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Prevalence of Donor-Specific Antibodies After Pediatric Liver Transplantation: A Meta-Analysis

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Our recent study showed that donor-specific HLA antibodies (DSAs) were common after pediatric liver transplantation (LT).[1] The aim was to conduct a meta-analysis of DSA prevalence after pediatric LT.

PubMed was used (as of March 1, 2016) with a search strategy: *Human leucocyte antigen antibod** OR *HLA antibod** OR *donor-specific antibod** OR *donor specific antibod** OR *DSAs* AND *liver transplantation* AND *(pediatric* OR *children)*. Studies published before January 1, 2000, were excluded based on a rationale for HLA antibody detection technology advancement.

References were screened, and data were extracted from the eligible studies based on 3 criteria: (1) patients underwent LT <18 years of age, (2) prevalence of DSAs was evaluated after LT, and (3) patients were on some form of immunosuppression at the time of DSAs. Studies with mixed population of adults and children were included if information was available for pediatric patients separately or if average age of patients were under 18 years at LT. Unit of analysis was the proportion of patients with DSAs of total number of patients analyzed for DSAs.

R version 3.1.1 (www.r-project.org) was used with meta package[2] to calculate overall prevalence with 95% confidence interval (CI). The overall prevalence was calculated with the use of logit transformation. A random-effects model with the method by DerSimonian and Laird was used. The average prevalence estimate across the studies is obtained under the random-effects model. In addition, 95% prediction interval (PI) was calculated to obtain a predicted range of true DSA prevalence for a new analogous study. The details of PI have been described elsewhere.[3]

Literature search yielded 28 references of which 8 were included in the analysis. One study missed in the aforementioned search was included based on an earlier knowledge of its existence (total of 9 studies). Reasons for exclusion were mixed population (n = 5), intestinal transplantation (n = 5), case reports (n = 3), review (n = 2), editorial (n = 1), DSAs evaluated only prior LT (n = 1), overlapping study population (n = 1), patients not on immunosuppression (n = 1), and full text not available (n = 1). Some of the studies had multiple reasons for exclusion.

Age at the time of LT varied between studies (Table 1). Two of the studies included patients not on immunosuppression at the time of DSAs (Table 1 footnote).

Total sample size was 322 patients (Figure 1). Average prevalence of DSAs was 41% (95% CI, 29%-54%) although prevalence varied across studies as evident with the heterogeneity statistics (I^2 = 77% [95% CI, 56%-88%], P < 0.001 for heterogeneity). The PI indicated that the true DSA prevalence for a new analogous study will fall 95% of times within interval of 11% to 80%.

There was little influence on heterogeneity when omitting 1 study at the time. The largest impact on heterogeneity was observed after excluding study by Waki et al[4] (I^2 from 77% to 66%) or study by Markiewicz-Kijewska et al[5] (I^2 from 77% to 71%). Average DSA prevalence was 51% (95% CI, 43%-58%) after excluding these 2 studies simultaneously. Heterogeneity also diminished (I^2 = 29% [95% CI, 0%-69%], P = 0.207), and the PI also became narrower as expected (34% to 67%). The other excluded study evaluated DSAs shortly after LT (at 3 weeks).[4]

This study has limitations. First, only 1 author extracted the data which can bias the extraction process. Second, the literature search was simple and based only on 1 database. Third, the impact of different study characteristics on heterogeneity was not assessed.

These limitations in mind, the average DSA prevalence was 41% (95% CI, 29%-54%) across 9 studies after pediatric LT although variability between studies was noticeable.

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TABLE 1.

List of included studies

Study (year)	Age at LT	Follow-up time[a]	LT type	DSA positive of total (%)	MFI level for positivity
Girnita (2010)[b]	4.1 y	8.2 y	DDLT/LDLT	9/12 (75.0)	N/A
Goh (2010)[c]	N/A	N/A	DDLT	6/21 (28.6)	1000
Feng (2012)	6.9 mo	6.1/8.4 y[d]	LDLT	9/18 (50.0)	N/A
Miyagawa-Hayashino (2012)	1. y	11 y	LDLT	32/67 (47.8)[e]	1000
Waki (2013)	2.2/4.3 y[f]	3 wk	LDLT	3/36 (8.3)	1000
Markiewicz-Kijewska (2015)	0.97 y	6.8 y	LDLT	5/33 (15.2)	N/A
Wozniak (2015)	3.7 y	12.3/12.2 y	DDLT/LDLT	27/50 (54.0)[g]	1000
Grabhorn (2015)	11.9/8.6 y[h]	10.0/4.8 y	DDLT/LDLT	20/43 (46.5)	1500
Kivelä (2016)	2.6 y	11.2 y[j]	DDLT	25/42 (59.5)[j]	1000

Girnita et al. Hum Immunol 2010; 71: 274-6. Goh et al. Liver Transpl 2010: 16: 308-13. Feng et al. JAMA 2012; 307: 283-93. Miyagawa-Hayashino et al. Liver Transpl 2012; 18: 1333-1342. Waki et al. Transplantation 2013; 95: 177-183. Markiewicz-Kijewska et al. Ann Transplant 2015; 20: 279-284. Wozniak et al. Transplantation 2015; 99: 1416–1422. Grabhorn et al. Transplantation 2015; 99: 1876-1881. Kivelä et al. Transplant Int 2016; 29: 494-505. Study by Feng et al was missed with the search strategy used.

[a] Follow-up time refers to time from LT to blood sample drawn for DSA analyses if applicable.

[b] Part of the total sample (group B) is only included. Based on mean age 4.1 and (assumed) standard deviation 8.7 indicates that some of patients were outliers considering their age at the time of LT.

[c] DSAs were evaluated after first LT and before second LT. Descriptive statistics provided only for second LT. DDLT assumed as LT type based on second LTs.

[d] Time from LT to study entry (median 73.0 months for nontolerant and 100.6 months for tolerant patients).

[e] Patients not on immunosuppression were included (n = 4; all DSA negative patients).

[f] For OT patients mean 2.2 years and non-OT mean 4.3 years.

[g] Tolerant (ie, not on immunosuppression) patients included (n = 7; 2 DSA positive).

[h] For excellent graft function patients mean age 11.9 years and for chronic rejection patients 8.6 years. Maximum age at the time of LT was 26 years in excellent graft group.

[i] Median follow-up time for LT patients (n = 42) only.

[j] Combined liver-kidney transplantation patients (n = 8; 1 DSA positive) excluded.

DDLT, deceased donor liver transplantation; DSA, donor-specific antibody; LDLT, living donor liver transplantation; MFI, mean fluorescence intensity; OT, operational tolerant.

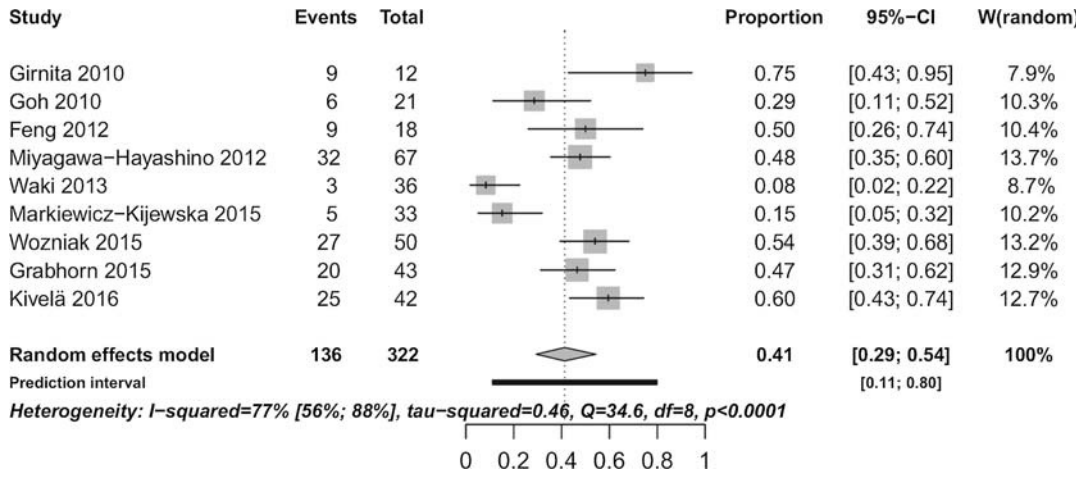

FIGURE 1. Average (95% CI) prevalence of 41% (29% to 54%) (grey diamond) for DSAs after pediatric LT. I^2 is shown with 95% CI. I^2 depicts that 77% of variability in DSA prevalence estimates across studies is beyond sampling error (ie, due to heterogeneity). CIs for individual studies were calculated with the method by Clopper-Pearson. Between-study variance (τ^2) was estimated with the method by DerSimonian and Laird. The prediction interval (black solid line) refers to a predicted interval of true DSA prevalence for a new analogous study.

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