate increased significantly after the vaccine, with a mean increase of heart rate of 2.6 beats per minute (bpm). With this increase, the QRS duration, QT, QTc, and QTcf interval also decreased significantly after the vaccine (Supplementary Fig. 2). To adjust for the influence of heart rate change, we used a linear regression model. After correction, the QRS duration, QT interval, QTc interval, and QTcf interval decreased 0.9, 3.8, 4.1, and 3.9 ms after the vaccination. The QT interval decreased with heart rate, while the QTc interval increased with it. The QTcf showed no significant change with heart rate.

Accuracy and cost of ECG screening for BNT162b2-related cardiac adverse events

Using the 5 patients who exhibited significant cardiac adverse effects (1 with myocarditis and 4 with new-onset significant arrhythmia), the sensitivity and specificity of the screening method were determined (Supplementary table 2). Using the current screening method via serial comparison of ECGs, both the sensitivity and the specificity to detect significant cardiac adverse effects were very high, at 100% and 99.1%, respectively. The positive and negative predictive values were 9.8% and 100%, respectively. However, if we used only post-vaccine ECG to screen for cardiac adverse effect, the specificity would have dropped to 86.0% and positive predictive value would be only 0.72%. The total cost of the present study was US$70,234, which corresponded to US$14.3 per student (Supplementary table 3). The cost of identifying a case of clinically significant cardiac adverse effect is US$14,094.

Table 4 EKG parameters change before and after the 2nd dose of BNT162b2 vaccine

ECG parameters	Pre-vaccine	Post-vaccine	Paired difference	*P* value
Heart rate (bpm)	81.2 (13.4)	83.8 (13.2)	2.6 (13.4)	<.001
QRS duration (ms)	94.0 (11.0)	92.9 (9.5)	−1.1 (8.8)	<.001
QT (ms)	349.7 (24.3)	342.4 (23.2)	−7.3 (21.2)	<.001
QTc (ms)	405.0 (18.8)	402.9 (17.8)	−2.1 (16.7)	<.001
QTcf (ms)	385.3 (15.3)	381.4 (14.6)	−4.0 (11.9)	<.001

Discussion

From this mass ECG screening study after the second dose of BNT162b2 vaccine, several important findings were obtained: (1) Although cardiac-related symptoms were fairly common, the incidence of myocarditis was 0.02%. (2) The depolarization and repolarization parameters (QRS duration and QT interval) decreased significantly after the vaccine with increasing heart rate, and new onset significant arrhythmia was 0.08% after vaccination in this healthy young population. (3) ECG screening with pre- and post-vaccine comparison had high sensitivity and specificity to detect significant cardiac adverse effects.

Cardiac-related adverse events after BNT162b2 vaccination

Among various vaccines that are available, mRNA vaccines are the only ones approved for use in teenagers [2, 4]. BNT162b2 has a better safety profile than mRNA-1273 Moderna, and is widely used for teenagers worldwide [5, 10, 11]. However, cardiac-related adverse effects, as peri- and myocarditis, are of particular concern because of possible serious complications [12]. In early June 2021, the US Food and Drug Administration issued a warning about the rare adverse effect of myocarditis after being administered mRNA COVID-19 vaccines [13]. In a report from the USA, the incidences of myocarditis were 70.7 and 105.8 cases per million in 12–15- and 16–17-year-old males receiving a second dose of the BNT162b2 vaccine [14]. In a study in Israel, the incidence of myocarditis after a second dose of BNT162b2 was 1.51 per 10,000 in 16–19-year-old males [15, 16]. In the present study, no clinical myocarditis was diagnosed and only one case of subclinical mild myocarditis was found among 4928 students. This result corresponds with previous findings that the incidence of clinical and even subclinical myocarditis is very low in those receiving a BNT162b2 vaccine.

In addition to myocarditis, arrhythmia is also aconcern after receiving an mRNA vaccine. Several previous reports described non-sustainedventricular tachycardia and even sudden cardiac death in patients with COVID-19vaccine-related myocarditis [16–18]. Nevertheless, a recentlarge-scale study in the UK showed no increase of cardiac arrhythmia after receivingthe COVID-19 vaccine, except for the second dose of the mRNA-1273 vaccine [11]. In the present-study, compared with the baseline ECG, only 4 patients had new-onset significantarrhythmia, including PVCs, extreme

sinus bradycardia, and atrial tachycardia. Therefore, we speculated that, after the second dose of BNT162b2vaccine, the new onset arrhythmia does occur in some patients but incidence isonly 0.08%. The arrhythmia triggering effect by BNT162b2 vaccine needs furtherstudy to elucidate.

Change of ECG parameters after vaccination

Prolonged QT interval is an important marker of repolarization heterogeneity, ventricular arrhythmia and poor prognosis in patients with channelopathy, heart failure, and cardiomyopathy [19–22]. Testing of QT interval is also prerequisite in new drug development [23]. In the present study, after BNT162b2 vaccination, the QRS duration and QT/QTc/QTcf interval were not prolonged and actually got shorter after correction for heart rates. The initial clinical trial of BNT162b2 has shown the incidence of side effects as fever and chills was nearly doubled compared to that of the 1st dose [3]. In the present study, we also found the cardiovascular related symptoms were significantly higher after the 2nd dose of BNT162b2 vaccine compared to that of the 1st dose. Therefore, the increasing heart rate and shortening of QRS duration and QT interval may relate to high sympathetic tone after the 2nd dose of BNT162b2 vaccine. Through this finding, we suggest that the BNT162b2 vaccine is unlikely to cause repolarization heterogeneity and subsequently life-threatening arrhythmia in the healthy young population.

ECG screening for mRNA vaccine-related myocarditis

ECG, as a noninvasive and inexpensive tool, is frequently used for mass screening of the risk of sudden cardiac death and cardiovascular disease in both athletes and school-aged students [24–28]. However, to the best of our knowledge, it has never been used for the screening of myocarditis. In conventional viral myocarditis, at-risk patients are difficult to define and the time from infection to disease onset is short. However, in patients with myocarditis related to mRNA vaccine, the onset of symptoms is around 2 to 7 days after vaccination, and high-risk patients have already been defined, that is, young males receiving a second dose of mRNA vaccine [14, 15]. Kaltman et al. defined the key questions for determining whether it is worthwhile to conduct a screening program [29]. Regarding BNT162b2-related myocarditis, this condition is an important public health issue and can affect the vaccination rate. The duration from the vaccination to disease onset is often longer than 2 days. ECG is an acceptable, safe, and inexpensive method, and the early recognition and early treatment of myocarditis can decrease morbidity and mortality. Therefore, post-vaccine myocarditis may be worth screening. However, whether ECG screening can adequately recognize the targeted condition in these high-risk young males is unknown.

From the present study, using the comparison of pre- and post-vaccine ECG screening, both sensitivity and specificity were very high, at 100% and 99.1%, respectively. The effectiveness of this screening method is thus acceptable. Nevertheless, the cost-effectiveness of screening for BNT162b2-related cardiac adverse effects require further discussion because of mostly benign course of mRNA vaccine-related cardiac adverse effects and high cost of screening. The focusing study on high-risk patients may be another consideration.

Study limitations

Because of financial and understaffed constraints, we enrolled the students of only four schools to participate in this study. This limited the statistical power of this study to find patients with myocarditis. However, we were nonetheless able to enroll 4928 patients and the obtained data of pre- and post-vaccine ECGs are valuable. The vaccination rate is low in the study population. It is because (1) the incidence of COVID-19 at the study period in our country was low; (2) the students and their parents were afraid of vaccine related adverse effects due to media exaggeration; and (3) not all patients who received the 2nd dose of BNT162b2 vaccine completed the study. These all decrease the study power of the present study.

We performed the ECG screening during the 2nd dose of BNT162b2 vaccine as the cardiac adverse effects were higher after the 2nd dose. Therefore, the pre-vaccine ECG was actually after 1st vaccine dose. Nevertheless, the 1st ECG screening in the present study was at least 10 weeks after the 1st vaccine which may mitigate the influence of the vaccine. Although the ECG change may be more significant around 3–4 days after vaccine, we perform ECG 2 days after vaccination to see if this policy can be the tool of early detection of cardiac adverse events. This could decrease the detection rate of cardiac adverse effects.

In the present study, we relied on the school reporting system for the serious cardiac outcomes including arrhythmia and myocarditis/pericarditis, and not all of the students receive complete cardiology workup including troponin, echocardiography, and Holter ECG monitoring. In addition, still 18 of patients with ECG changed did not seek for medical investigation after positive screening result. These may underestimate the incidence of minor form myocarditis/pericarditis and arrhythmia.

As many students with severe underlying disease, especially cardiomyopathy or severe congenital heart disease, would not receive COVID-19 vaccine at school system by government policy, we cannot know whether the current findings apply to those with severe underlying disease.

Conclusion

After the second dose of BNT162b2 vaccine in a young population, cardiac-related symptoms were common. The incidences of subclinical myocarditis and significant arrhythmia were 0.1%. Serial ECG screening had high sensitivity and specificity to detect significant cardiac adverse effect.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-022-04786-0.

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Authors' contributions Shuenn-Nan Chiu: conceptualized and designed the study, coordinated and collected the data, investigation, methodology, project administration, drafted the initial manuscript, analyzed the initial study, and reviewed and revised and final proved the manuscript. Chia-Chen Hsu: conceptualized and designed the study, analyzed the study, coordinated and supervised data collection, investigation, methodology, project administration, critically revised the initial manuscript, reviewed and revised and final proved the manuscript. Yih-Sharng Chen, Yu-Chuan Hua, Jou-Kou Wang: conceptualized and designed the study, funding acquisition, analyzed the study, coordinated and supervised data collection, investigation, methodology, project administration, critically revised the initial manuscript, reviewed and revised and final proved the manuscript. Wei-Chieh Tseng, Chun-Wei Lu, Ming-Tai Lin, Chun-An Chen, Mei-Hwan Wu: coordinated and collected the data, investigation, methodology, project administration, revised the initial manuscript, reviewed and final proved the manuscript. Yu-Ting Chen, Ting-Chou Hung Chien, Chien-Lun Tseng: coordinated and collected the data, software management, investigation, methodology, project administration, revised the initial manuscript, reviewed and final proved the manuscript.

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Data availability The original data is available when requested.

Declarations

Competing interests The authors declare no competing interests.

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