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De novo food allergy in pediatric liver transplantation recipients

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Abstract

Background: Food allergy (FA) prevalence is increasing in pediatric liver transplantation (LT). However, the clinical course is still limited.

Objective: This retrospective cohort study aimed to identify the prevalence, risk factors, and the natural history of *de novo* FA in children post LT.

Methods: Medical records of pediatric LT recipients from Jan 2001 - Dec 2014 were reviewed. *De novo* FA was diagnosed by symptoms after exposure to culprit food occurring after LT, and improvement after diet elimination. FA was confirmed if reproduced symptoms after re-challenge or documented sensitization or indicated gastrointestinal eosinophilia.

Results: Among 46 post LT children, 54.3% developed *de novo* FA at a median time of 12.2 months [Interquartile range (IQR) 6.2, 21.3 months] post LT. The confirmed FA was 39.1%. Gastrointestinal symptom was the most common manifestation followed by skin, anaphylaxis, and others. Culprit foods were cow's milk, shellfish, egg, wheat, soybean, peanut, coconut, fish and monosodium glutamate. The risk factors of FA were transplantation during age below 2 years [hazard ratio (HR), 2.62; 95% confidence interval (CI), 1.04 - 6.59; $p = 0.03$), atopic history in family (HR, 5.67; 95% CI, 1.33 - 24.12; $p = 0.01$), and Epstein-Barr (EBV) viremia (HR, 2.39; 95% CI, 1.02 - 5.63; $p = 0.04$).

Conclusions: *de novo* FA in pediatric LT is not uncommon. Age at LT younger than 2 years, family history of atopy, and EBV viremia are associated with developing FA. Development of tolerance after elimination culprit diets for 3 years is similar to general population.

Key words: Food allergy, liver transplantation, tolerance, outgrown, *de novo* food allergy

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Introduction

Food allergy (FA) is defined as an immune-mediated adverse reaction to food, divided by immunopathology to IgE-mediated, non IgE-mediated, and mixed type.[1] Over the past 2 decades, the prevalence of FA was doubled and its phenotypic expression increased in Westernized societies.[2] In the US 28% of 480 children from birth cohort study reported adverse reactions to foods, but in only 8% of these reactions were reproduced.[3] In Thailand, the prevalence of adverse food reactions by questionnaire in school children under age of 7 years ranged from 6.25% to 13.1% and the prevalence of confirmed IgE-mediated FA by food challenge were 0.45% to 1.11%.[4,5] However, the prevalence of FA are highlighted in some special conditions particularly the patients undergo solid organ transplantation.[6]

Presently, liver transplant (LT) is the treatment of choice in liver failure and provides an excellent outcome and survival rate.[7] The quality of life and long term health aspects are increasingly concerned. Interestingly, the incidence of novel FA or *de novo* FA following LT has been reported to be 5 to 57% in various populations but the pathogenesis remains

elucidate.[6,8-11] While the incidence of this condition was increasing, several risk factors such as tacrolimus use, EBV viremia and younger age at transplantation have been reported but these remain inconclusive.[8,9,12,13] Furthermore, the natural history is also unclear leading to the reluctance of health care providers and child caregivers for dietary management. Therefore, this study aimed to 1) determine the prevalence of *de novo* FA, 2) identify risk factors of *de novo* FA, and 3) demonstrate the natural history of *de novo* FA in post LT children.

Methods

Study design

Retrospective cohort study

Patients and Samples

Patients who underwent LT between Jan 2001 and Dec 2014 were reviewed using patient's records and telephone interviewing by one researcher. The patients who had survived after LT at least 30 months were included in this study. Demographic data including gender, underlying diseases, indication for LT, age at LT, follow-up period, immunosuppressive drug regimen, and atopic history such as allergic rhinitis (AR), asthma, atopic dermatitis (AD) and FA were collected. The FA history focusing on the onset, symptoms, treatment, and reaction after re-consumption either by incidence or intention were gathered. The evidence of sensitization was identified by skin prick test and specific IgE (sIgE). The patients were routinely followed-up by the gastroenterologists (ST and CL). Patients with suspected FA were evaluated and diagnosed by the allergists (RS and WM). *De novo* FA was defined as symptoms and/or signs of FA developed after LT. We classified FA into 2 groups which were confirmed and probable FA as the following criteria;[14,15]

Confirmed FA was defined as the symptoms and/or signs of FA that resolved after food elimination, combined with either reproducible symptoms and/or signs when reintroducing the culprit foods or the evidence of food sensitization (SPT or sIgE) or evidence of gastrointestinal eosinophilia without other specific causes.

Probable FA was diagnosed from a history of symptoms and/or signs of FA that improved after avoidance without the re-challenge of culprit foods, nor laboratory tests to confirm the food reactions. The other causes that mimic FA such as infection, drug adverse effects were excluded.

IgE-mediated FA included urticaria, angioedema, acute onset gastrointestinal or respiratory symptoms, and anaphylaxis. The reaction occurred within 2 hours after ingestion of the culprit foods.[14] The evidence of food sensitization was used to support the IgE-mediated reaction.

Non IgE-mediated FA included subacute or delayed onset of gastrointestinal symptoms (> 2 hours after taking the culprit foods). They were food protein-induced proctocolitis, food protein-induced enterocolitis, and food protein-induced enteropathy.[14]

Mixed IgE- and non-IgE mediated FA included moderate to severe AD and eosinophilic gastrointestinal disorders (EGIDs). In order to diagnose EGIDs, esophagogastroduodenoscopy and endoscopic biopsies were performed and the diagnosis was based on the abnormal numbers or distribution of eosinophils in tissue histopathology.[15]

Evidence of food sensitization was determined by SPT or prick to prick (PTP) or sIgE. In SPT and PTP, histamine chloride and sodium chloride (0.9%) were used as positive and negative controls, respectively. Skin test applicator of Duotip-test (Lincoln Diagnostics, Illinois, USA) was performed on the skin at forearm for either the SPT or PTP. The standard food allergenic extracts (ALK Abelló, Port Washington, NY, USA) of cow's milk, soy, wheat, egg yolk, egg white, and mixed shellfish were applied for SPT. The selected cooked and/or fresh foods were performed for prick-to-prick skin test (PTP) in cases of unavailable commercial standard allergen. The sIgE was measured by the ImmunoCAP assay (Thermo Fisher Scientific, Uppsala, Sweden). The wheal size > 3 mm larger than negative control in SPT and PTP or sIgE > 0.35 IU/mL were considered the positive result.

Outgrowing of FA was defined as the ability to re-consume the culprit foods without any reaction for more than 1 month.

Study protocol was approved by the Research Ethical Committee of the Faculty of Medicine Ramathibodi Hospital. Informed consent was obtained from a caregiver before enrollment in the study.

Statistical analysis

Data were analyzed using the statistics package SPSS 17.0 and Stata software version 12.0. A descriptive analysis was performed on all study variables, using median with quartile for numeric variables. The differences of baseline characteristic were assessed by Chi-square and Mann-Whitney U test. Risk factors for *de novo* FA post LT were determined by the univariate analysis of log-rank test and presented as Hazard Ratio. Probability of having *de novo* FA post LT was described by Kaplan-Meier survival analysis. The differences with a *P* value less than 0.05 are considered statistically significant. The Log-rank test comparing two survival rates was calculated to determine the statistical power.

Results

Patient demographics

Between January 1, 2001 and Dec 30, 2014, a total of 52 pediatric patients underwent LT at Ramathibodi Hospital. Forty-six patients survived and were eligible for including in the study. Twenty-five patients (54.3%) had *de novo* FA and 18 of them (39.1%) had confirmed FA (**Figure 1**). The demographic data are described in **Table 1** that the baseline characteristics were not different between *de novo* FA and non *de novo* FA except family history of atopy (p = 0.031). There were eight donors who reported the symptoms of allergic rhinitis and only one of shellfish allergy. Standard immunosuppression regimen was composed of tacrolimus starting within 24 hours

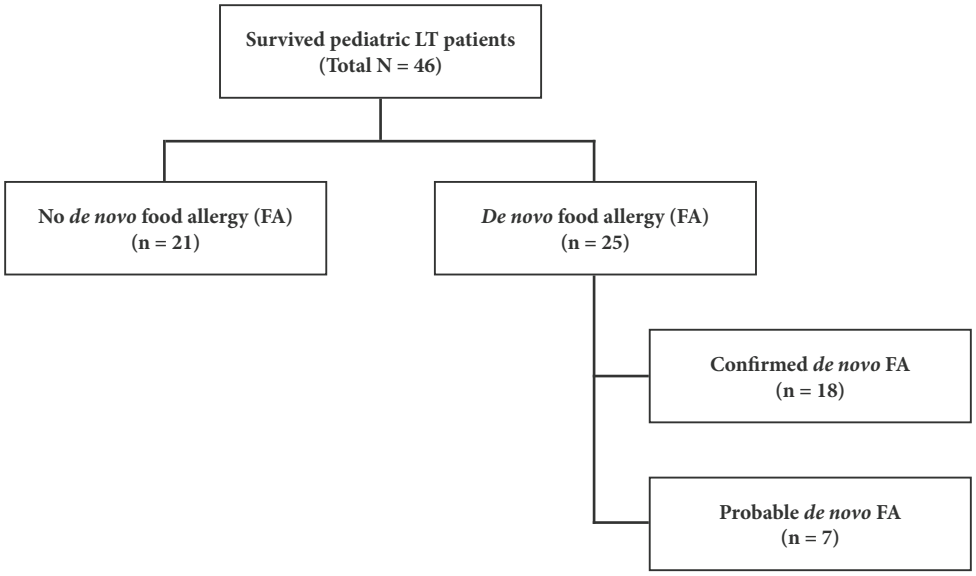

Figure 1. The overall *de novo* food allergy (FA) outcome in survived pediatric liver transplantation recipients

Table 1. Demographics of the patients

Variable	Overall n (%)	*De novo* food allergy		*P* value[$]
		De novo FA n (%)	Non *de novo* FA n (%)	
Gender (Male)	16 (34.8)	8 (32.0)	8 (38.1)	0.665[a]
Median age at transplantation; months (IQR)	19.1 (15.3, 34.2)	16.7 (12.2, 23.3)	29.2 (17.7, 64.4)	0.107[b]
Median follow-up period; months (IQR)	59.5 (57.2, 92.8)	67.4 (50.2, 98.6)	55.8 (42.8, 95.7)	0.337[b]
Median age at study; months (IQR)	89.3 (65.9, 128.9)	87.1 (60.7, 121.7)	103.8 (66.8, 173.4)	0.225[b]
Indication for transplantation				
Biliary atresia	37 (80.4)	22 (88.0)	15 (71.4)	0.264[c]
Others[d]	9 (19.6)	3 (12.0)	6 (28.6)	
PELDs (IQR)	18.0 (15, 21)	18.0 (14.5, 21.0)	18.5 (14.3, 21.8)	0.660[b]
Prior atopy before LT	5 (10.9)	3 (12.0)	2 (9.5)	0.788[a]
First-degree family history of atopy	16 (34.8)	12 (48.0)	4 (19.0)	0.031[a,*]
History of atopy in donor	8 (17.4)	6 (24.0)	2 (9.5)	0.260[c]
Allergic rhinitis	8	6	2	
Food allergy	1	1	0	
Long term immunosuppression				
Tacrolimus	26 (56.5)	16 (64.0)	10 (47.6)	0.282[a]
Tacrolimus and MMF	20 (43.5)	9 (32.0)	11 (52.4)	

Abbreviation; FA, food allergy; IQR, interquartile range; LT, liver transplant; MMF, mycophenolate mofetyl; PELDs, Pediatric End-stage Liver Disease score;
[a] Chi-square test
[b] Mann Whitney U test
[c] Fisher's exact test
[d] Allagille syndrome, progressive familial intrahepatic cholestasis (PFIC) type 2, tyrosinemia, glycogen storage disease, hemangioendothelioma
* $P < 0.05$
[$]The difference between *de novo* FA and non *de novo* FA

after the operation and continuing for life-long, combined with corticosteroid in the first 6 months after LT. Additional mycophenolate mofetil (MMF) was given to some patients as clinical indicated.

Clinical manifestations, allergic food and types of FA

Twenty-two out of 25 food allergic patients (88%) had multiple food allergies. The median time to diagnosis *de novo* FA after LT was 12.2 months (IQR 6.2, 21.3 months). EGIDs were diagnosed in 4 patients.

Table 2. The numbers of culprit food and outgrowing rate of each food allergen

Culprit food	*De novo* FA n/n total (%)	Outgrowing n/n total (%)
Cow's milk	18/85 (21.2)	12/18 (66.7)
Soy	14/85 (16.5)	4/14 (28.5)
Shellfish	14/85 (16.5)	8/14 (57.1)
Hen's egg	13/85(15.3)	6/13 (46.2)
Fish	8/85 (9.5)	1/8 (12.5)
Wheat	6/85 (7.0)	4/6 (66.7)
Others	12/85 (14.1)	0/12 (0)

Among 85 items of allergic food items in 25 *de novo* FA patients, IgE-mediated FA was the most common reaction (49.4%), follow by mixed (29.4%), and non IgE-mediated reaction (21.2%). The major culprit foods were milk, soy, shellfish, hen's egg and others (**Table 2**).

The presenting symptoms were gastrointestinal symptoms (52%), followed by skin (urticaria/angioedema, eczema), anaphylaxis, anemia and respiratory (stridor) as described in **Table 3**. One case of multiple food allergy post LT has identical twins and his twin was healthy with no clinical of any atopic diseases.

Risk factors for de novo FA post LT

Risk factors for *de novo* FA post LT were the age at LT of less than 2 years [hazard ratio (HR), 2.62; 95% confidence interval (CI), 1.04 - 6.59; $p = 0.03$), Epstein-Barr (EBV) viremia of more than 100 copies prior to developing FA (HR, 2.39; 95% CI,

Table 3. Clinical features of *de novo* FA in pediatric LT

No.	Indication	Outgrowing	Age at LT (months)	Culprit food	sIgE (IU/mL)	SPT/PTP [wheal diameter (mm)]	Clinical	Type of allergic reaction	Food allergy
1	BA	21.6	36	CM Soy Shellfish EW	3.19 0.36 1.25 1.52	NA NA NA NA	AD	Mixed	Confirmed (OC)
2	BA	19.2	51.6	CM, shellfish	NA	NA	Diarrhea (EGID)	Mixed	Probable
3	Tyrosinemia type 1	15.6	15.6	Shrimp Fish (Nile tilapia) Blood cockle	NA NA NA	3 10 (cooked) NA	angioedema	IgE-mediated	Confirmed (OC)
4	BA	22.8	9.6	Shrimp Cashew nut	NA NA	NA NA	Urticaria, angioedema, anaphylaxis	IgE-mediated	Confirmed (accidental OC)
5	BA	15.6	21.6	EW Wheat CM Soy Shrimp	15.5 29.8 37.6 14.8 6.79	NA NA NA NA NA	Diarrhea (EGID), anemia, hypoalbuminemia	Mixed	Confirmed
6	BA	36	40.8	EY Wheat Soy Fish Shrimp	1.42 0.51 1.57 6.39 (Cod) 0.39	NA NA NA NA NA	Diarrhea (EGID), anemia	Mixed	Confirmed
7	BA	20.4	30	Soy Shellfish	8.99 3.52	NA NA	Diarrhea, mouth itching	Mixed, IgE-mediated	Confirmed
8	BA	34.8	24	CM Soy Shellfish	0.01 0.00 NA	NA NA NA	AD, Diarrhea (EGID)	Mixed	Confirmed (accidental OC)
9	Allagille syndrome	46.8	6	CM	NA	NA	Diarrhea	Non-IgE mediated	Probable
10	BA	34.8	12	Fish (Nile tilapia) Soy CM Shrimp Egg	NA 5.76 22.4 0.53 6 (EW), 9.28 (EY)	15, 10 (fresh, cooked) NA NA NA NA	Angioedema, vomiting, abdominal pain, rash, AD	IgE-mediated	Confirmed

Table 3. (Continued) Clinical features of *de novo* FA in pediatric LT

No.	Indication	Outgrowing	Age at LT (months)	Culprit food	sIgE (IU/mL)	SPT/PTP [wheal diameter (mm)]	Clinical	Type of allergic reaction	Food allergy
11	BA	10.8	12	Coconut milk Peanut Soy Shrimp Squid	NA 48.6 36.2 17.0 NA	13 NA NA NA 5	Angioedema, urticaria, vomiting, diarrhea	IgE-mediated	Confirmed
12	BA	4.8	12	Shellfish CM Egg Peanut	0.05 0.13 0.03 (EW), 0.03 (EY) NA	NA NA NA NA	Angioedema, diarrhea, AD	IgE-mediated, non IgE-mediated and mixed	Confirmed (accidental OC)
13	BA	15.6	36	Squid	NA	NA	Angioedema	IgE-mediated	Probable
14	BA	20.4	24	MSG[†]	NA	NA	Urticaria	IgE-mediated	Confirmed (OC)
15	BA	14.4	6	Coconut milk[†] Pumpkin[†] Fish CM Egg Soy Shellfish	NA NA 0.03 (Cod) 8.93 23.9 (EW), 12.9 (EY) 4.68 0.32	NA NA NA NA NA NA NA	Angioedema, diarrhea, anaphylaxis	IgE-mediated	Confirmed
16	ALF	10.8	2.4	CM EW Coconut milk[†] Shrimp Soy	NA NA NA NA NA	Negative 4 Negative Negative Negative	Urticaria, angioedema, AD, anemia	IgE-mediated, mixed	Confirmed (accidental OC)
17	BA	33.6	12	CM	NA	NA	Diarrhea	Non-IgE-mediated	Confirmed (accidental OC)
18	BA	9.6	2.4	CM Wheat Egg Soy Peanut Shrimp Fish	79.8 > 100 84.5 (EW), 13.0 (EY) 22.4 13.1 41.9 36.7 (Cod)	NA NA NA NA NA NA NA	AD, stridor (vocal cord edema)	IgE-mediated, mixed	Confirmed (accidental OC)
19	BA	9.6	9.6	CM, soy	NA	NA	Diarrhea	Mixed	Probable
20	BA	9.6	6	CM Soy Crab EW	0.64 3.93 0.03 0.22	NA NA NA NA	Diarrhea, AD	Mixed	Probable
21	BA	13.2	3.6	CM Wheat	48.0 > 100	NA NA	AD	Mixed	Confirmed (accidental OC)
22	BA	15.6	2.4	Soy CM Egg *CMPA diagnosed before LT	0.00 0.01 0.12 (EW), 0.12 (EY)	NA NA NA	Anaphylaxis (soy), AD, diarrhea	IgE-mediated, non IgE-mediated	Probable
23	BA	16.8	6	CM Soy Fish (Nile tilapia) Wheat	0.04 0.01 NA 0.03	NA NA NA 4	Hypersecretion, vomiting, diarrhea and fever suspected FPIES	Mixed, non IgE-mediated	Probable

Table 3. (Continued) Clinical features of *de novo* FA in pediatric LT

No.	Indication	Outgrowing	Age at LT (months)	Culprit food	sIgE (IU/mL)	SPT/PTP [wheal diameter (mm)]	Clinical	Type of allergic reaction	Food allergy
24	BA	21.6	14.4	CM	0.03	NA	Anemia, diarrhea	Non IgE-mediated	Confirmed (OC)
25	BA	20.4	3.6	CM	NA	NA	Diarrhea	Non IgE-mediated	Confirmed (OC)

Abbreviation; AD, atopic dermatitis; ALF, Acute liver failure; BA, biliary atresia; CM, cow's milk; CMPA, cow's milk protein allergy; EGID, Eosinophilic gastroenteritis disease; EW, egg white; EY, egg yolk; FPIES: Food Protein-Induced Enterocolitis Syndrome; NA: Not available; OC: oral challenge; PTP: prick to prick; sIgE: serum specific IgE; SPT: skin prick test

[†] Other culprit foods in this study were MSG, coconut milk, cashew nut, and pumpkin

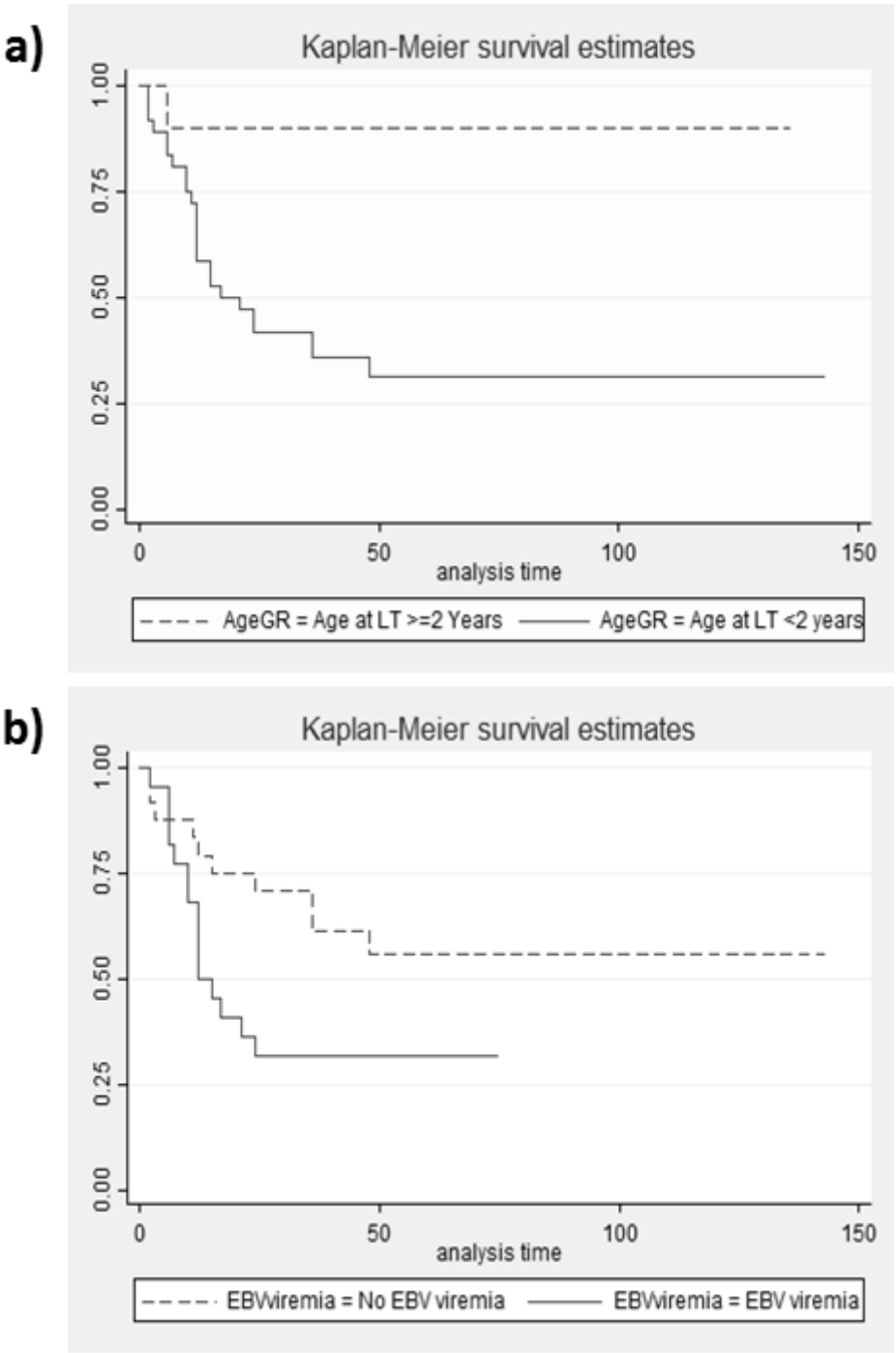

Figure 2. The Kaplan-Meier survival estimates of risk factors for *de novo* FA post liver transplantation (LT). a) The age of LT at less than 2 years, b) Epstein-Barr (EBV) viremia more than 100 copies prior to FA had developed

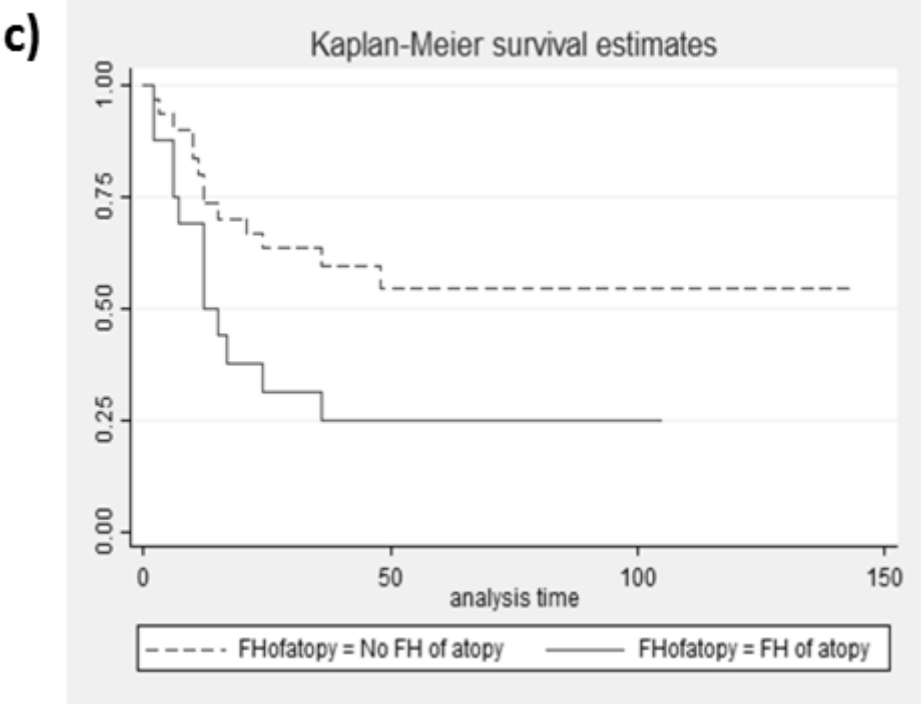

Figure 2. (Continued) c) family history of atopic diseases. The dash line and solid line represent the absence and presence of these factors, respectively.

1.02 - 5.63; p = 0.04), and family history of atopic diseases; hay fever, AD, FA, AR, and/or asthma (HR, 5.67; 95% CI, 1.33 - 24.12; p = 0.01) (**Figure 2a-c**). CMV viremia was found in 68% of *de novo* FA but none in non *de novo* FA group. The small number of patients in each group led to an insufficient statistical power to provide a conclusive analysis of risk factors for CMV, hepatitis B, and herpes simplex virus infection in this population. Other factors including predisposing individual atopic history before LT, severity of end-stage liver disease that measured by Pediatric End-Stage Liver Disease (PELD) score, are not statistically different. Log-rank test comparing two survival rates of Ha = 0.76, Hazards ratio 2.39 (lowest HR in our study). The statistical power is enough at power of 80, total n = 48. The sub-group analysis of the biliary atresia participants were found the similar trend of the risk factors of FH of atopy (HR 3.12;95%CI, 1.32-7.36; p = 0.009) and EBV viremia (HR 1.80; 95%CI, 0.76-4.24; p = 0.182). However, the factor of age at LT < 2 years was not enough to calculate.

Outgrowing of food allergy

Among 25 *de novo* FA patients, 19% develops tolerance to at least 1 food allergen after 3 years of elimination diet. Due to many patients had multiple FA, the outgrowing rate within 3 years after food elimination was determined by numbers of food items. Of the total 85 items of culprit food, 35 (41.2%) items were reported of tolerance after re-challenge. The most common outgrown food allergen were cow's milk and wheat occurring in 66.7%, followed by shellfish, egg, soy, and fish (**Table 2**).

Discussion

This retrospective study highlighted the high prevalence of *de novo* FA (54.3%) in the 46 survived children underwent LT. It was clearly higher than that of global and Thai children but similar to previous reports of FA in pediatric LT. The prevalence of FA in normal population is approximately 1% to 10.8% in westernized countries by food challenges and 3% to 35% by self-reported allergy.[2] In Thailand, the nationwide survey of the FA has not been reported. However, two studies of questionnaire survey and oral food challenge (OFC) in Bangkok (2005) and northern Thailand (2011) have shown the prevalence of FA of 13.1% (positive OFC 1.1%) in Thai preschool children and 6.25% (OFC 0.45%) in school children.[4,5] Our study demonstrated the same prevalence as the several worldwide reports of FA after LT which range from 6% to 57%.[9] The prevalence rate of *de novo* FA in this study was high compared to other reports, possibly due to the selective criteria of FA that we included all types of food allergic reactions; IgE-, non IgE-, and mixed types.

The pattern of FA presentation, types of reaction, food allergens, and outgrowing rate in LT children were mostly similar to those of normal children population. Our study demonstrated that gastrointestinal and skin manifestations were common presentations, and the most common reaction was IgE-mediated (49.4%). EGIDs were found in 4 cases or 8.7% of survived LT which was relatively high when compared to the report of 4 in 10,000 in healthy children, however, this was similar to the previous reports of 3-26% in post-LT children.[16-19]

The significant culprit foods were cow's milk, hen's egg, shellfish, fish, wheat, and soy. Reactions to these "major allergens" are similar to those occurring in Thai children population.[4,5] In addition, these are not different from previous reports of *de novo* FA or food sensitization in children after LT.[9] Considering the common food allergens among Asian countries, cow's milk protein was the most common in our study

while Shoda et al. reported that wheat was the most common in *de novo* FA in Japan.[20] Our finding of multiple food allergies, occurring approximately 2/3 (65.4%) of *de novo* FA patients, supported the consistence of published literature of *de novo* FA in pediatric LT.[6,8,21,22] Furthermore, they lead to multiple food avoidance causing the huge negative impact on the nutritional achievement and quality of life post LT.

Although, the prevalence of food allergy was high in our LT patients, the accumulative outgrowing rate during 3 years after food elimination reached 19%, particularly cow's milk, soy, wheat, and egg allergies. These findings were similar to childhood FA in normal population for cow's milk, hen's egg, soy, and wheat which typically resolves by 3 years of age.[2] In addition, other studies have supported that *de novo* FA after LT is a transient condition and can be outgrown after food elimination for several years.[21,23,24] Interestingly, our data presented a high rate of outgrowing of IgE-mediated shellfish allergy up to 2/3 which was contrast to the natural history in normal population showing a low chance to develop tolerance.[25]

The pathogenesis of *de novo* FA is unknown. Potential mechanism related to chronic tacrolimus use and imbalance immunological function in liver themselves, have been hypothesized base on the reports in LT children both in retrospective, prospective, case-controlled, and in vitro studies.[6,9,11,12,26,27] Chronic exposure to oral tacrolimus, the calcineurin inhibitor, might skew the Th2 response and alter gastrointestinal barrier, and eventually increases a risk of FA development due to the improper allergen exposure.[28] However, the present study showed that outgrowing of *de novo* FA patients did not related to a change in immunosuppressive protocol. Therefore, we speculate the potential etiologies of *de novo* FA are multifactorial rather than from long-term tacrolimus use only. More studies are required to identify the exact mechanism of *de novo* FA after LT.

Potential risk factors associated with *de novo* FA are controversial. Our study identified family history of atopy, young age at LT, particularly less than 2 years old, and EBV viremia as the risk factors. Several studies support our finding that LT at young age contributes to de novo FA.[11,16,27,29] The potential mechanism of young age and risk for *de novo* FA probably due to the immature immune tolerance mechanism in gastrointestinal and hepatic themselves.[2,9] Other reported potential risk factors included high PELD score prior to LT, underlying liver diseases, immunosuppressive regimens and donor's allergy.[20,27,29] However, we could not demonstrate the association of these factors with *de novo* FA. The discrepancy of these results among studies could be due to a difference in study design, the definition of FA and outcome measurement of FA. Moreover, most of our LT patients were biliary atresia with the same level of severity of liver failure before LT and received the homogeneous immunosuppressive regimen.

EBV is a herpes virus with contagious and suspected to be associated with several allergic diseases in normal population.[30,31] Currently, the role of EBV infection in FA is controversial due to inconsistent results from both epidemiological and in vitro studies. It has been suspected to be either a risk or protective factor for FA.[30,32] Contributing factors for the variable results include the variety of EBV detection methods, the range of age group, co-infection with cytomegalovirus (CMV), and the different endpoint outcomes (sensitization or allergy).[8,30,33] Most of the study evaluated the seroprevalence that may be inadequate to represent the viral activity. EBV, particularly primary infection, may related to atopic diseases due to it induces B cell proliferation and polyclonal antibody proliferation.[31,32] In addition, it may transform human B cells, resulting in enhance interleukin-5 production, and eventually may induce a chronic eosinophilic inflammation and produce interleukin-4, which has an important role in promoting the production of the IgE antibodies.[32,34] Therefore, we hypothesized that the EBV viremia which represents the reactivated EBV infection or viral replication, might exaggerate or precipitate the presentation of FA through activated IgE producing B cell proliferation and Th2 response. However, we did not examine the IgE producing B cell during EBV viremia in our patients to prove our hypothesis which beyond the scope of this retrospective study. Whether EBV viremia is the co-incidence finding or causal association with *de novo* FA requires further investigations.

Sidorchuk et al. reported the interaction of CMV and EBV infection on allergic diseases (asthma, allergic rhinitis, atopic dermatitis, but not include food allergy) and sensitization in the birth cohort survey. They found that the sensitization to common airborne or food allergens tended to be more prevalent in children with CMV-seropositive particularly when combined with EBV-seronegative.[35] In contrast, the present study detected both EBV and CMV viremia in patients with *de novo* FA with the CMV reactivation rate of 68% but none in those without FA, however, there was insufficient statistical assessment due to inadequate sample of CMV viremia in the latter group. The large cohort studies are helpful to clarify this association in *de novo* FA post LT.

To our knowledge, this study possibly be the first report of *de novo* FA after LT in Southeast Asia that could be our strength. In addition, we provided data of long-term follow-up that was enough to discover the long-term outcome of these allergic diseases. FA was also diagnosed by the same allergists and gastroenterologists with the standard supportive evidence of sensitization and tissue biopsy. However, the study had some limitations due to the nature of retrospective research, therefore, recall bias could occur such as uncertainty of timing to develop or outgrowing of FA. The overestimation of the prevalence rate of *de novo* FA was also the concerned issue, nevertheless, we tried to diminish this issue by classifying the diagnosis of *de novo* FA to be confirmed and probable FA. The confirmed *de novo* FA was 39.1% which was still higher than normal children population. In addition, the patients who suspected *de novo* FA post LT had not designed to regularly re-challenge to evaluate the outgrown, thus, the precise timing of outgrown was difficult to clarify from this study.

In conclusion, *de novo* FA after LT in pediatric patients is not uncommon. It suggests that children after LT, carry a high risk for the development of new onset FA. Age at transplantation less than 2 years, family history of atopy, and EBV viremia associated with the developing FA. Nevertheless, the natural history of this *de novo* FA is similar to general pediatric population with food allergy with 19% of the patients develop tolerance after 3 years of food elimination. The diagnosis is

challenging, therefore, high index of suspicion of FA should be considered in post-LT children. In addition, the larger cohort study should be further conducted to enhance the understanding of *de novo* FA in post-LT children.

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