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Safety and Efficacy of a Third Dose of the BNT162b2 Vaccine in Liver-Transplanted and Healthy Adolescents

*Palittiya Sintusek, MD, PHD, †‡Supranee Buranapraditkun, PHD, *Siriporn Khunsri, MSC, §Thanunrat Thongmee, PHD, §Preeyaporn Vichaiwattana, PHD, ‖Warunee Polsawat,MSC, and §Yong Poovorawan, MD

ABSTRACT

Objectives: According to our previous study, the 2-dose-BNT162b2 vaccination is less effective against the Omicron variant. This study aimed to assess the safety and efficacy of a 3-dose-BNT162b2 vaccination in liver-transplanted (LT) and healthy adolescents.

Methods: LT and healthy adolescents who met the inclusion criteria received a third dose of the BNT162b2 vaccine (30 μg). Antireceptor-binding domain immunoglobulin and T-cell-specific responses to severe acute respiratory syndrome coronavirus 2 spike peptides were assessed 3 months before the third dose (Visit −1) and 0 (Visit 0), 1 (Visit 1), and 2 months (Visit 2) after the third dose. Antinucleocapsid immunoglobulin and neutralizing antibodies were assessed at Visits 0 and 1. Adverse events (AEs) were monitored.

Results: Eleven LT and 14 healthy adolescents aged 14.64 (13.2, 15.7) years (44.2% male) had antireceptor-binding domain immunoglobulin geometric mean titers of 1412.47 (95% confidence interval [CI], 948.18–2041.11) and 1235.79 (95% CI, 901.07–1705.73) U/mL at Visit −1 but increased to 38 587.76 (95% CI, 24 628.03–60 460.18) and 29 222.38 (95% CI, 16 291.72–52 401.03) U/mL ($P < 0.05$) at Visit 1, respectively. This was consistent with neutralizing antibodies (42.29% and 95.37% vs 44.65% and 91.68%, $P < 0.001$) and interferon-γ-secreting cells in LT and healthy adolescents at Visit 0 versus Visit 1, respectively. For serious AEs, an LT girl with autoimmune overlap syndrome died 5 months postvaccination from acute liver failure.

Conclusions: In both LT and healthy adolescents, humoral and cellular immune responses were high after the 3-dose-BNT162b2 vaccination. However, serious AEs were suspected in LT adolescents with autoimmune diseases.

What Is Known

- The 2-dose BNT162b2 vaccination is less effective against the Omicron variant in both liver-transplanted (LT) and healthy adolescents.
- The serious short-term adverse events of the BNT162b2 vaccine in a healthy population are very rare and far outweigh the benefits of vaccines in terms of lives saved and disease severity reduction.

What Is New

- The humoral and cellular immune responses to the Omicron variant after the 3-dose BNT162b2 vaccination were high and comparable in LT and healthy adolescents.
- Immune-mediated liver injury after BNT162b2 vaccination is rare but it may occur, particularly in LT adolescents with underlying autoimmune diseases.

Key Words: third dose, booster, BNT162b2, liver transplant, adolescent, coronavirus disease 2019

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is considered a major global burden. Vaccination is an effective strategy for preventing infection and reducing individual morbidity if an infection does occur (1,2). Although the BNT162b2 vaccine has been approved for use in children over the age of 12 since May 2021, data on its efficacy and safety in immunocompromised hosts, including liver-transplanted (LT) adolescents, is scarce. Only one study from our group (3) and one from Spain (4) demonstrated that LT adolescents had a good immunogenic response after a 2-dose regimen (30 μg) of the BNT162b2 vaccine. However, during the era of virus mutation from the Delta variant (B1.617.2) to the Omicron variant (B1.1.529), none of the LT adolescents and only one-third of healthy adolescents had positive surrogate virus-neutralizing antibodies (NAs) (>30%) to the Omicron variant (B1.1.529) (3). Furthermore, the adverse events (AEs) of the BNT162b2 vaccine were mostly reported in short-term follow-ups, ranging from a week to approximately 2 months after the second dose (5,6). However, the vaccine's AEs should be monitored for a longer period of time, particularly in patients with underlying diseases that cause immune dysregulation.

Since the 2-dose BNT162b2 vaccine is less effective against Omicron variants than the Delta variant (B.1.617.2), a booster dose has been authorized in many countries for healthy adults and adolescents who received the second dose 5 months earlier (7–9). However, data on the efficacy of a 3-dose BNT162b2 vaccine in vulnerable adolescents with underlying diseases, such as juvenile-onset inflammatory rheumatic diseases (10), inflammatory bowel disease (11),

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From the *Thai Pediatric Gastroenterology, Hepatology and Immunology (TPGHAI) Research Unit, Division of Gastroenterology, Department of Pediatrics; †Division of Allergy and Clinical Immunology, Department of Medicine, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Thai Red Cross Society, Bangkok, Thailand; ‡Center of Excellence in Vaccine Research and Development (Chula Vaccine Research Center-Chula VRC), Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; §Center of Excellence in Clinical Virology, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, The Thai Red Cross Society, Bangkok, Thailand; and ‖Excellent Center for Organ Transplantation, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand.

Correspondence: Palittiya Sintusek, MD, PhD, Thai Pediatric Gastroenterology, Hepatology and Immunology (TPGHAI) Research Unit, Division of Gastroenterology, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, The Thai Red Cross Society, Bangkok 10330, Thailand. E-mail: Palittiya.s@chula.ac.th

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solid organ transplant recipients (12), and kidney transplant recipients (13), are scarce. In addition, data on antibody response to a booster dose in solid organ transplant recipients were obtained from a small sample of LT adolescents, which could not be generalized (12). Hence, the present study aimed to compare the efficacy and safety of the second and third doses of the BNT162b2 mRNA vaccine in LT adolescents to that in healthy adolescents. Long-term AEs associated with vaccination were also assessed in LT adolescents. Based on the result of this study, it should guide the appropriate regimen of COVID-19 vaccine for LT adolescents in the era of virus mutation.

METHODS

Study Design and Target Population

The present study is an ongoing prospective study that assessed the immunogenicity of the BNT162b2 mRNA vaccine in LT and healthy adolescents who had previously received the second dose (3). The eligible LT and healthy adolescents were recruited to receive the third dose of the BNT162b2 vaccine, while those receiving a booster dose of another COVID-19 vaccine, having unstable conditions (eg, high-grade fever), or unwilling to receive a booster dose were excluded from the study.

This clinical trial was previously registered in the Thai Clinical Trial Registry (TCTR20210830002) and approved by the Institute Research Board at Chulalongkorn University, Thailand (IRB no. 715/64).

After completion of informed consent, participants received a third dose (30 μg) of the BNT162b2 vaccine at least 6 months after the second dose. The exclusion criteria were participants who received other vaccines for COVID-19, no willing to participate in the study and dead. Blood samples were collected at 4-time points: 3 months after the second dose (Visit −1), the day before the third dose (Visit 0), Days 21–35 (Visit 1), and Days 50–70 (Visit 2) after the booster dose.

Adverse Events

All participants were monitored for 30 minutes following vaccination for any immediate AEs. On Days 0–7, a questionnaire about specific local and systemic symptoms after a booster dose was completed by the participants or their guardians via a Google form. The severity of AEs was graded into mild, moderate, severe, and hospitalization. The LT adolescents were continuously monitored at the LT clinic for liver injury by assessing liver function tests for at least 12 months after the first BNT162b2 dose.

Immunogenicity Study

The antireceptor-binding domain immunoglobulin (anti-RBD Ig) using an Elecsys SARS-CoV-2 S electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland), antinucleocapsid using a chemiluminescent microparticle immunoassay (Abbott Diagnostics, Sligo, Ireland), NAs against Omicron variants using the cPass severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralization antibody detection kit (Nanjing GenScript Biotech Co., Ltd., Nanjing, China), and interferon-γ-secreting T cells were measured using an interferon-γ enzyme-linked immunospot (ELISpot) assay (Mabtech, Stockholm, Sweden) according to our previous study (3). NAs against Omicron variants in this study were changed from Omicron BA.1 (accession no. EPI_ISL_8547017) to Omicron BA.2 (accession no. EPI_ISL_11698090), as previously described (14).

Anti-RBD Ig and interferon-γ-secreting T cells were analyzed at all visits (from Visit −1 to Visit 2), whereas antinucleocapsid and NAs were measured before and 1 month after the third dose (Visits 0 and 1).

In cases with COVID-19 infection is diagnosed, the diagnosis must be confirmed by the positive result from a rapid antigen test and/or reverse transcription polymerase chain reaction test.

Statistical Analysis

Categorical and continuous variables were presented as absolute numbers and percentages, medians with interquartile ranges, or means with standard deviations or 95% confidence intervals, as appropriate. The anti-RBD Ig was presented with a geometric mean titer (GMT). A Fisher exact test, Student's *t* test, or Mann–Whitney *U* test were used to determine statistically significant differences, as appropriate, with a $P < 0.05$. STATA version 15 was used for data analysis, and GraphPad Prism Version 9.2.0 for Windows was used for graph building.

RESULTS

Study Population

From September 2021 to August 2022, 16 LT adolescents and 27 healthy adolescents were enrolled in our study and received 2 doses of the BNT162b2 vaccine. Blood samples were collected for immunogenic studies at 4 different time points, as previously described (3). At Visits −1 and 0, blood samples were collected, and a booster dose was given to all participants on Visit 0. At Visit −1, no participants in either group had COVID-19 infection, while at Visit 0, 4 and 8 participants in the LT and healthy groups, respectively, had been infected, with an efficacy of the 2-dose BNT162b2 vaccine to prevent COVID-19 infection of 75% and 70.4% at a 6-month interval, respectively.

At Visit 0, 12 participants were excluded (3 in the LT group and 9 in the healthy group), leaving 31 participants eligible for a booster dose (13 in the LT group and 18 in the healthy group). There were 13 participants in the LT group; 4 of them had COVID-19 infection but were willing to receive a booster dose. There were 18 participants in the healthy group; 5 of them had COVID-19 infection but were willing to receive a booster dose. Blood samples were collected again 1 and 2 months after the booster dose (Visits 1 and 2). One month after the booster dose, none of the LT group and 2 of the healthy group had COVID-19 infection, with an efficacy of the 3-dose BNT162b2 vaccine to prevent COVID-19 in the Omicron era of 100% and 84.6%, respectively (Fig. 1). After a third dose of BNT162b2 injection, all of the participants in LT group and the healthy group went to school. However, most of the participants in the LT group reported mask-wearing nearly all the time in public areas, frequently washing hands, and keeping physical distancing.

Humoral Immune Response to COVID-19

The GMT of anti-RBD Ig decreased with time after the second dose in both groups. Following a booster dose (Visit 0), the participants were divided into 4 groups: the LT group without COVID-19 infection (n = 9), the LT group with COVID-19 infection (n = 4), the healthy group without COVID-19 infection (n = 13), and the healthy group with COVID-19 infection (n = 5). The time interval between each visit was not statistically significant among LT and healthy adolescents, with the time from the first dose to the third dose (Visit 0), Visit 1, and Visit 2 being 210.9 (21.5), 242.2 (22.3), and 308.7 (32.1) days, respectively. In both LT adolescents and healthy adolescents without COVID-19 infection, GMT of anti-RBD Ig and NA rising differed significantly at Visit 1 from those at Visit 0 ($P < 0.05$). However, there was no statistical difference between the 2 groups on each visit. At all visits, the GMT of anti-RBD Ig and NA were higher in both LT and healthy adolescents with COVID-19 infection than in those without COVID-19 infection, with no statistical difference. Comparing participants who not infected and infected, the third dose

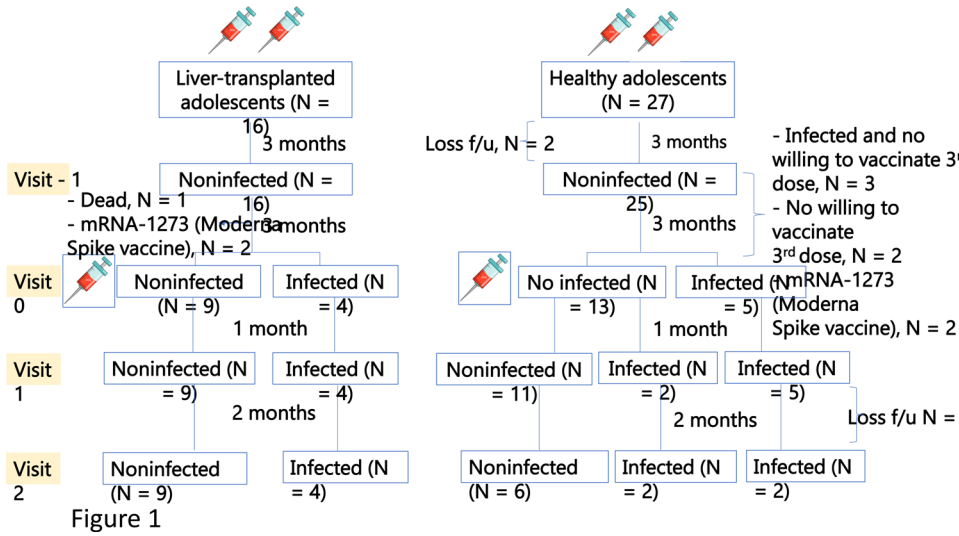


Figure 1

FIGURE 1. Algorithm demonstrates the participant flow in each visit after the second dose of BNT162b2.

increased anti-RBD IgG titers and NA to Omicron variant to the levels observed after natural infection Figure 2A, B.

Cellular Immune Response to COVID-19

The T-cell-specific response to the SARS-CoV-2 spike peptide pools (S1 and S2) was assessed using an interferon-γ ELISpot assay before the third dose (Visits −1 and 0) and at Visits 1 and 2. After the third dose of the BNT162b2 vaccine, the number of interferon-γ-secreting cells increased in both LT and healthy adolescents who had not been infected with SARS-CoV-2 before vaccination but decreased in both LT and healthy adolescents who had been infected with COVID-19 before vaccination but were willing to receive the third dose. However, these differences were not statistically significant (Fig. 2C).

BNT162b2 Vaccine Safety

The most common short-term AEs were similar after each BNT162b2 dose. After the third dose, the most common local AEs (pain, swelling, and redness) were pain and swelling in the injected arm, while the most common systemic AEs (fever, headache, myalgia, nausea, vomiting, diarrhea, joint pain, chill, and dizziness) were myalgia and headache, with no long-term AEs reported during a 12-month follow-up period after the booster dose (Fig. 3). However, there was one girl diagnosed autoimmune hepatitis with ulcerative colitis underwent liver transplant for 13 months. She had increased transaminitis and new onset of chronic watery diarrhea after liver transplant. Liver function tests before vaccination were TB 1.13 mg/dL AST 172, ALT 81, and GGT 97 U/L. Colonoscopy with biopsy was performed previously, active ulcerative colitis and CMV colitis were the diagnosis of diarrhea. After increasing immunosuppressants and tissue CMV eradication, clinical diarrhea was improved with 3–4 stools/day. She was on tacrolimus, mesalamine, prednisolone, and azathioprine at the time of the first dose of BNT162b2 injection. Two weeks after injection, she had protracted diarrhea with no pathogen identified. Five months after the first dose, she developed fulminant acute liver failure for an unknown cause. She finally died from a pulmonary hemorrhage, and her parents denied an autopsy or liver necropsy (Fig. 4). Aside from this girl, 5 other LT adolescents had increased transaminases before vaccination. One of them had a liver biopsy, which revealed mild, nonspecific portal inflammation and human herpesvirus RNA copies greater than 500 000 copies/mL in liver tissue. There was no graft rejection, and everyone was stable, but they still had increased transaminases so far. During the follow-up period, no serious AEs or increased transaminases were observed in 10 LT children who had normal liver function tests before vaccination (BNT162b2 or mRNA-1273).

DISCUSSION

The present study demonstrated that a booster dose of the BNT162b2 vaccine elicited a significantly high immunogenic response in LT and healthy adolescents who had previously received 2 BNT162b2 doses. There was no statistically significant difference in anti-RBD Ig, NAs, or T-cell-specific response to SARS-CoV-2 spike peptide pools between LT and healthy adolescents. During a 3-month follow-up after a booster dose, efficacy was 100% and 84.6% in LT and healthy adolescents, respectively. Furthermore, no serious AEs occurred after BNT162b2 vaccination during a short-term follow-up period. However, 1 LT girl developed active autoimmune liver disease and ulcerative colitis during vaccination and died 5 months after the first BNT162b2 dose from acute liver failure from an unknown cause.

LT patients are at high risk for infection (15) and prevention with immunization should be prioritized (16). However, evidence supporting the COVID-19 vaccination program and vaccine platform for these patients is scarce. To the best of our knowledge, this is the first study to demonstrate that LT adolescents can respond similarly to healthy adolescents to a booster BNT162b2 dose. This study assessed the immunogenicity of the BNT162b2 vaccine since the first dose and demonstrated a gradual waning of immunity over 6 months after the second dose and a strong immunologic response after a booster dose, which is consistent with previous research in healthy adolescents (17–19). Moreover, 1 month after a booster dose, NA titers increased from <30% (negative) after the second dose (3) to 95.37%, and T-cell-specific responses in LT adolescents with no previous COVID-19 showed an increasing trend. This humoral and cellular response reflected the high efficacy of a third BNT162b2 dose in LT adolescents. Studies on the efficacy of the third BNT162b2 dose in LT adults demonstrated a great improvement in humoral response from 2 doses (56%–80%) to a booster dose (91%–98%) of the BNT162b2 vaccine (20–25). In terms of T-cell-specific response, 1 study reported an increase in T-cell response from 32% to 72% after a booster dose (21). When compared to our data, it appears that LT children had a higher immune response rate than LT adults.

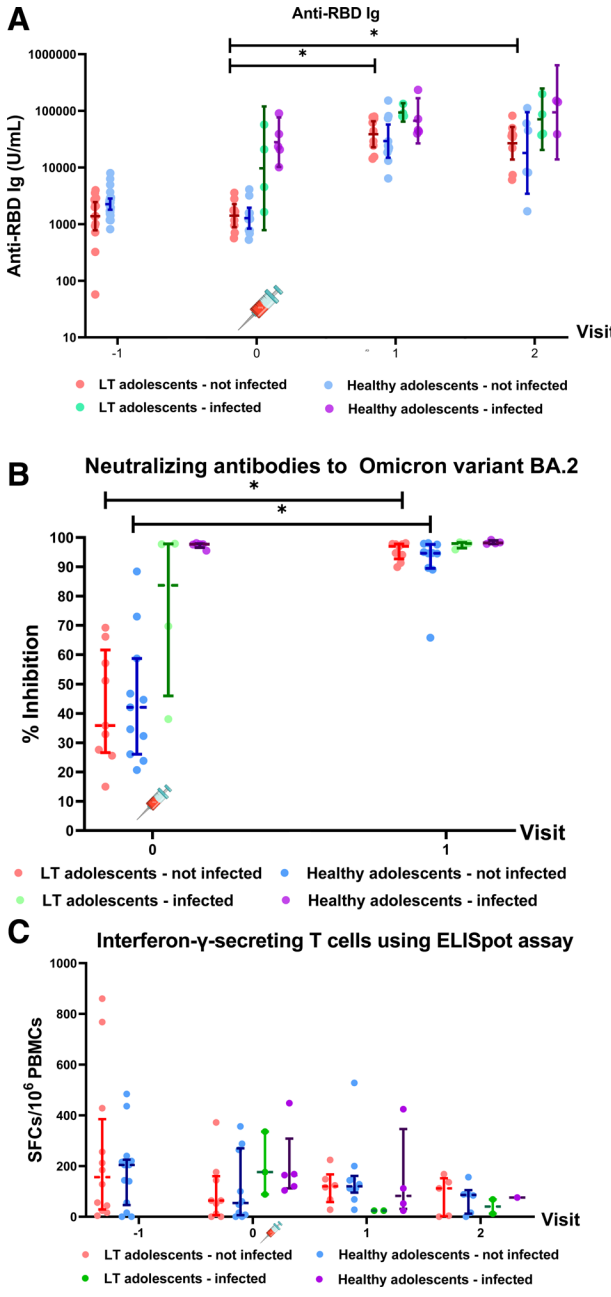


FIGURE 2. Humoral and cellular immune responses before and after the third dose of the BNT162b2 vaccine in liver-transplanted and healthy adolescents with and without COVID-19 infection data points are individual reciprocals. * denotes $P < 0.05$. A) Antireceptor-binding domain immunoglobulin (anti-RBD Ig). The line represents the geometric mean titers, while the bar represents the 95% confidence interval (CI). B) Percentage of virus-neutralizing antibody inhibition against the Omicron variant (BA.2). The line represents the mean, while the bar represents the 95% CI. C) T-cell-specific response to severe acute respiratory syndrome coronavirus 2 spike peptide pools (S1 + S2) using the interferon-γ ELISpot assay. The line represents the median, while the bar represents the interquartile ranges 1 and 3.

Although no exact antibody cutoff level has been established to prevent COVID-19, particularly in the era of the Omicron variants and other variants of concern, some studies supported the correlation between high antibody levels and the degree of protection against infection and disease severity (26). Hence, the present study demonstrated adequate protection against COVID-19 in the Omicron variant era with the completion of 3 doses of BNT162b2 vaccination in LT adolescents.

The immune response to the BNT162b2 vaccine peaked 2–4 weeks after injection, but gradually waned over time. However, some studies reported a rapid decline in antibody levels with time in LT adults (20), but not in our LT adolescents in the present study. The immune response to vaccination in LT children might be more rigorous than in LT adults because of many factors, such as their younger age (20) and less comorbidity (21). Previous research on hepatitis B revaccination in LT children demonstrated a good response and slow-waning immunity, which differed from adult studies (27) and could explain why the immune response in LT children and adults could not be comparable. Hence, it is important to consider a specific study in the child population rather than generalizing the vaccination regimen based on adult data. So far strategies to prevent COVID-19 development and reduce disease severity are required, particularly given waning immunity over time and the effect of other variants of concern. Studies on the efficacy and proper timing of a further booster dose in LT adolescents are indeed required.

Currently, a booster dose may increase the immune response in immunocompromised hosts and is prioritized for this vulnerable group, despite the scarcity of data on AEs. As a result, AEs should be concerned, monitored, and reported at the same time. In the present study, there was no increase in the rate of liver graft rejection or liver injury during the long-term follow-up, except for an LT girl with underlying autoimmune overlap syndrome. This LT girl died 5 months after receiving her first BNT162b2 dose. Roy et al. (28) found that while immune-mediated liver injury following COVID-19 vaccination was extremely rare, it occurred in one-fourth of patients with autoimmune disease, implying vaccine as a possible trigger for immune-mediated liver injury in a predisposed individual. This could be explained by molecular mimicry and immune cross-reactivity in predisposed individuals (29). Furthermore, mRNA-based vaccines have intrinsic immunostimulatory properties that could be recognized by intracellular receptors, resulting in the downstream activation of proinflammatory cytokines (30). However, the majority of cases of immune-mediated liver injury occurred 17.3 (11.2–23.4) (28), 21.1 (15) (31), or 10 (1–53) (32) days after the first dose of the COVID-19 vaccine, which was quite far from our case. However, the severe liver injury in the present case might be a coincidence rather than a causal association with the BNT162b2 vaccine. On the other hand, BNT162b2 might stimulate the disease to flare up, resulting in severe AEs. However, the purpose of this reported case is to raise awareness about vaccination in unstable patients or patients with underlying autoimmune diseases, as well as to advocate for long-term closed monitoring if a vaccine was given to such high-risk individuals. The present study does not intend to promote vaccine hesitancy in the general population, as there is strong evidence that the benefits of vaccines in preventing COVID-19 development and disease severity outweigh the reported AEs (33).

Our study is a long cohort study in both LT and healthy adolescents, with a follow-up period exceeding 1 year. The present study assessed not only humoral immune response via anti-RBD Ig measurement, but also NAs associated with immune protection and T-cell-specific response, which reflect viral load and disease burden. However, the present study has some limitations. First, there were a limited number of participants recruited, and many dropped out during this long-term follow-up period. Our single-center data cannot be

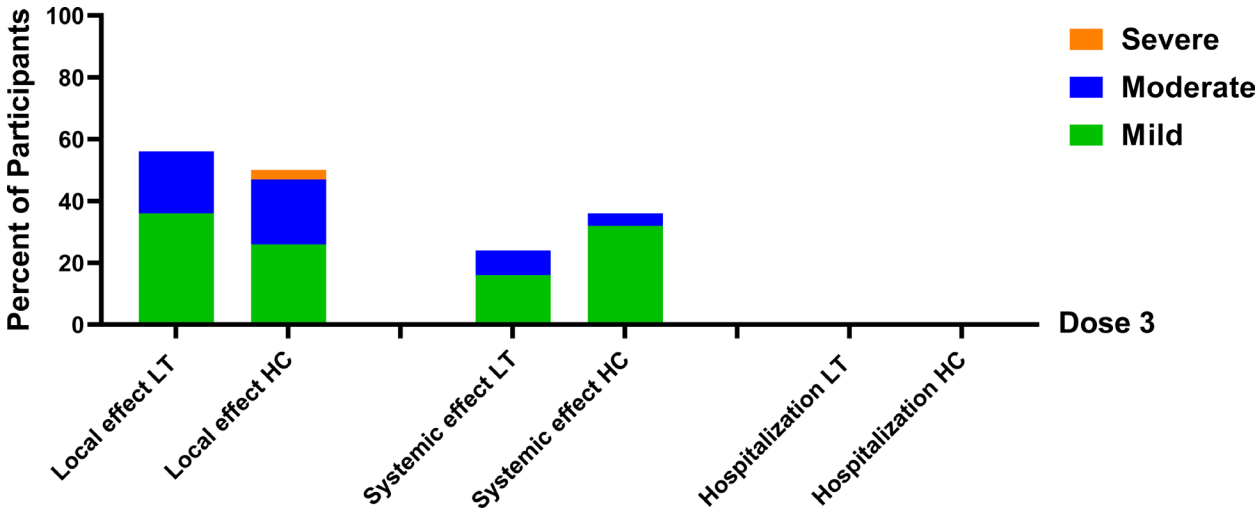
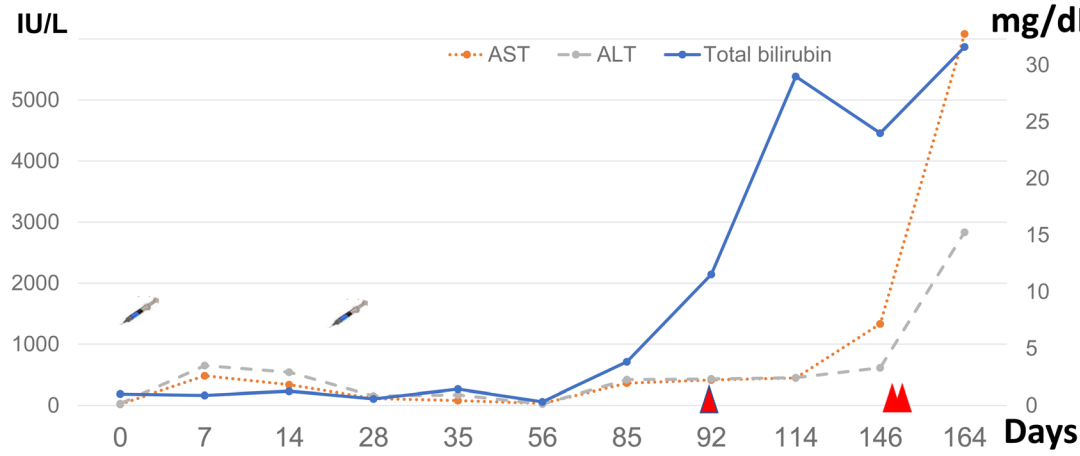


FIGURE 3. Adverse events occurred 7 days after the third BNT162b2 dose. C, healthy control/adolescents; LT, liver-transplanted adolescents.



Clinical course				Persistent diarrhea r/o active ulcerative colitis (septic work-up: all negative)						
							Fever, right abdominal pain, pale stool, and jaundice			
Liver biopsy	▲ Portal inflammation with cholangitis, no acute cellular rejection									
	▲ Cirrhosis with severe hepatitis, portal inflammation, and ductopenia							Acute liver failure, pulmonary hemorrhage, and death		
Tacrolimus (level)	4.3	7.2	off							
Cyclosporin (level)			88	101	116	63	54	211	263	494
Mesalamine (MKD)	50	50	50	50	50	50	50	50	60	60
Prednisolone (MKD)	1	1	1	1	0.8	0.8	0.8	0.8	0.8	0.8
Azathioprine (MKD)	2.5	2.5	2.5	2.5	2.5	2.5	3	3	3	3

FIGURE 4. The timeline of a liver-transplanted girl who died 5 months after receiving the BNT162b2 vaccine with indeterminate acute liver failure and pulmonary hemorrhage.

generalized to all LT children and adolescents. Accordingly, further multicenter studies on larger cohorts are required.

In conclusion, in LT and healthy adolescents, the immunologic response to the 2-dose BNT162b2 vaccination decreased over time but improved after a booster dose. However, serious AEs occurred in 1 LT girl with autoimmune overlap syndrome who received 2 BNT162b2 doses. Hence, decisions about mRNA vaccine administration to patients with immune dysregulation should be made with caution. Other modalities, such as vaccination with other types of vaccines and contact precaution strategies, might be beneficial for high-risk patients.

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