

## Outcomes after liver transplantation in accordance with ABO compatibility: A systematic review and meta-analysis

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Author contributions: Lee EC, Kim SH, Park SJ designed the research; Lee EC performed the research and wrote the paper; Kim SH supervised the study and revised the paper.

Conflict-of-interest statement: No conflicts of interest were declared for all authors.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at [kshlj@ncc.re.kr](mailto:kshlj@ncc.re.kr). No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: May 26, 2017  
Peer-review started: May 26, 2017  
First decision: June 23, 2017  
Revised: July 7, 2017  
Accepted: August 15, 2017

Article in press: August 15, 2017

Published online: September 21, 2017

### Abstract

#### AIM

To evaluate the differences in outcomes between ABO-incompatible (ABO-I) liver transplantation (LT) and ABO-compatible (ABO-C) LT.

#### METHODS

A systematic review and meta-analysis were performed by searching eligible articles published before November 28, 2016 on MEDLINE (PubMed), EMBASE, and Cochrane databases. The primary endpoints were graft survival, patient survival, and ABO-I-related complications.

#### RESULTS

Twenty-one retrospective observational studies with a total of 8247 patients were included in this meta-analysis. Pooled results of patient survival for ABO-I LT were comparable to those for ABO-C LT. However, ABO-I LT showed a poorer graft survival than ABO-C LT (1-year: OR = 0.66, 95%CI: 0.57-0.76,  $P < 0.001$ ; 3-year: OR = 0.74, 95% CI 0.64-0.85,  $P < 0.001$ ; 5-year: OR = 0.75, 95%CI: 0.66-0.86,  $P < 0.001$ ). Furthermore, ABO-I LT was associated with more incidences of antibody-mediated rejection (OR = 74.21, 95%CI: 16.32- 337.45,  $P < 0.001$ ), chronic rejection (OR = 2.28, 95%CI: 1.00-5.22,  $P = 0.05$ ), cytomegalovirus infection (OR = 2.64, 95%CI: 1.63-4.29,  $P < 0.001$ ), overall biliary complication (OR = 1.52, 95%CI: 1.01-2.28,  $P = 0.04$ ), and hepatic artery complication (OR = 4.17, 95%CI: 2.26-7.67,  $P < 0.001$ ) than ABO-C LT. In subgroup analyses, ABO-I LT and ABO-C LT showed a comparable graft survival in pediatric patients and those using rituximab, and ABO-I LT showed an

increased acute cellular rejection in cases involving deceased donor grafts.

### CONCLUSION

Although patient survival in ABO-I LT was comparable to that in ABO-C LT, ABO-I LT was inferior to ABO-C LT in graft survival and several complications. Graft survival of ABO-I LT could be comparable to that of ABO-C LT in pediatric patients and those using rituximab.

**Key words:** ABO-incompatibility; Liver transplantation; Graft survival; Patient survival; Complications

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**Core tip:** This meta-analysis analyzed more than 8000 cases of ABO-incompatible (ABO-I) and ABO-compatible (ABO-C) liver transplantation (LT). Although patient survival was similar, ABO-I LT was inferior to ABO-C LT in graft survival and several ABO-I-related complications. Graft survival of ABO-I LT was comparable to that of ABO-C LT in pediatric patients and those using rituximab.

Lee EC, Kim SH, Park SJ. Outcomes after liver transplantation in accordance with ABO compatibility: A systematic review and meta-analysis. *World J Gastroenterol* 2017; 23(35): 6516-6533 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i35/6516.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i35.6516>

## INTRODUCTION

In an animal experiment in 1969, Starzl *et al*<sup>[1]</sup> reported that the liver is a privileged organ that could be transplanted with relatively lower prevalence of acute rejection than those associated with the kidney or heart. Furthermore, in 1979, Starzl *et al*<sup>[2]</sup> reported 11 cases of successful ABO-incompatible (ABO-I) liver transplantation (LT) without graft rejections<sup>[2]</sup>. Since then, however, there has been a series of reports of heightened prevalence of antibody-mediated rejection (AMR), lower graft survival, hepatic artery thrombosis (HAT), and cholangitis in ABO-I LT compared to ABO-compatible (ABO-C) LT<sup>[3-6]</sup>. Nevertheless, the application of various desensitization strategies, such as plasma exchange (PE) (or plasmapheresis), splenectomy, graft local infusion (GLI), mycophenolate mofetil (MMF), rituximab, and intravenous immunoglobulin (IVIG) to ABO-I LT highlight the potential of ABO-I LT as a promising alternative to ABO-C LT, and the introduction of rituximab has brought about substantial improvements in the outcomes of ABO-I LT<sup>[7-12]</sup>. Currently, its importance is expanding in the East, where the proportion of uses of ABO-I allografts for

living donor liver transplantation (LDLT) is higher than that in the West, and particularly in Korea and Japan—two countries that show notably higher proportions of interfamilial organ donation.

However, there are still heated debates with regard to the prevalence of graft survival, patient survival, ABO-I-related complications, such as rejection, infection, biliary stricture, and HAT associated with ABO-I LT and ABO-C LT, with much heterogeneity in different reports. Therefore, considering the fact that cases of ABO-I LT would inevitably rise due to demands for donor organs far outnumbering the supply and increased difficulty of matching appropriate ABO-C liver allografts, a comprehensive analysis of the results from previous reports of LT across the ABO blood group barrier is needed.

## MATERIALS AND METHODS

### Study selection

Systematic review and meta-analysis were performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines<sup>[13]</sup>. Databases of Medline (Pubmed), EMBASE, and Cochrane library were used to search for relevant articles among publications dated November 28, 2016. Publication year and language were not specified or limited for the search. The following keywords for the database search were used: (ABO OR = blood group OR = blood type) AND (incompatibility OR = mismatch OR = barrier) AND liver transplantation. Title and abstracts of identified articles were screened independently by two investigators (Lee EC, Shim JR), and full-text articles with potential relevance were obtained.

### Eligibility criteria

The included studies were articles that compared ABO-I LT and ABO-C LT with a minimum of one outcome of interest. The following types of articles were excluded: abstracts, meeting papers, case reports/series, reviews, meta-analyses, letters, editorial comments, animal studies, single-arm studies, and studies unable to extract data. When there were overlapping cohorts examined by the same institutions, data from the most recent studies were used.

### Assessment of methodological quality

Because there was no randomized controlled trial study included in this review, methodological quality was assessed based on a maximum score of 9 for “selection of patients”, “comparability”, and “outcome of study” as per the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies<sup>[14]</sup>. All of the studies included in this meta-analysis were assessed by two investigators (Lee EC, Shim JR), and disagreements were resolved by a consensus.

**Data extraction**

Data for the following items were extracted: first author, publication year, study periods, region, sample size, population, recipient age, donor age, urgent indication, donor type, prescription for ABO-I LT, immunosuppression, graft survival, patient survival, AMR, acute cellular rejection (ACR), CR (chronic rejection), bacterial infection, fungal infection, cytomegalovirus (CMV) infection, overall biliary complication, bile leak, biliary stricture, hepatic artery (HA) complication, hepatic vein (HV) complication, and portal vein (PV) complication. For studies that divided ABO-C LT into ABO-C non-identical LT and ABO-Identical (ABO-Id) LT and reported separate outcomes for each<sup>[15-20]</sup>, the outcomes were combined for the purpose of this meta-analysis. If the required data were not clearly articulated in the selected articles, we requested the original data *via* an email to the corresponding authors. All data were independently investigated and cross-checked by two investigators (Lee EC, Shim JR), and another investigator (Kim SH) provided the final confirmation.

**Statistical analysis**

This meta-analysis was performed in compliance with the Cochrane guidelines for systematic review<sup>[21]</sup>. Categorical variables were analyzed with odds ratios (OR) with 95% confidence interval (CI) using the Mantel-Haenszel method, and continuous variables were analyzed with weighted mean differences (WMD) with 95%CI using an inverse variance method. Heterogeneity among studies was assessed with Higgin's  $I^2$  index<sup>[22]</sup> or Cochran's  $Q$  test<sup>[21,23]</sup>. The random-effects model was used when  $I^2$  was  $> 50\%$  or  $P$ -value (Cochran's  $Q$  test) was  $< 0.10$ , and the fixed-effects model was used in all other cases. Heterogeneous results were further examined with a sensitivity analysis using the leave-one-out method and subgroup analyses. Possible publication bias was assessed using funnel plots and Egger's regression test, which evaluates a funnel plot asymmetry<sup>[24,25]</sup>. If a publication bias with  $P$ -value  $< 0.10$  (Egger's regression test) was detected, the impact on the outcomes of the meta-analysis was assessed after enhancing the symmetry using the trim-and-fill method of Duvall and Tweedie<sup>[26]</sup>. The presence of publication bias in fewer than 10 studies was considered unreliable as per the Cochrane Handbook for Systematic Reviews<sup>[27]</sup>. A  $P$ -value of  $< 0.05$  was considered statistically significant. Statistical analyses were performed using the Review Manager (RevMan) software version 5.3 (<http://tech.cochrane.org/revman>) and R package "meta" (<https://cran.r-project.org/web/packages/meta>).

**RESULTS****Search results**

A total of 986 citations were found in the primary

search using combinations of keywords for database search, of which 762 irrelevant or duplicated citations were excluded. After retrieving the titles and abstracts from the remaining 224 articles, another 186 articles were excluded. From the 38 potentially relevant studies, additional studies were excluded for the following reasons: single-arm studies ( $n = 9$ ), overlapping cohorts from the same institutions ( $n = 4$ ), studies investigating multiple desensitization protocols ( $n = 1$ ), timing of rituximab administration ( $n = 1$ ), and pathology ( $n = 1$ ), and unable data extraction ( $n = 1$ ). As a result, 21 studies were included in this meta-analysis<sup>[5,15-20,28-41]</sup>. The flow diagram of study selection is shown in Figure 1.

**Characteristics of included studies**

This meta-analysis included 21 retrospective observational studies that were conducted on a total of 8247 patients<sup>[5,15-20,28-41]</sup>. Of these patients, 1494 underwent ABO-I LT, while 6753 underwent ABO-C LT. There has been no randomized clinical trial conducted on this topic. Study periods ranged from 1984-2014. For studies involving less than 10% heterogeneity in study population (adult vs pediatric), donor type (deceased vs living), urgent indication [*i.e.*, fulminant hepatic failure (FHF), acute liver failure (ALF), re-transplantation, and critically ill patients in the intensive care unit], and use of rituximab for ABO-I LT, these parameters were classified according to the majority. One registry study was included in this meta-analysis<sup>[35]</sup>. Characteristics of the included studies are summarized in Table 1.

**Methodological quality assessment**

All studies included in this meta-analysis showed a Newcastle-Ottawa Scale (NOS) score  $\geq 6$ . Four case or propensity score matched studies were included<sup>[29,30,35,41]</sup>. Quality assessments of included cohort studies are presented in Table 2.

**Graft and patient survival**

Graft survival and patient survival were reported by 16 and 15 studies, respectively. ABO-I LT showed poorer outcomes than those of ABO-C LT in the pooled results of graft survival (1-year: OR = 0.66, 95%CI: 0.57-0.76,  $P < 0.001$ ; 3-year: OR = 0.74, 95%CI: 0.64-0.85,  $P < 0.001$ ; 5-year: OR = 0.75, 95%CI: 0.66-0.86,  $P < 0.001$ ; 10-year: OR = 0.80, 95%CI: 0.69-0.93,  $P = 0.004$ ; Figure 2).

There were no differences in 1-, 3-, and 5-year patient survival in accordance with ABO compatibility (1-year: OR = 0.88, 95%CI: 0.67-1.16,  $P = 0.38$ ; 3-year: OR = 0.89, 95%CI: 0.64-1.23,  $P = 0.47$ ; 5-year: OR = 0.89, 95%CI: 0.66-1.20,  $P = 0.45$ ; Figure 3). However, there was a significant difference in the 10-year patient survival between ABO-I and ABO-C groups (10-year: OR = 0.46, 95%CI: 0.28-0.78,  $P = 0.004$ ; Figure 3). There was no significant

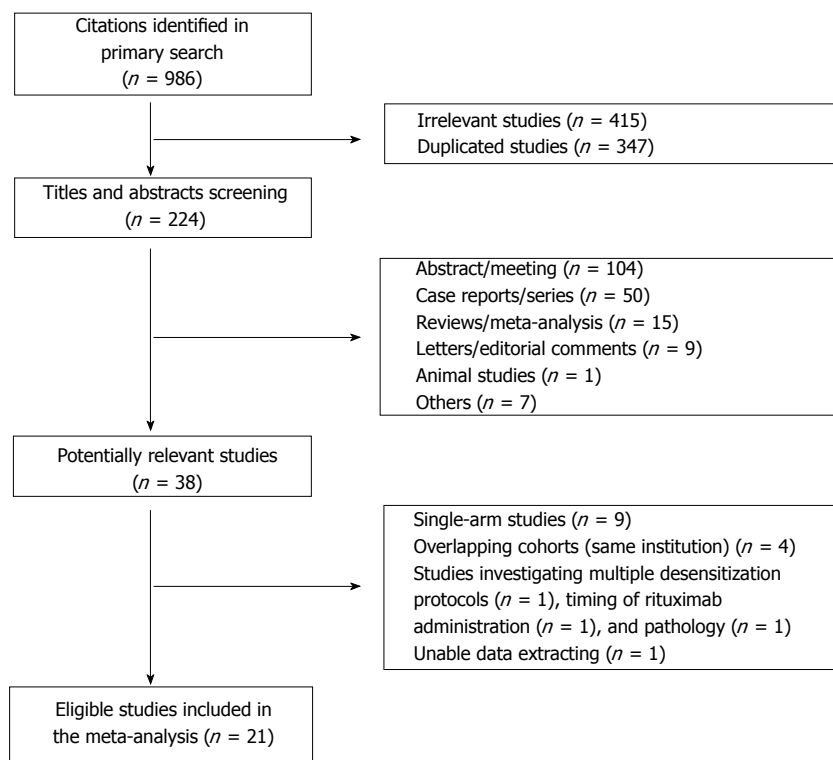


Figure 1 Flow diagram showing the selection of articles for meta-analysis.

heterogeneity in graft and patient survival.

### Complications

**Rejection:** AMR, ACR, and CR were reported by 4, 14, and 4 studies, respectively. Pooled results showed that the risks for AMR (OR = 74.21, 95%CI 16.32-337.45,  $P < 0.001$ ; Figure 4A) and CR (OR = 2.28, 95%CI: 1.00-5.22,  $P = 0.05$ ; Figure 4C) were significantly higher in ABO-I LT than in ABO-C LT, but there was no statistically significant difference in the risk for ACR (OR = 1.23, 95%CI: 0.93-1.62,  $P = 0.15$ ; Figure 4B). There was no significant heterogeneity in the results for rejection.

**Infection:** Bacterial and fungal infections were each reported by 4 studies, while CMV infection was reported by 5 studies. Although there were no differences in bacterial infection (OR = 0.72, 95%CI: 0.46-1.14,  $P = 0.16$ ; Figure 4D) and fungal infection (OR = 0.66, 95%CI: 0.37-1.18,  $P = 0.16$ ; Figure 4E) in accordance with ABO-compatibility, CMV infection was more prevalent in ABO-I LT than in ABO-C LT (OR = 2.64, 95%CI: 1.63-4.29,  $P < 0.001$ ; Figure 4F). There was no significant heterogeneity in the results for infection.

**Biliary:** There were no statistically significant differences in overall biliary complication (OR = 1.75, 95%CI: 0.89-3.43,  $P = 0.10$ ; Figure 5A), bile leak (OR = 1.85, 95%CI: 0.46-7.39,  $P = 0.39$ ; Figure 5B), and biliary stricture (OR = 1.37, 95%CI: 0.70-2.70,  $P =$

0.36; Figure 5C) in accordance with ABO compatibility. However, there were high heterogeneities in overall biliary complication ( $\chi^2 = 15.22$ , degree of freedom [d.f.] = 7,  $P = 0.03$ ;  $I^2 = 54\%$ ), bile leak ( $\chi^2 = 4.25$ , d.f. = 2,  $P = 0.12$ ;  $I^2 = 53\%$ ), and biliary stricture ( $\chi^2 = 9.36$ , d.f. = 5,  $P = 0.10$ ;  $I^2 = 47\%$ ).

**Vascular:** HA complication (OR = 4.17, 95%CI: 2.26-7.67,  $P < 0.001$ ; Figure 5D) was significantly more prevalent in ABO-I LT than in ABO-C LT. However, there were no significant differences between ABO-I LT and ABO-C LT in HV complication (OR = 1.60, 95%CI: 0.64-4.00,  $P = 0.32$ ; Figure 5E) and PV complication (OR = 1.83, 95%CI: 0.70-4.76,  $P = 0.22$ ; Figure 5F). There was no severe heterogeneity in vascular complications.

### Sensitivity and subgroup analyses

In this meta-analysis, there were high heterogeneities in overall biliary complication, bile leak, and biliary stricture. We performed a sensitivity analysis on these variables using the leave-one-out method and found that omitting the study of Sanchez *et al.*<sup>(41)</sup> with a wide range of CI (overall biliary complication: OR = 85.00, 95%CI: 7.97-906.81; Bile leak: OR = 10.82, 95%CI: 1.17-100.44) eliminated the heterogeneity in overall biliary complication and bile leak. Particularly, post-sensitive analysis results showed that ABO-I LT was associated with higher prevalence of overall biliary complications than ABO-C LT (OR = 1.52, 95%CI: 1.01-2.28,  $P = 0.04$ ; Table 3).

Table 1 Characteristics of the included studies

Ref.	Publication (yr)	Study periods (yr)	Region	Arms	Sample size	Population <sup>3</sup>	Recipient age	Donor age	Urgent Indications <sup>3,4</sup>	Donor type <sup>3</sup>	Prescription for ABO-I LT	Immunosuppression
Song <i>et al.</i> <sup>[28]</sup>	2016	2008-2013	South Korea	ABO-I ABO-C	235 1301	Adult	52.8 ± 8.0 51.7 ± 5.9	29.2 ± 9.1 28.2 ± 7.6	No	Living	Rituximab, PE, GLI (±), Splenectomy (±), Cyclophosphamide	Steroids, Basiliximab, Tac, MMF
Kim <i>et al.</i> <sup>[29]</sup>	2016	2010-2013	South Korea	ABO-I ABO-C	472 942	Adult	50 (22-65) 51 (20-68)	32 (18-68) 30 (18-62)	No	Living	Rituximab, PE, GLI (±)	Steroids, Basiliximab, Tac, MMF
Kim <i>et al.</i> <sup>[30]</sup>	2016	2011-2014	South Korea	ABO-I ABO-C	252 752	Adult	51.3 ± 6.7 51.1 ± 6.7	30.1 ± 11.2 28.8 ± 11.3	No	Living	Rituximab, PE, IVIG, Preoperative MMF	Steroids, Basiliximab, Tac, MMF
Ikegami <i>et al.</i> <sup>[31]</sup>	2016	1997-2013	Japan	ABO-I ABO-C	19 389	Adult	47.7 ± 15.7 51.7 ± 11.9	36.6 ± 11.3 37.4 ± 10.5	No	Living	Rituximab3, IVIG (±), PE, GLI (±), Splenectomy (±), Preoperative MMF (±)	Steroids, Tac (or CsA), MMF
Lee <i>et al.</i> <sup>[32]</sup>	2015	2006-2013	Taiwan	ABO-I ABO-C	46 340	Adult	53.5 (19-67) 54.7 (18-70)	NA NA	No	Living	Rituximab, Plasmapheresis (or PE)	Steroids, Tac, MMF
Shen <i>et al.</i> <sup>[33]</sup>	2014	2010-2013	China	ABO-I ABO-C	35 66	Adult	46.7 ± 12.1 42.6 ± 10.2	NA NA	Yes	Deceased	Rituximab, IVIG	Steroids, Basiliximab, Tac, MMF
Heffron <i>et al.</i> <sup>[34]</sup>	2010	1998-2008	United States	ABO-I ABO-C	12 21	Pediatric	NA NA	NA NA	Yes	Deceased	-	Steroids, Daclizumab, Tac, MMF
Stewart <i>et al.</i> <sup>[35]</sup>	2009	1990-2006	United States	ABO-I ABO-C	1302 3902	Infant	0.3 0.4	8.1 8.3	No	Deceased	NA	NA
Iwamoto <i>et al.</i> <sup>[36]</sup>	2008	2000-2007	Japan	ABO-I ABO-C	15 37	Adult	NA NA	NA NA	No	Living	NA	NA
Toso <i>et al.</i> <sup>[20]</sup>	2007	1991-2005	Canada	ABO-I ABO-C1 ABO-Id	14 29 65	Adult	42 (17-61) 47 (16-62) 47 (17-66)	NA NA NA	Yes	Deceased	Lymphocyte-depleting antibodies5, Plasmapheresis (±)	Steroids, Daclizumab, CsA (or Tac), AZA (or MMF, Sirolimus)
Saito <i>et al.</i> <sup>[37]</sup>	2007	2000-2001	Japan	ABO-I ABO-C	10 81	All ages	NA NA	NA NA	No	Deceased, Living	NA	NA
Koukoutsis <i>et al.</i> <sup>[38]</sup>	2007	1984-2005	United Kingdom	ABO-I ABO-C1 ABO-Id	4 73 203	Adult	NA NA NA	NA NA NA	Yes	Deceased	NA	NA
Ueda <i>et al.</i> <sup>[38]</sup>	2006	1990-2003	Japan	ABO-I ABO-C1 ABO-Id	74 114 380	Pediatric	NA NA NA	NA NA NA	No	Living	Steroids pulse weekly, PGE1, CsA -> AZA (1 mo after LT)	Steroids, Tac
Heffron <i>et al.</i> <sup>[38]</sup>	2006	1999-2005	United States	ABO-I ABO-C	16 122	Pediatric	6.5 ± 6.2 8.1 ± 6.2	NA NA	No	Deceased	Plasmapheresis (±)	Steroids, Daclizumab, Tac, MMF
Bjorro <i>et al.</i> <sup>[37]</sup>	2003	1990-2001	Nordic countries	ABO-C1 ABO-Id	76 143	All ages	NA NA	44.8 (22-55) 42.3 (12-85) 41.0 (2-75)	Yes	Deceased	NA	NA
Chui <i>et al.</i> <sup>[39]</sup>	1997	1986-1996	Australia	ABO-I ABO-C	7 36	All ages	13 (6-32) NA	NA NA	Yes	Deceased	Plasmapheresis (±), Splenectomy (±)	Steroids, CsA, AZA
Cacciarelli <i>et al.</i> <sup>[36]</sup>	1995	1988-1993	United States	ABO-I ABO-C1 ABO-Id	14 22 108	Pediatric	2.2 ± 1.1 4.2 ± 1.0 3.7 ± 0.5	NA NA NA	No	Deceased	OKT3 (or ATG, CsA)	Steroids, ATG (or OKT3, CsA), Tac

Lo <i>et al</i> <sup>(40)</sup>	1994	1988-1993	United States	ABO-I ABO-C	29 196	All ages	NA NA	NA NA	Deceased	Yes	NA	ATG (±)	Steroids, CsA (or OKT3), AZA
Sanchez <i>et al</i> <sup>(41)</sup>	1993	1985-1991	United States	ABO-I ABO-C	182 182	Adult	45 (16-61) 47 (17-59)	NA NA	Deceased	No	NA	NA	NA
Reding <i>et al</i> <sup>(45)</sup>	1992	1984-1989	Belgium	ABO-I ABO-C† ABO-Id	16 16 38	All ages	NA NA NA	NA NA NA	Deceased	Yes	NA	OKT3 (±)	Steroids, CsA, AZA(±)
Gugenheim <i>et al</i> <sup>(3)</sup>	1990	1984-1988	France	ABO-I ABO-C	17 217	All ages	30 (12-49) NA	NA NA	Deceased	Yes	NA	-	Steroids, CsA, AZA

<sup>1</sup>Compatible, but not identical; <sup>2</sup>Propensity or case matched patients; <sup>3</sup>If there are minority groups that make up less than about 10%, the article is categorized as covering the majority; <sup>4</sup>Such as FHF, ALF, retransplantation, and critically ill patients in the intensive care unit; <sup>5</sup>Documented as "lymphocyte-depleting antibodies", but not clarified exactly. ABO-C: ABO-compatible; ABO-I: ABO-incompatible; ABO-Id: ABO-identical; ATC: anti-thymocyte globulin; AZA: Azathioprine; CsA: Cyclosporin A; GLI: Graft local infusion; IMiF: Intravenous immunoglobulin; LT: Liver transplantation; MMF: Mycophenolate mofetil; NA: Not applicable; OKT3: Muromonab-CD3; PE: Plasma exchange; Tac: Tacrolimus.

Although there were no significant heterogeneities in most comparisons, such as in graft survival, patient survival, and complications, we attempted to minimize potential heterogeneities and detail the subgroup-specific differences through subgroup analyses. Possible confounding factors-the parameters that were speculated to impact the outcomes of this meta-analysis-included study population (adult vs pediatric), use of rituximab for ABO-I LT, urgent indication, and donor type (deceased vs living). There were no significant differences in most subgroup comparisons.

However, studies that involved pediatric patients<sup>[16,18,34,35,38]</sup> showed better 1-year (OR = 0.88, 95%CI: 0.68-1.15 vs OR = 0.59, 95%CI: 0.50-0.69; *P* = 0.01) and 3-year graft survivals (OR = 0.95, 95%CI: 0.71-1.26 vs OR = 0.67, 95%CI: 0.57-0.80; *P* = 0.04) after ABO-I LT than those involving adult patients. Furthermore, in such studies, there were no significant differences between ABO-I LT and ABO-C LT in 1-, 3-, 5-, and 10-year graft survivals (1-year: OR=0.88, 95%CI: 0.68-1.15, *P* = 0.35; 3-year: OR = 0.95, 95%CI: 0.71-1.26, *P* = 0.71; 5-year: OR = 0.82, 95%CI: 0.63-1.07, *P* = 0.14; 10-year: OR = 0.71, 95%CI: 0.41-1.23, *P* = 0.22).

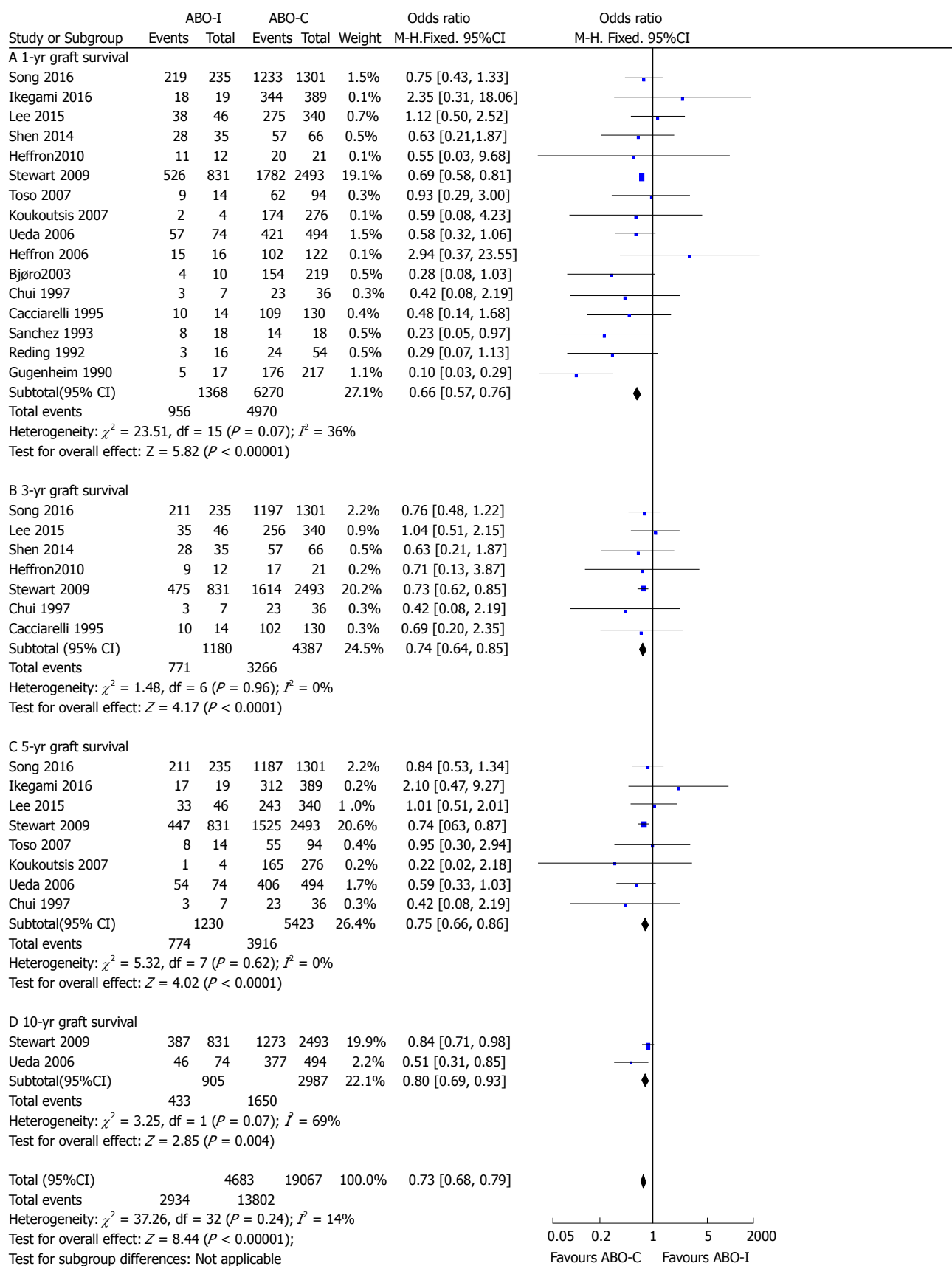
Meanwhile, using rituximab in ABO-I LT patients<sup>[28-33]</sup> showed better 1-year graft survival (OR = 0.88, 95%CI: 0.58-1.33 vs OR = 0.44, 95%CI: 0.30-0.66; *P* = 0.02) after ABO-I LT compared to cases not using rituximab<sup>[15,16,18, 34,38-40, 42]</sup>. Moreover, in such cases, 1-, 3-, and 5-year graft survival of ABO-I LT were not significantly different from those of ABO-C LT (1-year: OR = 0.88, 95%CI: 0.58-1.33, *P* = 0.55; 3-year: OR = 0.81, 95%CI: 0.56-1.18, *P* = 0.28; 5-year: OR = 0.96, 95%CI: 0.66-1.39, *P* = 0.83). On the other hand, when rituximab was not used, incidence of biliary stricture (OR = 1.00, 95%CI: 0.46-2.15 vs OR=4.32, 95%CI: 1.18- 15.81; *P* = 0.06) and ACR (OR = 0.86, 95%CI: 0.57-1.30 vs OR = 1.61, 95%CI: 1.01-2.58; *P* = 0.048) tended to be higher in ABO-I LT than in ABO-C LT. However, there was no difference in AMR incidence (OR=48.32, 95%CI: 2.31-1011.61 vs OR = 245.87, 95%CI: 13.04-4636.62; *P* = 0.45) and patient survival (1-year: OR = 0.88, 95% CI 0.59-1.31 vs OR = 0.67, 95%CI: 0.44-1.04, *P* = 0.38; 3-year: OR = 0.90, 95%CI: 0.64-1.27 vs OR = 0.80, 95%CI: 0.31-2.06, *P* = 0.82; 5-year: OR = 0.90, 95%CI: 0.61-1.31 vs OR = 1.00, 95%CI: 0.20-5.08, *P* = 0.89) in accordance with the use of rituximab.

Studies that involved urgent indications<sup>[15,17,19,20,33,34,39,40,42]</sup> had worse 1-year graft survival (OR = 0.37, 95%CI: 0.23-0.59 vs OR=0.70, 95%CI: 0.61-0.81; *P* = 0.01) but better 5-year patient survival (OR = 2.38, 95%CI: 0.86-6.63 vs OR = 0.79, 95%CI: 0.57-1.08, *P* = 0.043) for ABO-I LT than those for ABO-C LT when compared to studies without urgent indications.

In addition, compared to cases that involved the use of deceased donor liver allografts, those that involved the use of living donor liver allografts<sup>[18,28-32,36]</sup> showed lower prevalence of ACR (OR = 0.87, 95%CI: 0.58-1.32 vs OR = 1.69, 95%CI: 1.14-2.50; *P* = 0.02) and biliary stricture (OR = 1.00, 95%CI: 0.46-2.15 vs OR = 4.49, 95%CI: 1.36-14.87; *P* = 0.04) in ABO-I LT. Results of sensitivity analysis and subgroup analysis are summarized in Table 3.

**Publication bias**

In this meta-analysis, 1-year patient survival was found to have a potential publication bias with a funnel plot asymmetry (Figure 6A) and a *P* = 0.06 calculated by the Egger's regression test. Other variables did not show a significant publication bias. After adjusting for funnel plot asymmetry using the trim-and-fill method<sup>[26]</sup> (Figure 6B), ABO-I LT showed a significantly poorer 1-year patient survival than ABO-C LT (OR=0.73, 95%CI: 0.56-0.95, *P* = 0.02; *I*<sup>2</sup> = 25.8%).



**Figure 2 Comparison of graft survival between ABO-incompatible and ABO-compatible liver transplantation.** ABO-C: ABO-compatible; ABO-I: ABO-incompatible; LT: Liver transplantation.

**Table 2** Modified Newcastle-Ottawa quality assessment scale for cohort studies included in the meta-analysis

Ref.	Selection			Comparability <sup>1</sup>	Outcome			Overall Quality Score (Maximum 9)
	Representativeness	Selection	Ascertainment		Assessment	Length of follow-up	Adequacy of follow-up	
Song <i>et al</i> <sup>[28]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Kim <i>et al</i> <sup>[29]</sup>	↓	↓	↓	↑	↓	↓	↓	8
Kim <i>et al</i> <sup>[30]</sup>	↓	↓	↓	↑	↓	↓	↓	8
Ikegami <i>et al</i> <sup>[31]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Lee <i>et al</i> <sup>[32]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Shen <i>et al</i> <sup>[33]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Heffron <i>et al</i> <sup>[34]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Stewart <i>et al</i> <sup>[35]</sup>	↓	↓	↓	↑	↓	↓	↓	8
Iwamoto <i>et al</i> <sup>[36]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Toso <i>et al</i> <sup>[20]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Saito <i>et al</i> <sup>[37]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Koukoutsis <i>et al</i> <sup>[19]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Ueda <i>et al</i> <sup>[18]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Heffron <i>et al</i> <sup>[38]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Björro <i>et al</i> <sup>[17]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Chui <i>et al</i> <sup>[39]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Cacciarelli <i>et al</i> <sup>[16]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Lo <i>et al</i> <sup>[40]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Sanchez <i>et al</i> <sup>[41]</sup>	↓	↓	↓	↑	↓	↓	↓	8
Reding <i>et al</i> <sup>[15]</sup>	↓	↓	↓	↑	↓	↓	↓	6
Gugenheim <i>et al</i> <sup>[5]</sup>	↓	↓	↓	↑	↓	↓	↓	6

<sup>1</sup>A maximum of two downward arrows (↓↓) can be given for comparability. ↓ : Consistent with criteria and low risk of bias; ↑ : Not consistent with criteria and high risk of bias.

## DISCUSSION

Since the first attempt of ABO-I LT by Starzl *et al*<sup>[1,21]</sup>, poor outcomes after ABO-I LT, including AMR, lower graft survival, HAT, and cholangitis, were insurmountable barriers for expanding the application of transplantation across the ABO blood group barrier, from a few urgent cases to cases of chronic liver disease and liver cancer<sup>[3-6]</sup>. Extraordinary improvements have been made in the outcomes of ABO-I LT with the introduction of multiple desensitization strategies, such as PE (or plasmapheresis), splenectomy, GLI, rituximab, MMF, and IVIG, as well as with advances of immunosuppression agents<sup>[7-12]</sup>. However, whether ABO-I LT is comparable to ABO-C LT remains a topic of debate.

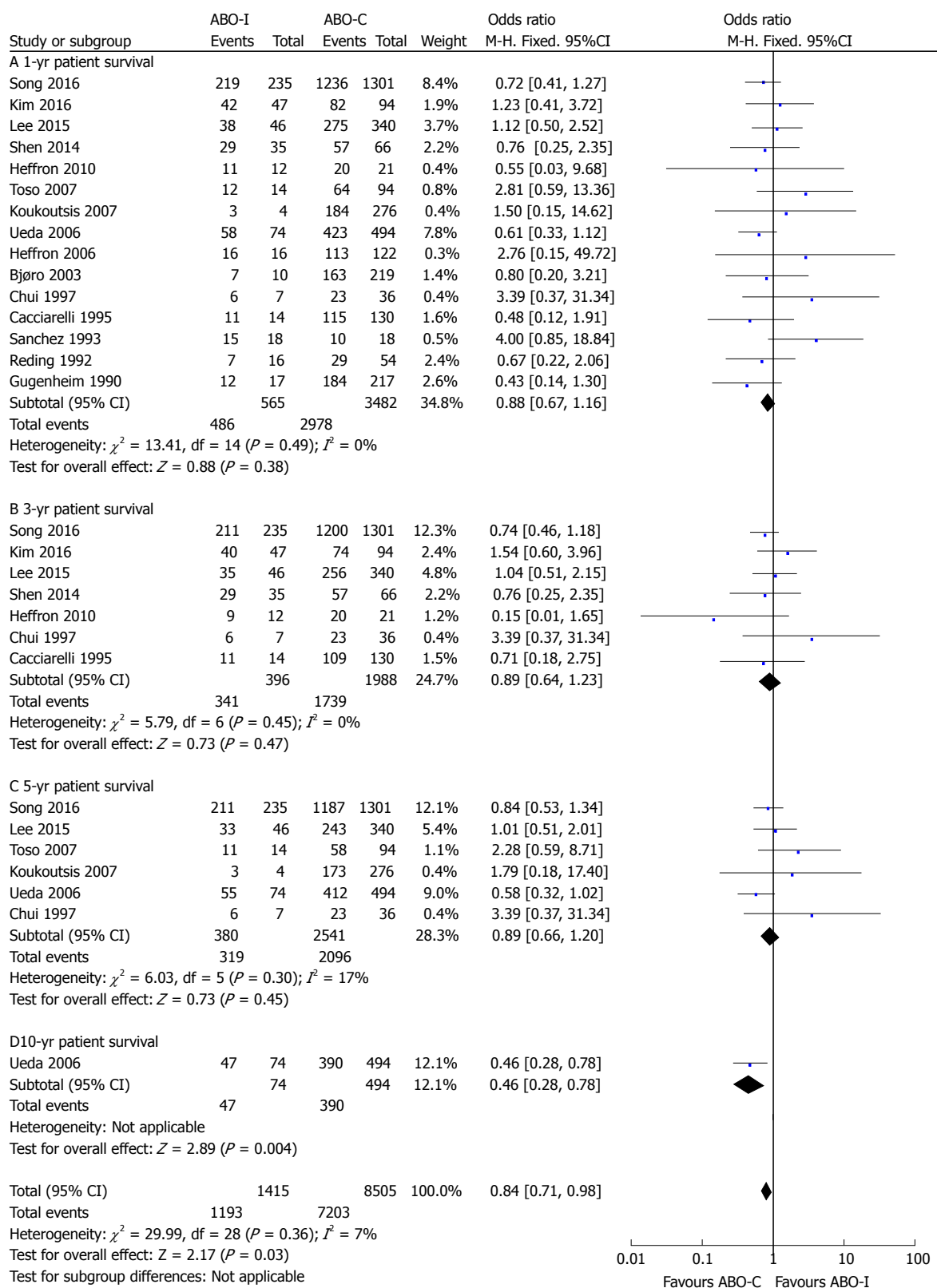
This meta-analysis revealed that pooled results of graft survival were poorer in ABO-I LT than in ABO-C LT. However, patient survival did not significantly vary in accordance with ABO compatibility in most cases. The data on 10-year patient survival had low reliability, as they were only reported by one study-although

produced based on a long-term follow-up<sup>[18]</sup>.

Meanwhile, the cumulative meta-analysis in order by the median year of study period showed that the cumulative results of graft and patient survival remained consistent since the early 2000s (Supplementary Figures 1 and 2). This is mainly due to the stabilization of the desensitization protocol through the application of PE (or plasmapheresis)<sup>[42-44]</sup>, muromonab-CD3 (OKT3)<sup>[42-44]</sup>, splenectomy<sup>[9]</sup>, PV infusion<sup>[10,45]</sup>, HA infusion<sup>[46,47]</sup>, rituximab<sup>[48-50]</sup>, and IVIG<sup>[7,8,51]</sup> in ABO-I LT. However, from a different perspective, the fact that ABO-I LT patients showed a poorer graft survival than ABO-C LT patients and that cumulative meta-analysis of graft survival remained mostly unchanged since the early 2000s implies that the current desensitization protocol for ABO-I LT still requires an improvement.

With regard to ABO-I-related complications, the prevalence of AMR, CR, CMV infection, and HA complication was higher in ABO-I LT than in ABO-C LT. Overall biliary complication-after omitting a study of Sanchez *et al*<sup>[41]</sup> with a wide range of CI in the





**Figure 3 Comparison of patient survival between ABO-incompatible and ABO-compatible liver transplantation.** ABO-C: ABO-compatible; ABO-i: ABO-incompatible; LT: Liver transplantation.

sensitivity analysis—was more prevalent in ABO-I LT than in ABO-C LT.

In the subgroup analyses, studies that only involved pediatric patients<sup>[16,18,34,35,38]</sup>, compared to those that did not, showed better 1-year and 3-year

graft survivals after ABO-I LT than those after ABO-C LT. Furthermore, in such cases, 1-, 3-, 5-, and 10-year graft survivals after ABO-I LT were comparable to those after ABO-C LT. There were several reports that pediatric ABO-I LT was more successful than

Table 3 Sensitivity analysis and subgroup analysis

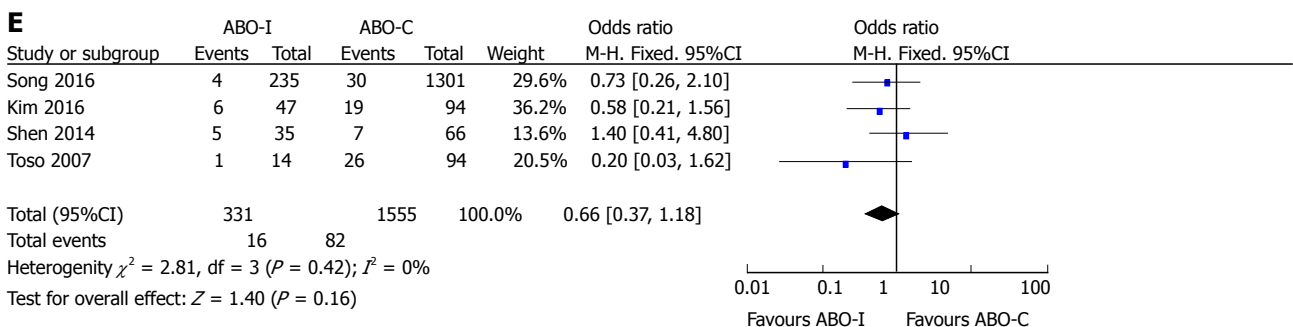
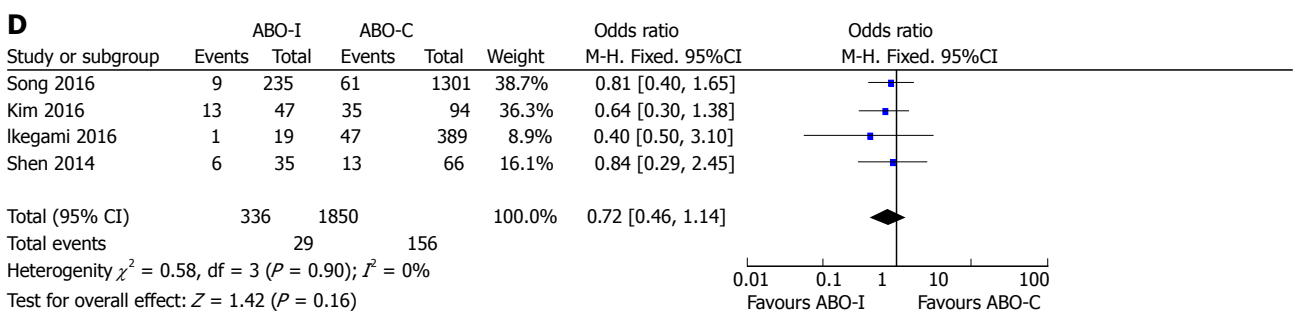
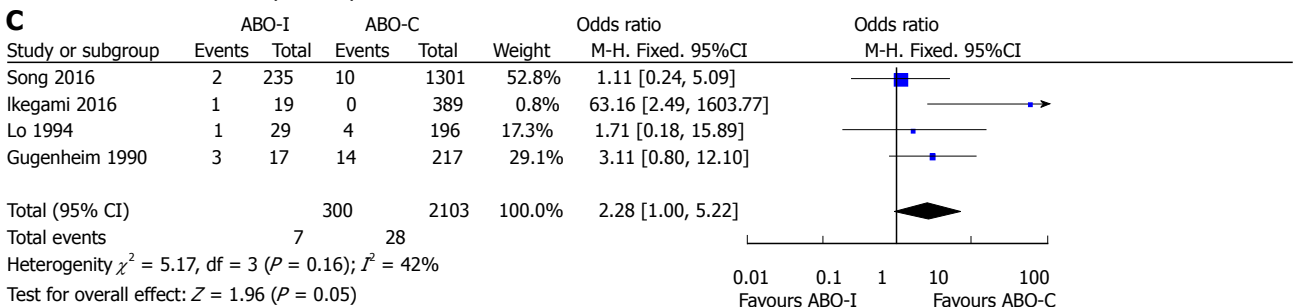
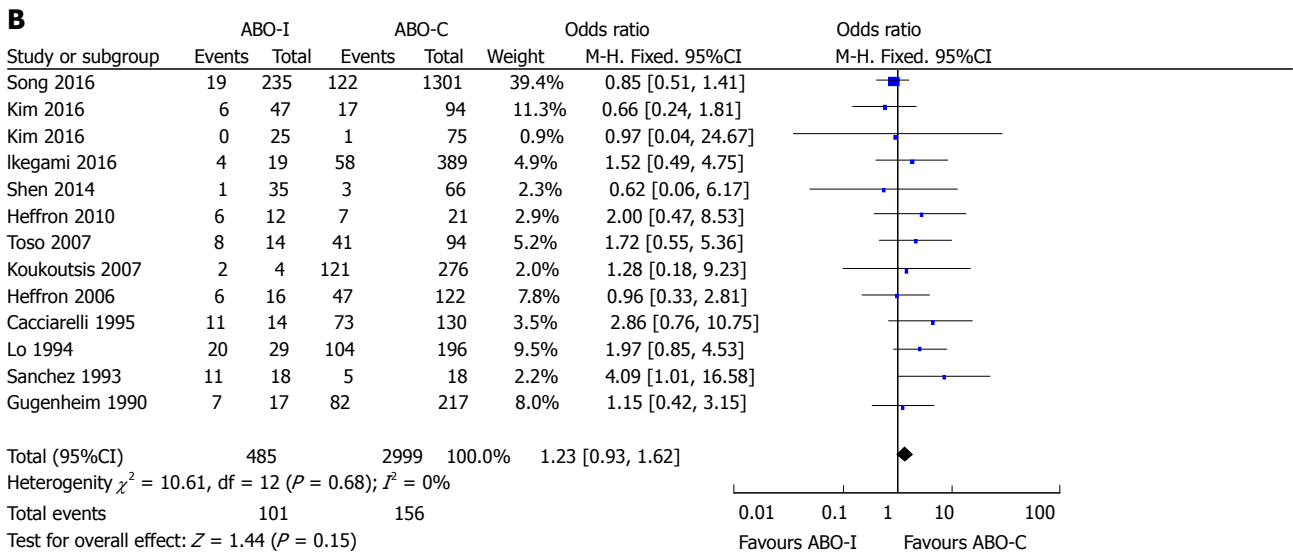
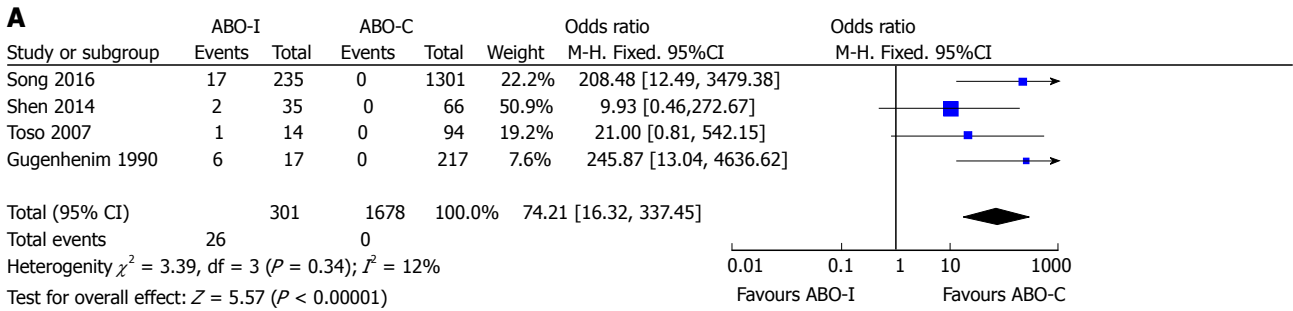
Variables	No. of studies	OR = [95%CI]	P <sup>1</sup> value	I <sup>2</sup> (%)
Sensitivity analysis				
Overall biliary complication		1.75 [0.89-3.43]	0.10	54
Omitting Sanchez <i>et al</i> <sup>[41]</sup>	7	1.52 [1.01-2.28]	0.04	0
Omitting Cacciarelli <i>et al</i> <sup>[16]</sup>	7	1.81 [0.87-3.76]	0.11	61
Omitting Heffron <i>et al</i> <sup>[38]</sup>	7	1.86 [0.87-3.95]	0.11	60
Omitting Toso <i>et al</i> <sup>[20]</sup>	7	1.86 [0.84-4.13]	0.13	60
Omitting Iwamoto <i>et al</i> <sup>[36]</sup>	7	1.81 [0.84-3.92]	0.13	61
Omitting Shen <i>et al</i> <sup>[33]</sup>	7	1.89 [0.90-3.96]	0.09	59
Omitting Lee <i>et al</i> <sup>[32]</sup>	7	1.69 [0.72-3.94]	0.23	56
Omitting Kim <i>et al</i> <sup>[29]</sup>	7	2.07 [0.98-4.37]	0.06	50
Bile leak		1.85 [0.46-7.39]	0.39	53
Omitting Sanchez <i>et al</i> <sup>[41]</sup>	2	0.98 [0.38-2.49]	0.96	0
Omitting Kim <i>et al</i> <sup>[30]</sup>	2	2.47 [0.19-31.38]	0.49	77
Omitting Kim <i>et al</i> <sup>[29]</sup>	2	3.62 [0.53-24.77]	0.19	46
Biliary stricture		1.37 [0.70-2.70]	0.36	47
Omitting Sanchez <i>et al</i> <sup>[41]</sup>	5	1.28 [0.62-2.62]	0.51	54
Omitting Lo <i>et al</i> <sup>[40]</sup>	5	1.11 [0.54-2.26]	0.78	42
Omitting Ikegami <i>et al</i> <sup>[31]</sup>	5	1.55 [0.71-3.39]	0.27	49
Omitting Kim <i>et al</i> <sup>[30]</sup>	5	1.47 [0.74-2.95]	0.27	51
Omitting Kim <i>et al</i> <sup>[29]</sup>	5	1.72 [0.91-3.25]	0.09	28
Omitting Song <i>et al</i> <sup>[28]</sup>	5	1.20 [0.43-3.31]	0.73	49
Subgroup analysis				
1-yr graft survival		0.66 [0.57-0.76]	< 0.001	36
Rituximab for ABO-I LT (yes/no)	4 vs 7	0.88 [0.58-1.33] vs 0.44 [0.20-0.66]	0.02	0 vs 49
Living donor (yes/no)	4 vs 12	0.79 [0.56-1.13] vs 0.64 [0.55-0.74]	0.27	0 vs 44
Urgent indication (yes/no)	8 vs 8	0.37 [0.23-0.59] vs 0.70 [0.61-0.81]	0.01	27 vs 8
Pediatric2 (yes/no)	5 vs 12	0.88 [0.68-1.15] vs 0.59 [0.50-0.69]	0.01	12 vs 45
3-yr graft survival		0.74 [0.64-0.85]	< 0.001	0
Rituximab for ABO-I LT (yes/no)	3 vs 3	0.81 [0.56-1.18] vs 0.60 [0.26-1.41]	0.53	0 vs 0
Living donor (yes/no)	2 vs 5	0.84 [0.57-1.25] vs 0.72 [0.62-0.84]	0.47	0 vs 0
Urgent indication (yes/no)	3 vs 4	0.59 [0.27-1.31] vs 0.74 [0.64-0.86]	0.58	0 vs 0
Pediatric2 (yes/no)	3 vs 5	0.95 [0.71-1.26] vs 0.67 [0.57-0.80]	0.04	0 vs 0
5-yr graft survival		0.75 [0.66-0.86]	< 0.001	0
Rituximab for ABO-I LT (yes/no)	3 vs 2	0.96 [0.66-1.39] vs 0.56 [0.33-0.96]	0.11	0 vs 0
Living donor (yes/no)	4 vs 4	0.83 [0.61-1.14] vs 0.73 [0.63-0.86]	0.46	10 vs 0
Urgent indication (yes/no)	3 vs 5	0.60 [0.26-1.39] vs 0.76 [0.66-0.87]	0.6	0 vs 0
Pediatric 2 (yes/no)	2 vs 7	0.82 [0.63-1.07] vs 0.73 [0.62-0.86]	0.44	42 vs 0
10-yr graft survival		0.80 [0.69-0.93]	0.004	69
Rituximab for ABO-I LT (yes/no)	0 vs 1	NA vs 0.51 [0.31-0.85]	NA	NA
Living donor (yes/no)	1 vs 1	0.51 [0.31-0.85] vs 0.84 [0.71-0.98]	0.07	NA vs NA
Urgent indication (yes/no)	0 vs 2	NA vs 0.70 [0.44-1.11]	NA	NA vs 69
Pediatric 2 (yes/no)	2 vs 1	0.71 [0.41-1.23] vs 0.81 [0.70-0.98]	0.65	72 vs NA
1-yr patient survival		0.88 [0.67-1.16]	0.38	0
Rituximab for ABO-I LT (yes/no)	4 vs 7	0.88 [0.59-1.31] vs 0.67 [0.44-1.04]	0.38	0 vs 0
Living donor (yes/no)	4 vs 11	0.79 [0.56-1.13] vs 1.04 [0.67-1.61]	0.35	0 vs 9
Urgent indication (yes/no)	8 vs 7	0.93 [0.56-1.52] vs 0.87 [0.62-1.20]	0.83	0 vs 21
Pediatric (yes/no)	4 vs 11	0.64 [0.38-1.09] vs 0.98 [0.71-1.35]	0.18	0 vs 5
3-yr patient survival		0.89 [0.64-1.23]	0.47	0
Rituximab for ABO-I LT (yes/no)	4 vs 3	0.90 [0.64-1.27] vs 0.80 [0.31-2.06]	0.82	0 vs 43
Living donor (yes/no)	3 vs 4	0.91 [0.64-1.32] vs 0.78 [0.38-1.62]	0.71	5 vs 15
Urgent indication (yes/no)	3 vs 4	0.81 [0.35-1.91] vs 0.90 [0.63-1.28]	0.83	43 vs 0
Pediatric (yes/no)	2 vs 5	0.46 [0.15-1.38] vs 0.94 [0.67-1.32]	0.22	18 vs 0
5-yr patient survival		0.89 [0.66-1.20]	0.45	17
Rituximab for ABO-I LT (yes/no)	2 vs 2	0.89 [0.61-1.31] vs 1.00 [0.20-5.08]	0.89	0 vs 57
Living donor (yes/no)	3 vs 3	0.79 [0.57-1.08] vs 2.38 [0.86-6.63]	0.04	0 vs 0
Urgent indication (yes/no)	3 vs 3	2.38 [0.86-6.63] vs 0.79 [0.57-1.08]	0.04	0 vs 0
Pediatric (yes/no)	1 vs 5	0.58 [0.32-1.02] vs 1.04 [0.72-1.48]	0.09	NA vs 0
10-yr patient survival		0.46 [0.28-0.78]	0.004	7
Rituximab for ABO-I LT (yes/no)	0 vs 1	NA vs 0.46 [0.28-0.78]	NA	NA
Living donor (yes/no)	1 vs 0	0.46 [0.28-0.78] vs NA	NA	NA
Urgent indication (yes/no)	0 vs 1	NA vs 0.46 [0.28-0.78]	NA	NA
Pediatric (yes/no)	1 vs 0	0.46 [0.28-0.78] vs NA	NA	NA
ACR		1.23 [0.93-1.62]	0.15	0
Rituximab for ABO-I LT (yes/no)	5 vs 5	0.86 [0.57-1.30] vs 1.61 [1.01-2.58]	0.048	0 vs 0
Living donor (yes/no)	4 vs 9	0.87 [0.58-1.32] vs 1.69 [1.14-2.50]	0.02	0 vs 0
Urgent indication (yes/no)	6 vs 7	1.56 [0.96-2.53] vs 1.08 [0.77-1.53]	0.23	0 vs 22

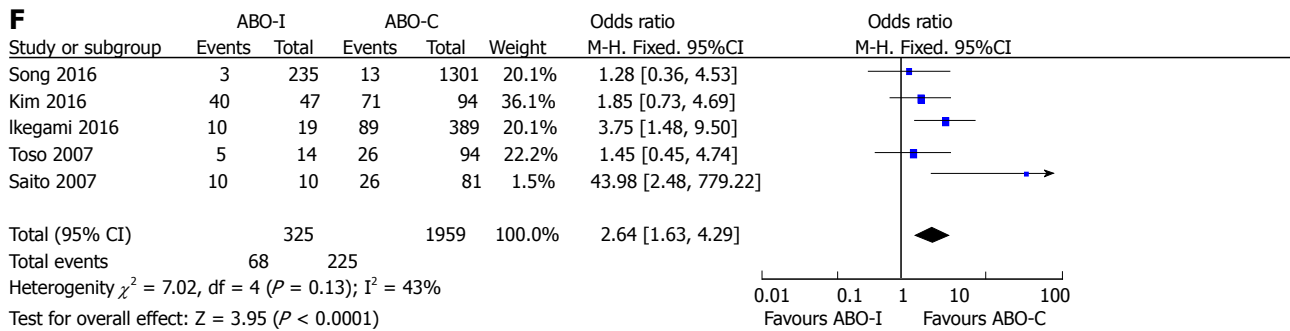
Pediatric (yes/no)	3 vs 10	1.64 [0.82-3.29] vs 1.16 [0.85-1.57]	0.37	0 vs 0
CR		2.28 [1.00-5.22]	0.05	42
Rituximab for ABO-I LT (yes/no)	2 vs 2	6.45 [0.13-333.04] vs 2.64 [0.83-8.44]	0.67	80 vs 0
Living donor (yes/no)	2 vs 2	6.45 [0.13-333.04] vs 2.64 [0.83-8.44]	0.67	80 vs 0
Urgent indication (yes/no)	2 vs 2	2.64 [0.83-8.44] vs 6.45 [0.13-333.04]	0.67	0 vs 80
Pediatric (yes/no)	0 vs 4	NA vs 2.28 [1.00-5.22]	NA	NA vs 42
AMR		74.21 [16.32-337.45]	< 0.001	12
Rituximab for ABO-I LT (yes/no)	2 vs 1	48.32 [ 2.31-1011.61] vs 245.87 [13.04-4636.62]	0.45	53 vs NA
Living donor (yes/no)	1 vs 3	208.48 [12.49-3479.38] vs 35.81 [6.02-212.88]	0.3	NA vs 18
Urgent indication (yes/no)	3 vs 1	35.81 [ 6.02-212.88] vs 208.48 [12.49-3479.38]	0.3	18 vs NA
Pediatric (yes/no)	0 vs 4	NA vs 74.21 [16.32-337.45]	NA	NA vs 12
Bacterial infection		0.72 [0.46-1.14]	0.16	0
Rituximab for ABO-I LT (yes/no)	4 vs 0	0.72 [0.46-1.14] vs NA	NA	0 vs NA
Living donor (yes/no)	3 vs 1	0.70 [0.42-1.15] vs 0.84 [0.29-2.45]	0.75	0 vs NA
Urgent indication (yes/no)	1 vs 3	0.84 [0.29-2.45] vs 0.70 [0.42-1.15]	0.75	NA vs 0
Pediatric (yes/no)	0 vs 4	NA vs 0.72 [0.46-1.14]	NA	NA vs 0
Fungal infection		0.66 [0.37-1.18]	0.16	0
Rituximab for ABO-I LT (yes/no)	3 vs 0	0.78 [0.42-1.44] vs NA	NA	0 vs NA
Living donor (yes/no)	2 vs 2	0.65 [0.31-1.33] vs 0.63 [0.09-4.40]	0.99	0 vs 62
Urgent indication (yes/no)	2 vs 2	0.63 [0.09-4.40] vs 0.65 [0.31-1.33]	0.99	62 vs 0
Pediatric (yes/no)	0 vs 4	NA vs 0.71 [0.39-1.28]	NA	NA vs 0
CMV infection		2.64 [1.63-4.29]	< 0.001	43
Rituximab for ABO-I LT (yes/no)	3 vs 0	2.2 [1.23-3.93] vs NA	NA	4 vs NA
Living donor (yes/no)	3 vs 2	2.25 [1.24-4.09] vs 6.43 [0.17-242.88]	0.58	4 vs 82
Urgent indication (yes/no)	1 vs 4	1.45 [0.45-4.74] vs 2.77 [1.12-6.86]	0.4	NA vs 53
Pediatric (yes/no)	0 vs 5	NA vs 2.64 [1.63-4.29]	NA	NA vs 43
Overall Biliary complication		1.75 [0.89-3.43]	0.1	54
Rituximab for ABO-I LT (yes/no)	3 vs 2	1.38 [0.62-3.07] vs 1.25 [0.35-4.51]	0.89	51 vs 0
Living donor (yes/no)	3 vs 5	1.52 [0.74-3.10] vs 2.36 [0.63-8.87]	0.57	46 vs 66
Urgent indication (yes/no)	2 vs 6	1.23 [0.48-3.21] vs 2.08 [0.85-5.07]	0.44	0 vs 66
Pediatric (yes/no)	2 vs 6	1.25 [0.35-4.51] vs 1.95 [0.85-4.46]	0.57	0 vs 67
Bile leak		1.85 [0.46-7.39]	0.39	53
Rituximab for ABO-I LT (yes/no)	2 vs 0	0.96 [0.38-2.46] vs NA	NA	0 vs NA
Living donor (yes/no)	2 vs 1	0.98 [0.38-2.49] vs 10.82 [1.17-100.44]	0.051	0 vs NA
Urgent indication (yes/no)	0 vs 3	NA vs 1.85 [0.46-7.39]	NA	NA vs 53
Pediatric (yes/no)	0 vs 3	NA vs 1.85 [0.46-7.39]	NA	NA vs 53
Biliary stricture		1.37 [0.70-2.70]	0.36	47
Rituximab for ABO-I LT (yes/no)	4 vs 1	1.00 [0.46-2.15] vs 4.32 [1.18-15.81]	0.06	52 vs NA
Living donor (yes/no)	4 vs 2	1.00 [0.46-2.15] vs 4.49 [1.36-14.87]	0.04	52 vs 0
Urgent indication (yes/no)	1 vs 5	4.32 [1.18-15.81] vs 1.44 [1.04-1.99]	0.11	NA vs 42
Pediatric (yes/no)	0 vs 6	NA vs 1.52 [1.11-2.08]	NA	NA vs 47
HV complication		1.60 [0.64-4.00]	0.32	NA
Rituximab for ABO-I LT (yes/no)	1 vs 0	1.60 [0.64-4.00] vs NA	NA	NA
Living donor (yes/no)	1 vs 0	1.60 [0.64-4.00] vs NA	NA	NA
Urgent indication (yes/no)	0 vs 1	NA vs 1.60 [0.64-4.00]	NA	NA
Pediatric (yes/no)	0 vs 1	NA vs 1.60 [0.64-4.00]	NA	NA
PV complication		1.83 [0.70-4.76]	0.22	0
Rituximab for ABO-I LT (yes/no)	3 vs 1	1.19 [0.31-4.65] vs 2.65 [0.29-24.07]	0.55	0 vs NA
Living donor (yes/no)	3 vs 2	1.19 [0.31-4.65] vs 3.27 [0.82-13.07]	0.31	0 vs 0
Urgent indication (yes/no)	2 vs 3	3.27 [0.82-13.07] vs 1.19 [0.31-4.65]	0.31	0 vs 0
Pediatric (yes/no)	0 vs 5	NA vs 1.83 [0.70-4.76]	NA	NA vs 0
HA complication		4.17 [2.26-7.67]	< 0.001	0
Rituximab for ABO-I LT (yes/no)	3 vs 3	2.52 [0.68-9.27] vs 4.43 [0.90-21.87]	0.59	0 vs 53
Living donor (yes/no)	4 vs 5	3.62 [1.20-10.91] vs 4.44 [2.13-9.25]	0.76	0 vs 10
Urgent indication (yes/no)	3 vs 6	5.50 [2.33-13.00] vs 3.30 [1.39-7.83]	0.41	0 vs 0
Pediatric (yes/no)	1 vs 8	0.47 [0.03-8.56] vs 5.26 [2.73-10.14]	0.11	NA vs 0

<sup>1</sup>P value for overall effect or test for differences in subgroup analysis; <sup>2</sup>Stewart *et al*<sup>[55]</sup> reported graft survival rates of pediatric and adults, respectively. ABO-I: ABO-Incompatible; ACR: Acute cellular rejection; AMR: Antibody-mediated rejection; CMV: Cytomegalovirus; CR: Chronic rejection; HA: Hepatic artery; HV: Hepatic vein; LT: Liver transplantation; PV: Portal vein.

adult ABO-I LT<sup>[52,53]</sup>. Egawa *et al*<sup>[52]</sup> reported that an advanced recipient age for ABO-I LDLT is associated with poor outcomes, including graft and patient survivals, intrahepatic biliary complications, and hepatic necrosis. Maternal anti-ABO antibodies (Ab) begin to disappear from week two after birth, and neonates begin to produce their own reservoir of anti-

ABO Ab from weeks 8-12 after birth, which reaches a level similar to that of adults by age 5-10<sup>[54,55]</sup>. Thus, younger pediatric patients may be immunologically immature, showing lower anti-ABO Ab levels and immature complement system<sup>[56,57]</sup>, which could be a possible explanation for our result of pediatric graft survival.





**Figure 4** Comparison of rejection and infection between ABO-incompatible and ABO-compatible liver transplantation. A: AMR; B: ACR; C: CR; D: Bacterial infection; E: Fungal infection; F: CMV infection. ABO-C: ABO-Compatible; ABO-I: ABO-incompatible; ACR: Acute cellular rejection; AMR: Antibody-mediated rejection; CMV: Cytomegalovirus; CR: Chronic rejection; LT: Liver transplantation.

In this meta-analysis, cases that used rituximab in ABO-I LT patients<sup>[28-33]</sup> showed better 1-year graft survival after ABO-I LT than those that did not use rituximab<sup>[5,15,16,18,34,38-40]</sup>. Furthermore, in such cases, 1-, 3-, and 5-year graft survivals of ABO-I LT were comparable to those of ABO-C LT. On the other hand, biliary stricture and ACR tended to be more prevalent after ABO-I LT when rituximab was not used. There were no differences in AMR and patient survival in accordance with the use of rituximab.

Rituximab is a chimeric human anti-CD20 monoclonal antibody, which destroys B cells via antibody-dependent cell-mediated cytotoxicity, direct antigen-antibody reaction, and complement-dependent cytotoxicity<sup>[58,59]</sup>. Since its first introduction as a prophylactic in Japan in 2002, multiple centers have used rituximab during ABO-I LT, which is considered to have contributed to the dramatic improvements in the outcomes of ABO-I LT<sup>[9,11,60,61]</sup>. In this meta-analysis, it was noted that using rituximab improved graft survival while reducing incidences of biliary stricture and ACR after ABO-I LT. However, its effects on AMR and patient survival were rather unclear, and we speculate this to be a result of excluding some studies from the subgroup analyses for lack of clear descriptions of desensitization methods in ABO-I LT<sup>[17,19,20, 35-37,41]</sup>.

Meanwhile, studies that involved urgent indications, such as FHF, ALF, re-transplantation, and critically ill patients in the intensive care unit<sup>[5,15,17,19,20,33,34,39,40]</sup>, showed worse 1-year graft survival but better 5-year patient survival in ABO-I LT than in ABO-C LT when compared to studies that did not involve urgent indications. Further, there were no significant differences in 3- and 5-year graft survivals between the two types of LT. This may be due to the fact that studies that only examined recipients with urgent indications mostly involved relatively lower prevalences of chronic liver disease and liver cancer but more advanced disease severity and inadequate desensitizations before ABO-I LT.

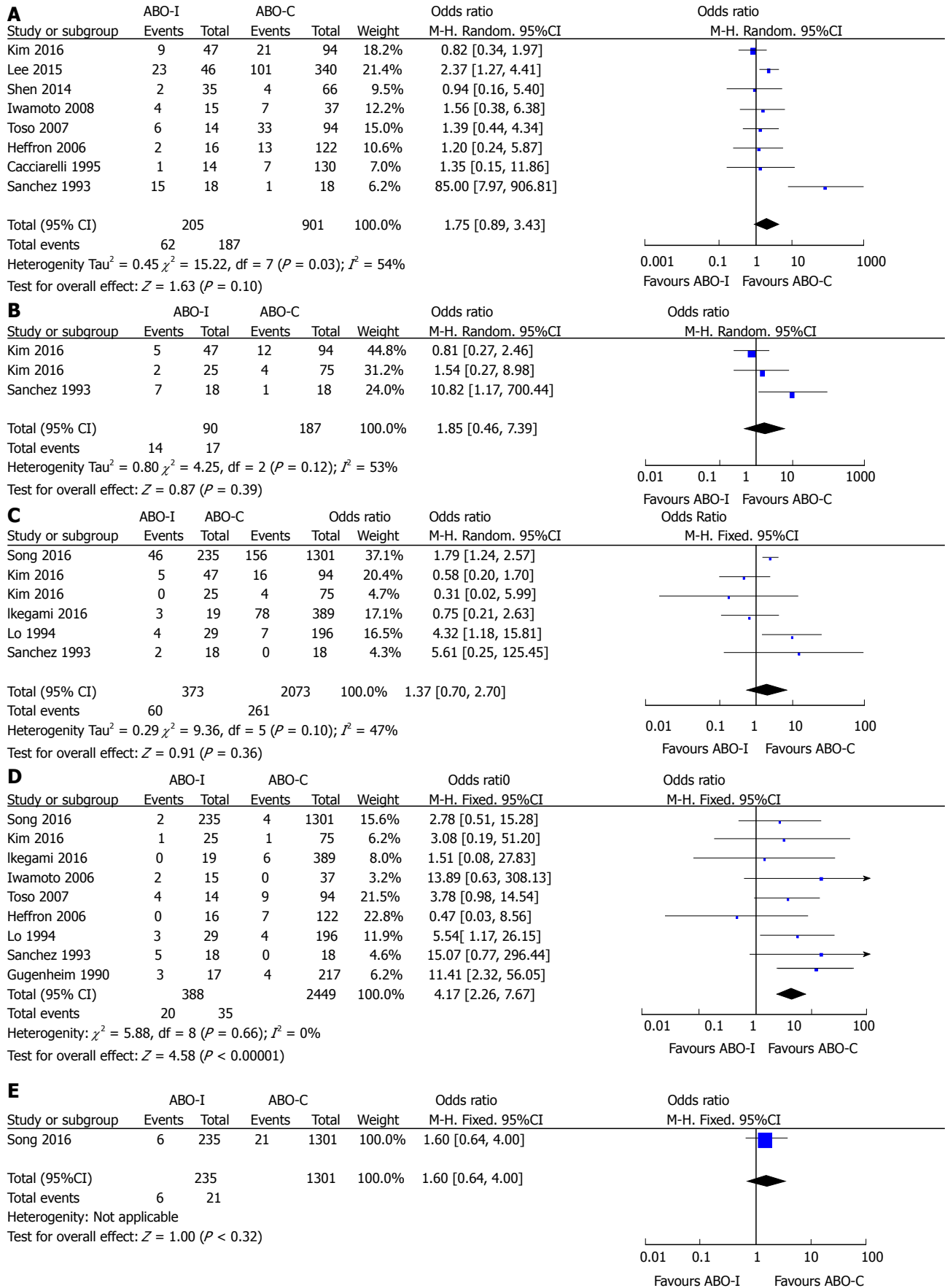
Shaked *et al*<sup>[62]</sup> showed that there were no differences in biopsy-proven ACR and graft loss by rejection between LDLT and deceased donor liver transplantation

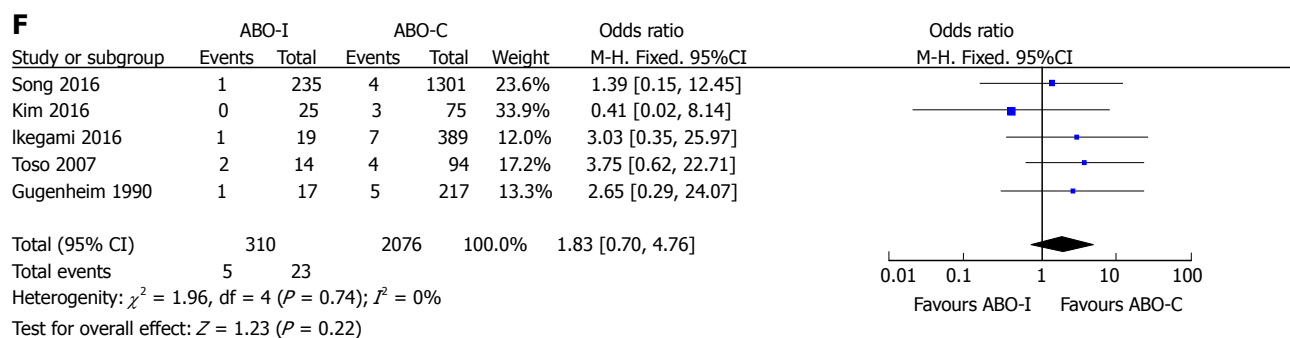
(DDLT). However, our subgroup analysis showed that ACR was less prevalent after ABO-I LT in cases that only used living donor liver grafts<sup>[18,28-32,36]</sup> than in cases that did not. In other words, there were no differences in ACR in accordance with ABO compatibility in cases of LDLT, but incidences of ACR increased in cases of ABO-I LT using deceased donor liver grafts. It could be assumed that compared to DDLT, LDLT has immunological advantages resulting from high genetic similarities between organ donor and recipient and short cold ischemic times<sup>[63,64]</sup>.

Further, biliary complications, such as bile leak and biliary stricture, are known to be more prevalent in LDLT with inherent weakness arising from a small duct size, possible multiplicity of bile duct, and cutting liver parenchyma, compared to those in DDLT<sup>[65-68]</sup>. However, our analysis revealed that using only living donor liver grafts<sup>[18,28-32,36]</sup> resulted in fewer cases of biliary stricture in ABO-I LT. One of the possible reasons is that studies only involving deceased donor grafts in our meta-analysis of biliary stricture<sup>[40,41]</sup> were published at least 20 years earlier than the studies involving living donor allografts<sup>[28-31]</sup>. Further, some of them involved urgent indications<sup>[40]</sup>, which would have resulted in the use of markedly different desensitization and immunosuppression methods and surgical techniques from those employed today.

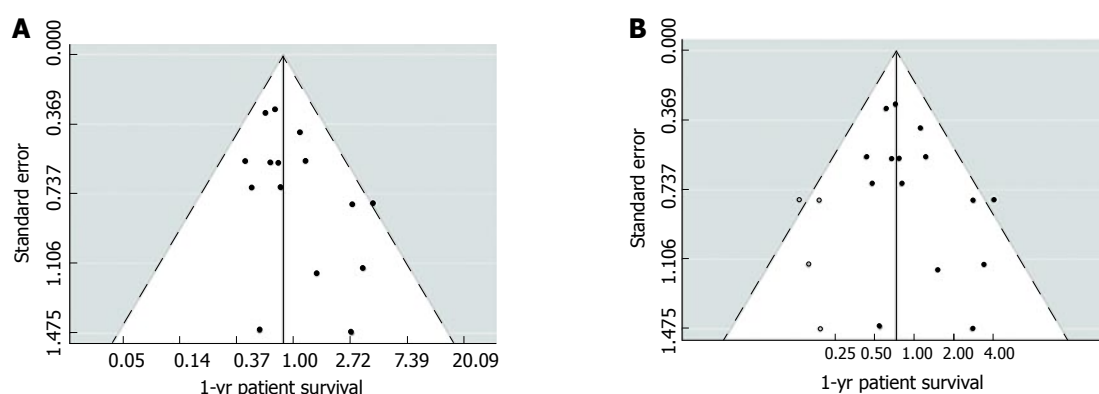
Meanwhile, in this meta-analysis, a potential publication bias was detected in the 1-year patient survival. Possible sources of asymmetry in the funnel plot would most definitely include small study effects, but poor methodological quality, true heterogeneity, artifactual, and chance could be other sources as well<sup>[21,25,69-72]</sup>.

This review has some limitations. First, it was based on non-randomized controlled trials because it is practically impossible to randomly allocate patients into either ABO-C LT or ABO-I LT group. Second, some articles lacked clear descriptions about patient demographics and study design, such as age, enrollment criteria, graft type, and desensitization and immunosuppression methods. Third, some results showed heterogeneity and potential publication bias.





**Figure 5** Comparison of biliary and vascular complications between ABO-Incompatible and ABO-Compatible liver transplantation. A: Overall biliary complication; B: Bile leak; C: Biliary stricture; D: HA complication; E: HV complication; F: PV complication. ABO-C: ABO-compatible; ABO-I: ABO-incompatible; HA: Hepatic artery; HV: Hepatic vein; LT: Liver transplantation; PV: Portal vein.



**Figure 6** (A) Funnel plot and (B) Adjusted funnel plot using the Trim-and-Fill method of studies reporting on 1-yr patient survival after ABO-incompatible liver transplantation vs ABO-Compatible liver transplantation. Closed circles represent observed published studies; open circles represent imputed unpublished studies. ABO-C: ABO-compatible; ABO-I: ABO-incompatible; LT: Liver transplantation.

This meta-analysis is the largest review that integrating more than 8000 cases of ABO-I LT and ABO-C LT. It revealed that ABO-I LT is associated with poorer graft survival and higher prevalence of AMR, CR, CMV infection, overall biliary complication, and HA complication than those of ABO-C LT. There were no significant differences in patient survival, ACR, bacterial infection, fungal infection, bile leak, biliary stricture, and HV and PV complications in accordance with ABO compatibility. In our subgroup analysis, graft survival in ABO-I LT was found to be comparable to that in ABO-C LT in pediatric patients. Use of rituximab was associated with better graft survival in ABO-I LT. In cases of DDLT, there was a higher incidence of ACR after ABO-I LT. Although substantial improvements and advances have been made in liver transplantations across the ABO blood group barrier, persistent limitations call for further endeavors to achieve better outcomes.

## ACKNOWLEDGMENTS

The authors wish to thank Jae Ryong Shim, MD for his contribution to this article.

## COMMENTS

### Background

Increased ABO-incompatible (ABO-I) liver transplantation (LT) is inevitable due to reduced organ donation and difficulty in finding suitable ABO-compatible (ABO-C) allografts. In particular, the importance of ABO-I LT is increasing in Asian countries where the use rate of ABO-I liver allograft is higher than that of Western countries due to the large number of organ donations in the family in living donor liver transplantation.

### Research frontiers

Outcomes after LT in accordance with ABO compatibility is still controversial. Therefore, it is necessary to evaluate the possibilities and the limitations of ABO-I LT by meta-analysis integrating outcomes of previous reports comparing ABO-I and ABO-C LT.

### Innovations and breakthroughs

ABO-I LT is comparable to ABO-C LT in terms of patient survival, but is inferior in graft survival, antibody-mediated rejection, chronic rejection, cytomegalovirus infection, overall biliary complication, and hepatic artery complication. However, in pediatric patients and those using rituximab, the graft survival of ABO-I LT was comparable to that of ABO-C LT.

### Applications

The authors performed a meta-analysis of outcomes after liver transplantation in accordance with ABO compatibility. In this way, the possibilities and the limitations of ABO-I LT can be clarified.

## Terminology

ABO-I transplantation is an assignment method for organ transplantation, which allows the use of available organs more efficiently regardless of the ABO blood type, which cannot otherwise be used due to hyperacute rejection.

## Peer-review

This meta-analysis is the largest review article of more than 8000 cases of ABO-I and ABO-C LT. The authors concluded that ABO-I LT, although patient survival was similar, was inferior to ABO-C LT in graft survival and several ABO-I-related complications. The article is well written and of highly clinical implications.

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**P- Reviewer:** Cerwenka H, Ramsay MA, Topaloglu S, **ZS- Editor:** Qi Y  
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ISSN 1007-9327

