REVIEW

Balancing Benefits and Risks: A Systematic Review and Meta-Analysis of ABO-Incompatible Kidney Transplantation

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Purpose: To update and expand clinical evidence comparing allograft and recipient survival as well as perioperative complications between ABO-incompatible and center-matched or concurrent ABO-compatible kidney transplant recipients.

Materials and Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, PubMed, Scopus, and Embase were searched from 2010 through December 2024 using prespecified Medical Subject Headings (MeSH) terms. Observational cohort and registry studies reporting patient survival, graft survival, or rejection episodes were included. Initial screening was restricted to English-language publications. Methodological quality was appraised via the Newcastle-Ottawa Scale. Random-effects and fixed-effects models were applied to calculate pooled risk ratios with 95% confidence intervals. Meta-regression, publication bias assessments, and confounding evaluations were allocated to supplementary files owing to data sparsity across unadjusted subsets.

Results: Data from 63 observational studies (5,852 ABO-incompatible and 47,950 ABO-compatible recipients) were synthesized. ABO-incompatible transplantation was associated with higher risks of overall rejection (risk ratio = 1.28, 95% confidence interval: 1.17–1.40) and antibody-mediated rejection (risk ratio = 2.14, 95% confidence interval: 1.48–3.09), whereas T-cell-mediated rejection showed comparable intervals (risk ratio = 0.86, 95% confidence interval: 0.72–1.04). Short- and long-term patient and graft survival estimates (at 1, 3, and 10 years) demonstrated wide compatibility between cohorts. However, 5-year patient survival showed lower compatibility with the null, favoring ABO-compatible transplants (risk ratio = 1.62, 95% confidence interval: 1.13–2.32). Surgical complications and postoperative bleeding were markedly higher in ABO-incompatible recipients.

Conclusion: ABO-incompatible kidney transplantation provides valuable expanded organ access with comparable 1-, 3-, and 10-year survival estimates, but carries elevated risks of rejection, early bleeding, and infections, alongside a noted divergence in 5-year patient survival.

Keywords: kidney transplantation; ABO-incompatible; ABO-compatible; graft rejection; graft survival; survival rate

INTRODUCTION

Chronic kidney disease (CKD) represents a growing global health burden, with its prevalence and associated mortality expanding rapidly worldwide.[1] End-stage kidney disease (ESKD) poses severe clinical challenges, and while kidney transplantation offers superior survival and quality of life compared to maintenance dialysis, the persistent shortage of donor organs remains a critical bottleneck.[2,3] To address this challenge, substantial effort has been directed toward expanding living donor programs, specifically by overcoming immunological barriers through ABO blood group-incompatible (ABOi) kidney transplantation.[4] The literature regarding ABOi transplantation primarily consists of retrospective observational cohort designs, single-center series, and large national registry analyses. Large registry data suggest that while ABOi recipients face higher initial risks of early graft loss, surgical bleeding, and infectious complications due to desensitization, long-term death-censored graft survival closely approaches that of conventional ABO-compatible (ABOc) transplants.[5,6] With contemporary titer-guided desensitization strategies utilizing rituximab, plasma exchange, or immunoadsorption, safety boundaries continue to evolve.[7]

Because clinical evidence accumulates rapidly, systematic reviews require periodic updates to integrate recent findings into existing clinical frameworks.[8] This systematic review and meta-analysis expands upon prior landmark syntheses[4,5] by integrating multicenter registries and matched/unmatched observational cohort studies published through December 2024. We evaluate rejections, fixed-time survival endpoints, and perioper-

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Table 1. Baseline characteristics and clinical features of observational studies included in the meta-analysis comparing ABO-incompatible and ABO-compatible kidney transplantation.

No.	Study	Year	Country	study follow-up (months)	Selection of controls	Use of rituximab	ABO-incompatible renal transplantation		ABO-compatible renal transplantation	
							No. Patients	Mean age (years)	No. Patients	Mean age (years)
1	Ashimine et.al [11]	2014	Japan	60	Consecutive		92	…	228	40.1
	Rituximab group					Yes	30	49	…	…
	Splenectomy group						51	44.5	…	…
	No rituximab or splenectomy group						11	48.4	…	…
2	Axelrod et. al [12]	2016	USA	60	Consecutive (records of the US Renal Data System)	Not specified	271	…	26504	…
3	Barnett et.al [7]	2014	UK	36	Matched	Tailored use (based on titre)	62	46.7	167	42.9
4	Becker et.al [13]	2015	Germany	48	Matched	Yes (single dose)	34	46	68	46
5	Bentall et.al [14]	2014	United states	٦٧-73	Consecutive	Yes	73	50.6	652	51.1
6	Bentall et.al [15]	2016	UK	24	Standard of retrospective cohort study design principles	Mixed	100	46.8	1257	45
7	Choi et.al [16]	2016	Korea	19.5	Consecutive	Yes	79	45.3	260	44.8

8	Chow et.al [17]	2017	Australia	44	Consecutive	No	25	47	34	38
9	Cozzi et.al [18]	2022	Italy	٣٦	Matched	Yes	17	44.6	34	45.8
10	de Weerd et.al [19]	2021	The Netherlands	12	matched	Mixed (varied)	296	54	1184	55
									1184	58
11	Deng et.al [20]	2024	Switzerland	72-78	matched	Yes	149	51	803	49
12	Dörje et.al [21]	2015	Norway	27.6	Matched	Yes	20	47.9	60	50
13	Flint et.al [22]	2011	Australia	22-26	Consecutive	No	37	50	52	46
14	Fuchinoue et.al [23]	2011	Japan		Consecutive		113	46	280	43.5
	No rituximab group			60		No	63	46		
	Rituximab group			60		Yes	50	52		
15	Galliford et.al [24]	2008	United Kingdom	12	Consecutive	Yes	10	44.9	101	40
16	García-Sobrino et.al [25]	2023	spain	…	Consecutive	No	46	50.27	62	45.83
17	Gaur et.al [26]	2022	India	12	Consecutive	Yes	67	40.37	873	40.47
18	Genberg et.al [27]	2008	Sweden	36	matched	Yes	15	35.1	30	42.4

19	Gloor et.al [28]	2003	USA	12	matched	No	18	47	81	
20	Habicht et.al [29]	2011	Germany	15.7	matched	Yes	21	45.6	47	45.9
21	Hamano et.al [30]	2020	Japan	60	Consecutive	Yes (low-dose, 30 patients)	37	47	70	43
22	Hatakeyama et.al [31]	2014	Japan	27-37	Consecutive	Yes (low-dose, 13 patients)	13	45	29	42
23	Hattori et.al [32]	2018	Japan	66-80	matched	Yes	102	14	788	11.7
24	Herzog et.al [33]	2018	Germany	24	matched	No	9	49.15	18	49.65
25	Hirzel et.al [34]	2022	Switzerland.	12	Consecutive	Not specified;	118	53.4	639	50.6
26	Hwang et.al [35]	2013	Korea	24	matched	Yes	35	44.1	138	42.8
27	Hwang et.al [36]	2011	Korea	3	matched	Yes	12	45.6	50	41.6
28	Jänigen et.al [37]	2019	Germany	12	matched	Yes	104	46	160	49.5
29	Jeon et.al [38]	2010	Korea	36		Yes	22	45	61	44
30	Jha et.al [39]	2016	India	10-16	Consecutive	Yes	20	42	669	40.15

31	Kahwaji et.al [40]	2011	USA	33-49	Consecutive	Yes	170	47.5	191	53
32	Kakuta et.al [41]	2019	Japan	24	Consecutive	Yes	65	52.1	94	42.6
33	Kauke et.al [3]	2016	Germany	12	matched	Yes	26	49.5	20	44.3
34	Kim et.al [42]	2021	South Korea	28	matched	Yes	80	63.7	222	63.9
35	Ko et.al [43]	2017	South Korea	36	ABO-compatible and HLA-compatible kidney transplant recipients	Yes	279	44·5	1541	42·6
36	Kohei et.al [44]	2012	Japan			Yes	102		83	40·4
	First era			84			45	40·4		
	Second era			60			57	44·0		
37	Kosoku et.al [45]	2018	Japan	60	matched	Yes	66	52	66	50
38	Kwon et.al [46]	2016	Korea	36	consecutive	Yes	67	42.6	600	46.4
							167	46.9	600	46.4
39	Kwon et.al [47]	2016	South Korea	12	consecutive	Yes	87	51.4	176	48.7

40	Langhorst et.al [48]	2020	Germany	76-90	ABO-compatible kidney transplant recipients with similar immunosuppression protocols	Yes	130	46	162	50
41	Lee et.al [49]	2016	Korea	36-38	consecutive	Yes	97	43.34	118	44.34
42	Masutani et.al [50]	2017	Japan	12	ABO-compatible kidney transplant recipients from same center and time period	Yes	101	47.4	226	41.7
43	Melexopoulou et.al [51]	2015	Greece	74-78	matched	Yes	30	39	30	37
44	Montgomery et.al [52]	2012	United States	36	Matched ABO-compatible live donor KT recipients from the Scientific Registry of Transplant Recipients	Mixed	738	46·9	3679	46·8
45	Naciri Bennani et.al [53]	2015	France	6	matched	Yes	44	48.8	44	51.1

46	Okumi et.al [54]	2016	Japan	56-108	ABO-compatible living kidney transplant					
	First era					No	103	38·1	452	35·9
	Second era					Yes	144	47·8	333	45·2
47	Park et.al [55]	2016	Korea	15	ABO-compatible spousal donor KT recipients	Yes	11	50·9	21	49·0
48	Prabhakar et.al [56]	2021	India	26	matched	Yes	100	40.89	100	40.81
49	Schachtner et.al [57]	2015	USA		matched	Yes	35	52	62	51
50	Setoguchi et.al [58]	2008	Japan	12	matched	No	48	40	133	38
51	Shin et.al [59]	2015	Korea	39-46	matched	Yes	73	44	396	43
52	Shishido et.al [60]	2012	Japan	107	matched	Mixed	52	11·9	271	9.7
53	Speer et.al [61]	2019	Germany	41-57	matched ABO-compatible KT recipients from same center and time period	Yes	48	45	96	44
54	Subramanian et.al [62]	2015	United States	60	matched	Yes	18	52.2	45	49.3

55	Thukral et.al [63]	2019	India	12	matched ABO-compatible KT recipients from same center and time period	Yes	30	42.97	30	38.8
56	Tyden et.al [64]	2007	Sweden	18	ABO-compatible living donor KT recipients from same centers and time period	Yes	60	…	274	…
57	van Agteren et.al [65]	2014	Netherland	38	matched	Yes	50	54	100	55
58	Wilpert et.al [66]	2010	Germany	36	Consecutive ABO-compatible transplants	Yes	40	46	43	44
59	Yachha et.al [67]	2017	India	15	Matched	Yes	33	35	33	35.79
60	Yin et.al [68]	2022	China	25	matched	Yes	100	32.1	200	31.1
61	Yokoyama et.al [69]	2016	Japan	12	consecutive		21	46.4	50	45.6
62	Yu et.al [70]	2017	Korea	21-25	ABO-compatible kidney transplants from spousal donors	Yes	150	48·0	566	48·4
63	Zschiedrich et.al [71]	2016	Germany	48-58	consecutive	Yes	97	47·0	106	49·0

ative complications to provide a consolidated risk-benefit profile.

MATERIALS AND METHODS

This study was conducted in accordance with the Cochrane Collaboration guidelines and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The study protocol was not prospectively registered in registries such as PROSPERO due to administrative constraints, which is acknowledged as an explicit methodological limitation.

Search Strategy and Eligibility Criteria

A comprehensive literature search was performed across PubMed, Scopus, and Embase for records published between January 2010 and December 2024. The final search was executed on December 31, 2024. The search syntax integrated MeSH terms and keywords: ("ABO compatible" OR "ABO incompatible") AND ("renal" OR "kidney"). The complete, unedited search strings for each database are detailed in **Supplemental Tables 1–3**.

Eligible studies comprised observational designs (including retrospective and prospective cohort studies, center-matched series, and national registry database extracts) that compared pediatric or adult ABOi kidney transplant recipients against an ABOc control group. Studies were required to report at least one primary or secondary clinical outcome. Exclusion criteria consisted of case reports, review articles, editor letters, animal models, conference abstracts with unextractable data, and non-English publications. The restriction to English-language literature was maintained due to logistically limited translation resources, introducing a potential geographic and selection bias.

Data Extraction and Outcome Definitions

Data extraction was conducted independently by two investigators using a pre-standardized Excel extraction form. Disagreements were resolved via joint consensus or adjudication by a third investigator. Primary endpoints included overall rejection, antibody-mediated rejection (AMR), T-cell-mediated rejection (TCMR), and patient and graft survival at fixed intervals of 1, 3, 5, and 10 years. Secondary outcomes spanned infectious complications (sepsis, pneumonia, urinary tract infection [UTI], BK virus [BKV], cytomegalovirus [CMV], Epstein-Barr virus [EBV]) and surgical/hemostatic complications (overall surgical revisions, postoperative bleeding). Outcomes were extracted as crude unadjusted event counts across both groups to allow consistent synthesis, as adjusted hazards or multivariate estimates were inconsistently reported across older single-center cohorts.

Quality and Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was utilized independently by two investigators to appraise the method-

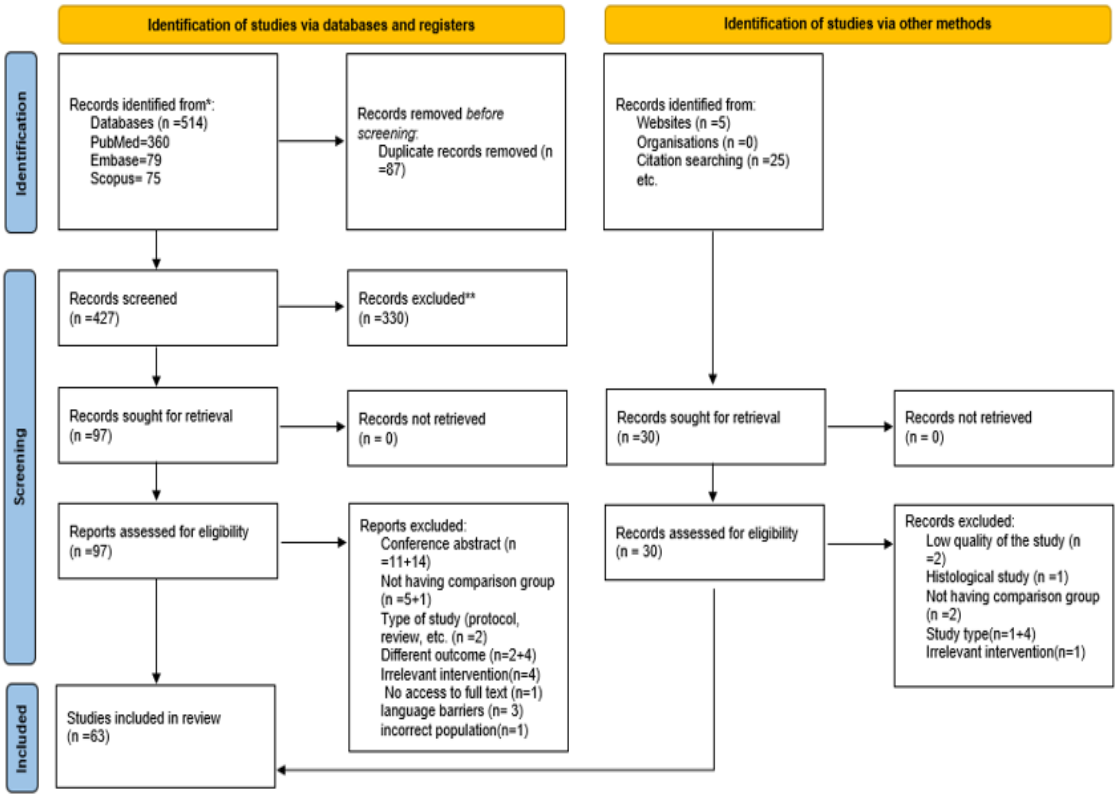


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flowchart of the systematic literature search and study selection process.

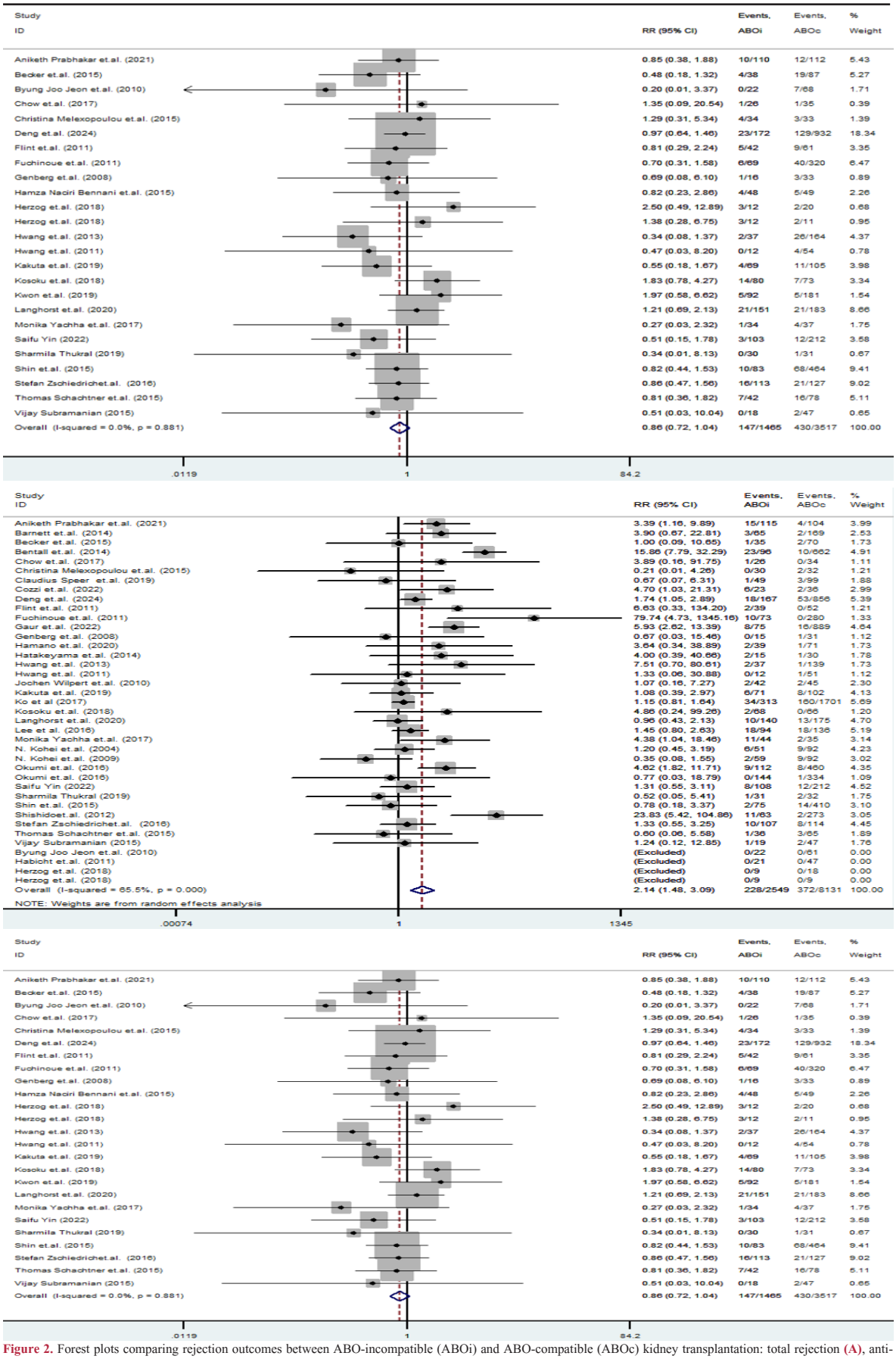
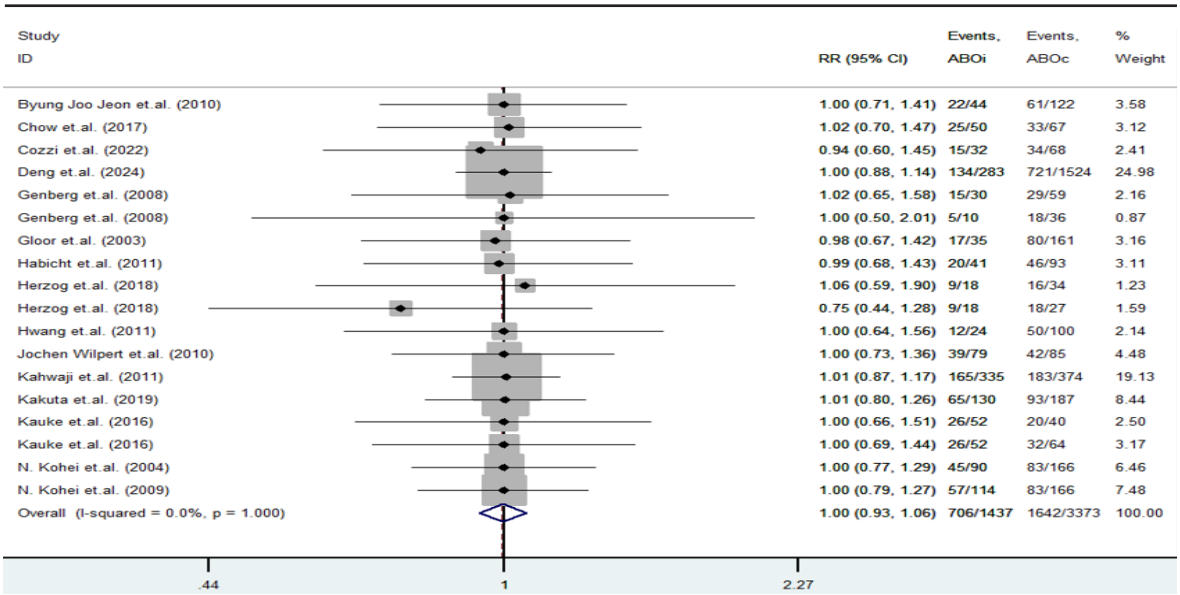
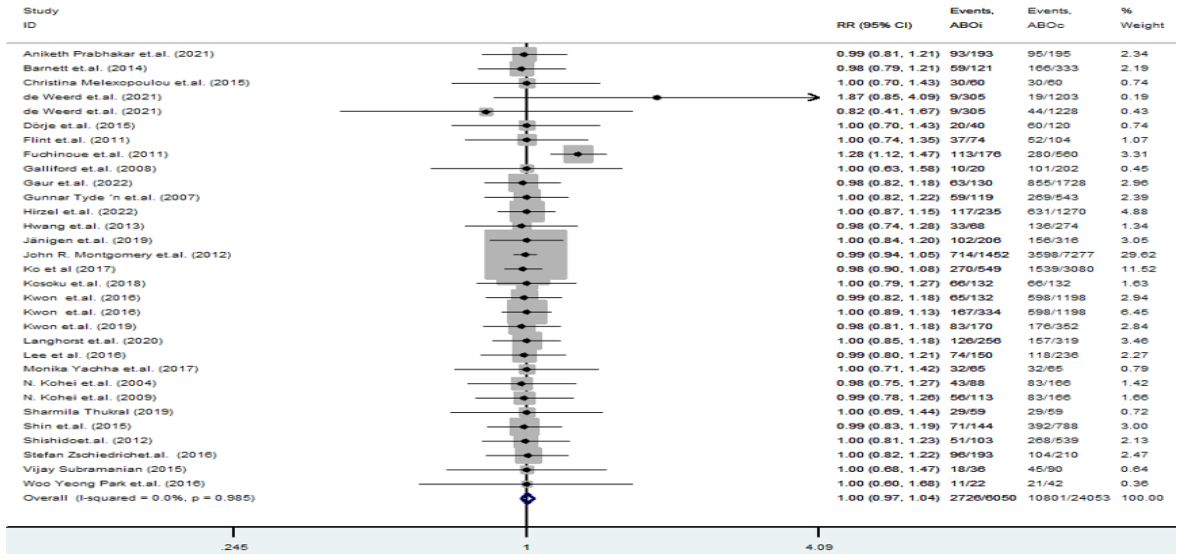


Figure 2. Forest plots comparing rejection outcomes between ABO-incompatible (ABOi) and ABO-compatible (ABOc) kidney transplantation: total rejection **(A)**, antibody-mediated rejection (AMR) **(B)**, and T-cell-mediated rejection (TCMR) **(C)**.

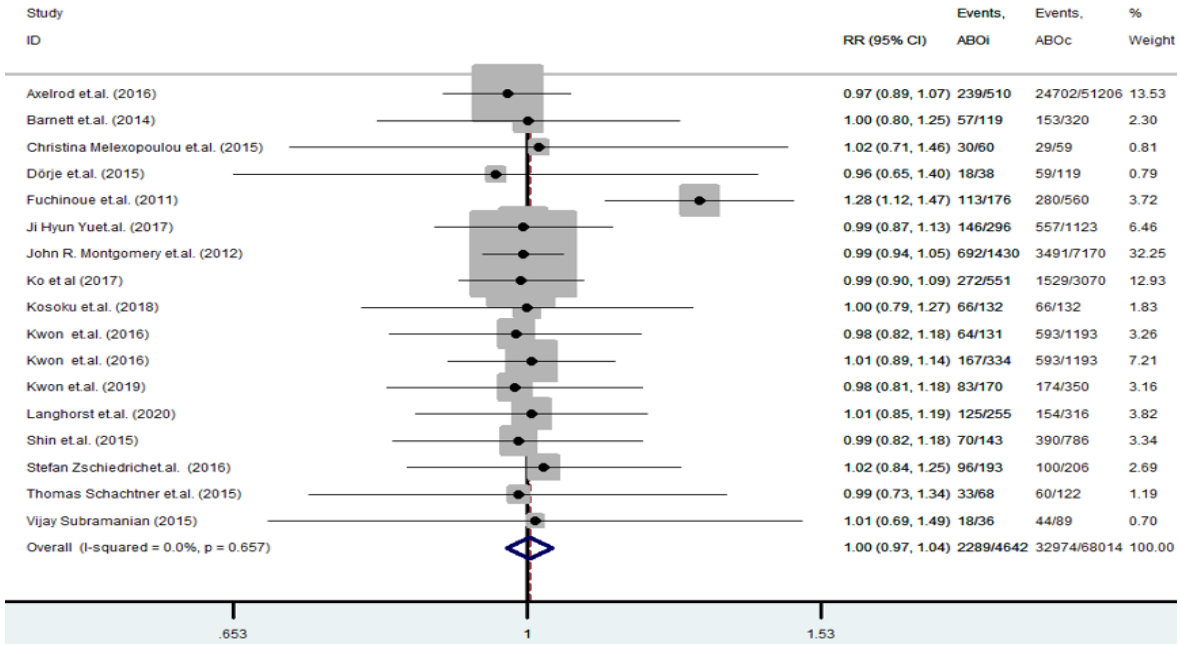
A


Study ID
RR (95% CI)
Events, ABOi
Events, ABOc
% Weight
Byung Joo Jeon et.al. (2010) 1.00 (0.71, 1.41) 22/44 61/122 3.58
Chow et.al. (2017) 1.02 (0.70, 1.47) 25/50 33/67 3.12
Cozzi et.al. (2022) 0.94 (0.60, 1.45) 15/32 34/68 2.41
Deng et.al. (2024) 1.00 (0.88, 1.14) 134/283 721/1524 24.98
Genberg et.al. (2008) 1.02 (0.65, 1.58) 15/30 29/59 2.16
Genberg et.al. (2008) 1.00 (0.50, 2.01) 5/10 18/36 0.87
Gloor et.al. (2003) 0.98 (0.67, 1.42) 17/35 80/161 3.16
Habicht et.al. (2011) 0.99 (0.68, 1.43) 20/41 46/93 3.11
Herzog et.al. (2018) 1.06 (0.59, 1.90) 9/18 16/34 1.23
Herzog et.al. (2018) 0.75 (0.44, 1.28) 9/18 18/27 1.59
Hwang et.al. (2011) 1.00 (0.64, 1.56) 12/24 50/100 2.14
Jochen Wilpert et.al. (2010) 1.00 (0.73, 1.36) 39/79 42/85 4.48
Kahwaji et.al. (2011) 1.01 (0.87, 1.17) 165/335 183/374 19.13
Kakuta et.al. (2019) 1.01 (0.80, 1.26) 65/130 93/187 8.44
Kauke et.al. (2016) 1.00 (0.66, 1.51) 26/52 20/40 2.50
Kauke et.al. (2016) 1.00 (0.69, 1.44) 26/52 32/64 3.17
N. Kohei et.al. (2004) 1.00 (0.77, 1.29) 45/90 83/166 6.46
N. Kohei et.al. (2009) 1.00 (0.79, 1.27) 57/114 83/166 7.48
Overall (I-squared = 0.0%, p = 1.000) 1.00 (0.93, 1.06) 706/1437 1642/3373 100.00
.44
1
2.27

B


Study ID
RR (95% CI)
Events, ABOi
Events, ABOc
% Weight
Aniketh Prabhakar et.al. (2021) 0.99 (0.81, 1.21) 93/193 95/195 2.34
Barnett et.al. (2014) 0.98 (0.79, 1.21) 59/121 166/333 2.19
Christina Melexopoulou et.al. (2015) 1.00 (0.70, 1.43) 30/60 30/60 0.74
de Weerd et.al. (2021) 1.87 (0.85, 4.09) 9/305 19/1203 0.19
de Weerd et.al. (2021) 0.82 (0.41, 1.67) 9/305 44/1228 0.43
Dörje et.al. (2015) 1.00 (0.70, 1.43) 20/40 60/120 0.74
Flint et.al. (2011) 1.00 (0.74, 1.35) 37/74 52/104 1.07
Fuchinoue et.al. (2011) 1.28 (1.12, 1.47) 113/176 280/560 3.31
Galliford et.al. (2008) 1.00 (0.63, 1.58) 10/20 101/202 0.45
Gaur et.al. (2022) 0.98 (0.82, 1.18) 63/130 855/1728 2.96
Gunnar Tyde 'n et.al. (2007) 1.00 (0.82, 1.22) 59/119 269/543 2.39
Hirzel et.al. (2022) 1.00 (0.87, 1.15) 117/235 631/1270 4.88
Hwang et.al. (2013) 0.98 (0.74, 1.28) 33/68 136/274 1.34
Jänigen et.al. (2019) 1.00 (0.84, 1.20) 102/206 156/316 3.05
John R. Montgomery et.al. (2012) 0.99 (0.94, 1.05) 714/1452 3598/7277 29.62
Ko et al (2017) 0.98 (0.90, 1.08) 270/549 1539/3080 11.52
Kosoku et.al. (2018) 1.00 (0.79, 1.27) 66/132 66/132 1.63
Kwon et.al. (2016) 0.99 (0.82, 1.18) 65/132 598/1198 2.94
Kwon et.al. (2016) 1.00 (0.89, 1.13) 167/334 598/1198 6.45
Kwon et.al. (2019) 0.98 (0.81, 1.18) 83/170 176/352 2.84
Langhorst et.al. (2020) 1.00 (0.85, 1.18) 126/256 157/319 3.46
Lee et al. (2016) 0.99 (0.80, 1.21) 74/150 118/236 2.27
Monika Yachha et.al. (2017) 1.00 (0.71, 1.42) 32/65 32/65 0.79
N. Kohei et.al. (2004) 0.98 (0.75, 1.27) 43/88 83/166 1.42
N. Kohei et.al. (2009) 0.99 (0.78, 1.26) 56/113 83/166 1.66
Sharmila Thukral (2019) 1.00 (0.69, 1.44) 29/59 29/59 0.72
Shin et.al. (2015) 0.99 (0.83, 1.19) 71/144 392/788 3.00
Shishidoet.al. (2012) 1.00 (0.81, 1.23) 51/103 268/539 2.13
Stefan Zschiedrichet.al. (2016) 1.00 (0.82, 1.22) 96/193 104/210 2.47
Vijay Subramanian (2015) 1.00 (0.68, 1.47) 18/36 45/90 0.64
Woo Yeong Park et.al. (2016) 1.00 (0.60, 1.68) 11/22 21/42 0.36
Overall (I-squared = 0.0%, p = 0.985) 1.00 (0.97, 1.04) 2726/6050 10801/24053 100.00
.245
1
4.09

C


Study ID
RR (95% CI)
Events, ABOi
Events, ABOc
% Weight
Axelrod et.al. (2016) 0.97 (0.89, 1.07) 239/510 24702/51206 13.53
Barnett et.al. (2014) 1.00 (0.80, 1.25) 57/119 153/320 2.30
Christina Melexopoulou et.al. (2015) 1.02 (0.71, 1.46) 30/60 29/59 0.81
Dörje et.al. (2015) 0.96 (0.65, 1.40) 18/38 59/119 0.79
Fuchinoue et.al. (2011) 1.28 (1.12, 1.47) 113/176 280/560 3.72
Ji Hyun Yuet.al. (2017) 0.99 (0.87, 1.13) 146/296 557/1123 6.46
John R. Montgomery et.al. (2012) 0.99 (0.94, 1.05) 692/1430 3491/7170 32.25
Ko et al (2017) 0.99 (0.90, 1.09) 272/551 1529/3070 12.93
Kosoku et.al. (2018) 1.00 (0.79, 1.27) 66/132 66/132 1.83
Kwon et.al. (2016) 0.98 (0.82, 1.18) 64/131 593/1193 3.26
Kwon et.al. (2016) 1.01 (0.89, 1.14) 167/334 593/1193 7.21
Kwon et.al. (2019) 0.98 (0.81, 1.18) 83/170 174/350 3.16
Langhorst et.al. (2020) 1.01 (0.85, 1.19) 125/255 154/316 3.82
Shin et.al. (2015) 0.99 (0.82, 1.18) 70/143 390/786 3.34
Stefan Zschiedrichet.al. (2016) 1.02 (0.84, 1.25) 96/193 100/206 2.69
Thomas Schachtner et.al. (2015) 0.99 (0.73, 1.34) 33/68 60/122 1.19
Vijay Subramanian (2015) 1.01 (0.69, 1.49) 18/36 44/89 0.70
Overall (I-squared = 0.0%, p = 0.657) 1.00 (0.97, 1.04) 2289/4642 32974/68014 100.00
.653
1
1.53

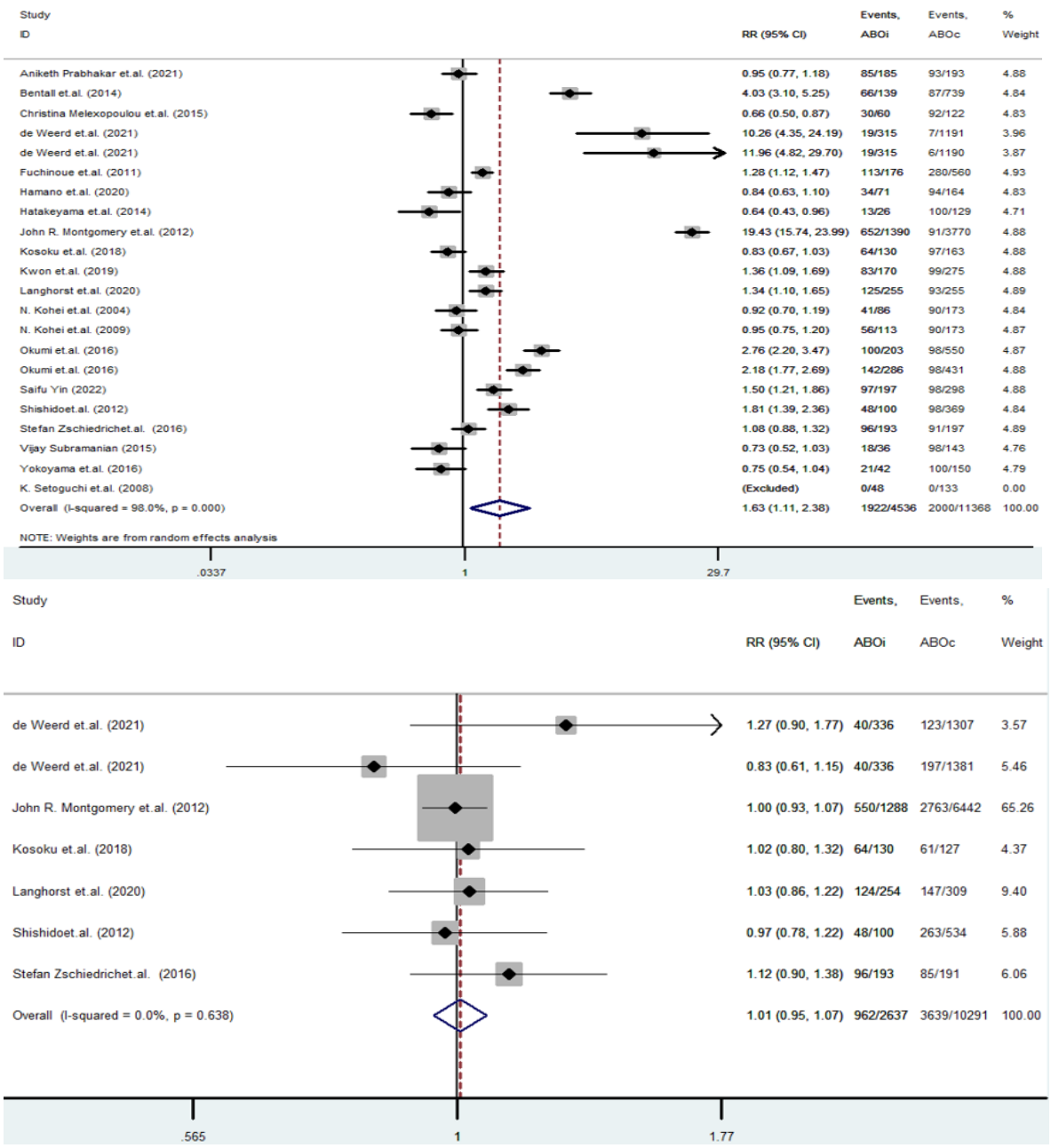


Figure 3. Forest plots of patient survival comparing ABO-incompatible (ABOi) versus ABO-compatible (ABOc) kidney transplantation: overall patient survival **(A)**, at 1 year **(B)**, 3 years **(C)**, 5 years **(D)**, and 10 years (E) after transplantation.

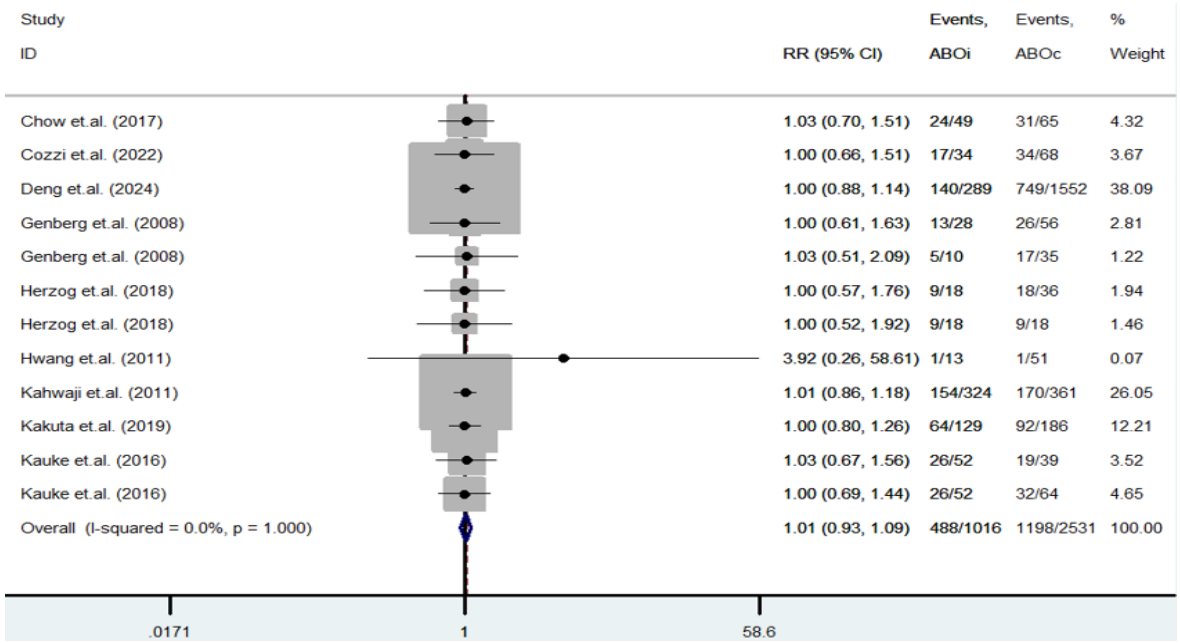
ological quality of the included observational studies across selection, comparability, and outcome ascertainment domains. Studies achieving a total score ≥ 5 stars were categorized as moderate-to-high quality.[9,10] Crucially, in compliance with standard meta-analytical guidance, quality scores were used strictly to describe the baseline vulnerability of the evidence base and were not utilized as arbitrary thresholds for study exclusion.

Statistical Analysis

Data synthesis was performed using STATA software. We calculated the Risk Ratio (RR) with its 95% Confidence Interval (CI) as the uniform effect measure for all clinical endpoints. Statistical heterogeneity was quantified using the inconsistency index (I^2). Reflecting the intrinsic clinical heterogeneity across transplant eras, center protocols, and registry structures, a random-effects model was employed as our primary analytical framework. Fixed-effects models were performed in parallel as sensitivity analyses. In accordance with contemporary statistical recommendations, P-values are reported strictly to denote compatibility thresholds, avoiding arbitrary significance classification; *P*-values below 0.001 are uniformly reported as "< 0.001". Graphical publication bias evaluations (funnel plots) and exploratory subgroup assessments (stratified by rituximab use and study design) are relegated to the supplementary data due to low reporting density within distinct data cells.

RESULTS

A


Study ID
RR (95% CI)
Events, ABOi
Events, ABOc
% Weight
Chow et.al. (2017) 1.03 (0.70, 1.51) 24/49 31/65 4.32
Cozzi et.al. (2022) 1.00 (0.66, 1.51) 17/34 34/68 3.67
Deng et.al. (2024) 1.00 (0.88, 1.14) 140/289 749/1552 38.09
Genberg et.al. (2008) 1.00 (0.61, 1.63) 13/28 26/56 2.81
Genberg et.al. (2008) 1.03 (0.51, 2.09) 5/10 17/35 1.22
Herzog et.al. (2018) 1.00 (0.57, 1.76) 9/18 18/36 1.94
Herzog et.al. (2018) 1.00 (0.52, 1.92) 9/18 9/18 1.46
Hwang et.al. (2011) 3.92 (0.26, 58.61) 1/13 1/51 0.07
Kahwaji et.al. (2011) 1.01 (0.86, 1.18) 154/324 170/361 26.05
Kakuta et.al. (2019) 1.00 (0.80, 1.26) 64/129 92/186 12.21
Kauke et.al. (2016) 1.03 (0.67, 1.56) 26/52 19/39 3.52
Kauke et.al. (2016) 1.00 (0.69, 1.44) 26/52 32/64 4.65
Overall (I-squared = 0.0%, p = 1.000) 1.01 (0.93, 1.09) 488/1016 1198/2531 100.00
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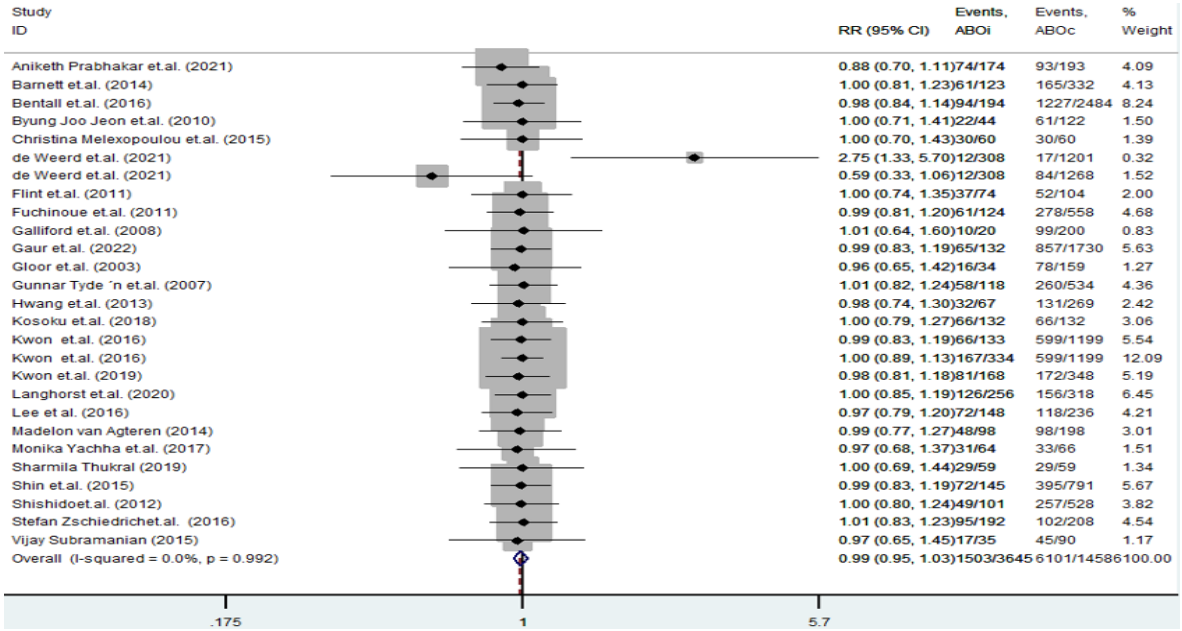
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RR (95% CI)
Events, ABOi
Events, ABOc
% Weight
Aniketh Prabhakar et.al. (2021) 0.88 (0.70, 1.11) 74/174 93/193 4.09
Barnett et.al. (2014) 1.00 (0.81, 1.23) 61/123 165/332 4.13
Bentall et.al. (2016) 0.98 (0.84, 1.14) 94/194 1227/2484 8.24
Byung Joo Jeon et.al. (2010) 1.00 (0.71, 1.41) 22/44 61/122 1.50
Christina Melexopoulou et.al. (2015) 1.00 (0.70, 1.43) 30/60 30/60 1.39
de Weerd et.al. (2021) 2.75 (1.33, 5.70) 12/308 17/1201 0.32
de Weerd et.al. (2021) 0.59 (0.33, 1.06) 12/308 84/1268 1.52
Flint et.al. (2011) 1.00 (0.74, 1.35) 37/74 52/104 2.00
Fuchinoue et.al. (2011) 0.99 (0.81, 1.20) 61/124 278/558 4.68
Galliford et.al. (2008) 1.01 (0.64, 1.60) 10/20 99/200 0.83
Gaur et.al. (2022) 0.99 (0.83, 1.19) 65/132 857/1730 5.63
Gloor et.al. (2003) 0.96 (0.65, 1.42) 16/34 78/159 1.27
Gunnar Tyde ´n et.al. (2007) 1.01 (0.82, 1.24) 58/118 260/534 4.36
Hwang et.al. (2013) 0.98 (0.74, 1.30) 32/67 131/269 2.42
Kosoku et.al. (2018) 1.00 (0.79, 1.27) 66/132 66/132 3.06
Kwon et.al. (2016) 0.99 (0.83, 1.19) 66/133 599/1199 5.54
Kwon et.al. (2016) 1.00 (0.89, 1.13) 167/334 599/1199 12.09
Kwon et.al. (2019) 0.98 (0.81, 1.18) 81/168 172/348 5.19
Langhorst et.al. (2020) 1.00 (0.85, 1.19) 126/256 156/318 6.45
Lee et al. (2016) 0.97 (0.79, 1.20) 72/148 118/236 4.21
Madelon van Agteren (2014) 0.99 (0.77, 1.27) 48/98 98/198 3.01
Monika Yachha et.al. (2017) 0.97 (0.68, 1.37) 31/64 33/66 1.51
Sharmila Thukral (2019) 1.00 (0.69, 1.44) 29/59 29/59 1.34
Shin et.al. (2015) 0.99 (0.83, 1.19) 72/145 395/791 5.67
Shishidoet.al. (2012) 1.00 (0.80, 1.24) 49/101 257/528 3.82
Stefan Zschiedrichet.al. (2016) 1.01 (0.83, 1.23) 95/192 102/208 4.54
Vijay Subramanian (2015) 0.97 (0.65, 1.45) 17/35 45/90 1.17
Overall (I-squared = 0.0%, p = 0.992) 0.99 (0.95, 1.03) 1503/3645 6101/14586 100.00
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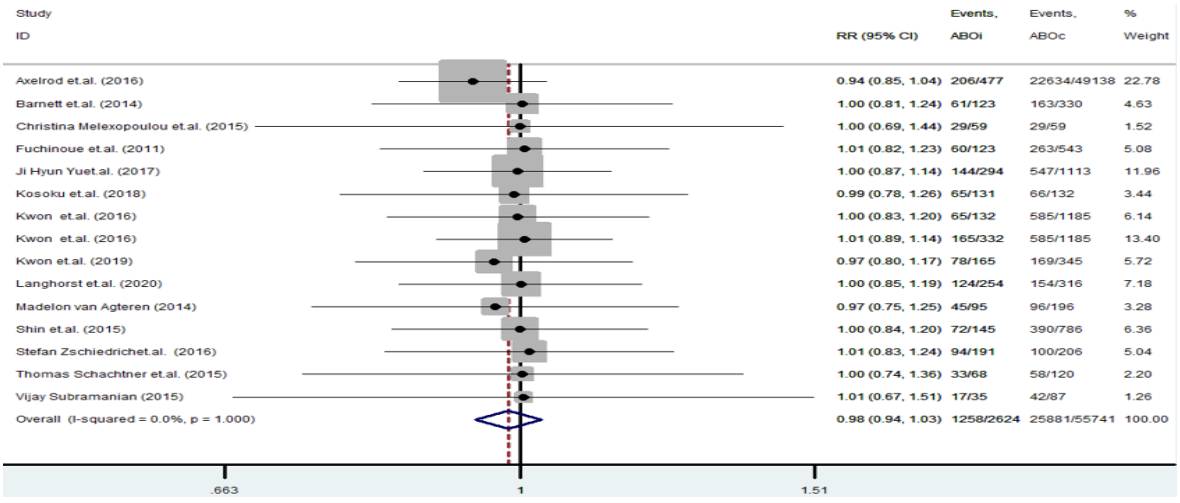
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RR (95% CI)
Events, ABOi
Events, ABOc
% Weight
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Barnett et.al. (2014) 1.00 (0.81, 1.24) 61/123 163/330 4.63
Christina Melexopoulou et.al. (2015) 1.00 (0.69, 1.44) 29/59 29/59 1.52
Fuchinoue et.al. (2011) 1.01 (0.82, 1.23) 60/123 263/543 5.08
Ji Hyun Yuet.al. (2017) 1.00 (0.87, 1.14) 144/294 547/1113 11.96
Kosoku et.al. (2018) 0.99 (0.78, 1.26) 65/131 66/132 3.44
Kwon et.al. (2016) 1.00 (0.83, 1.20) 65/132 585/1185 6.14
Kwon et.al. (2016) 1.01 (0.89, 1.14) 165/332 585/1185 13.40
Kwon et.al. (2019) 0.97 (0.80, 1.17) 78/165 169/345 5.72
Langhorst et.al. (2020) 1.00 (0.85, 1.19) 124/254 154/316 7.18
Madelon van Agteren (2014) 0.97 (0.75, 1.25) 45/95 96/196 3.28
Shin et.al. (2015) 1.00 (0.84, 1.20) 72/145 390/786 6.36
Stefan Zschiedrichet.al. (2016) 1.01 (0.83, 1.24) 94/191 100/206 5.04
Thomas Schachtner et.al. (2015) 1.00 (0.74, 1.36) 33/68 58/120 2.20
Vijay Subramanian (2015) 1.01 (0.67, 1.51) 17/35 42/87 1.26
Overall (I-squared = 0.0%, p = 1.000) 0.98 (0.94, 1.03) 1258/2624 25881/55741 100.00
.663
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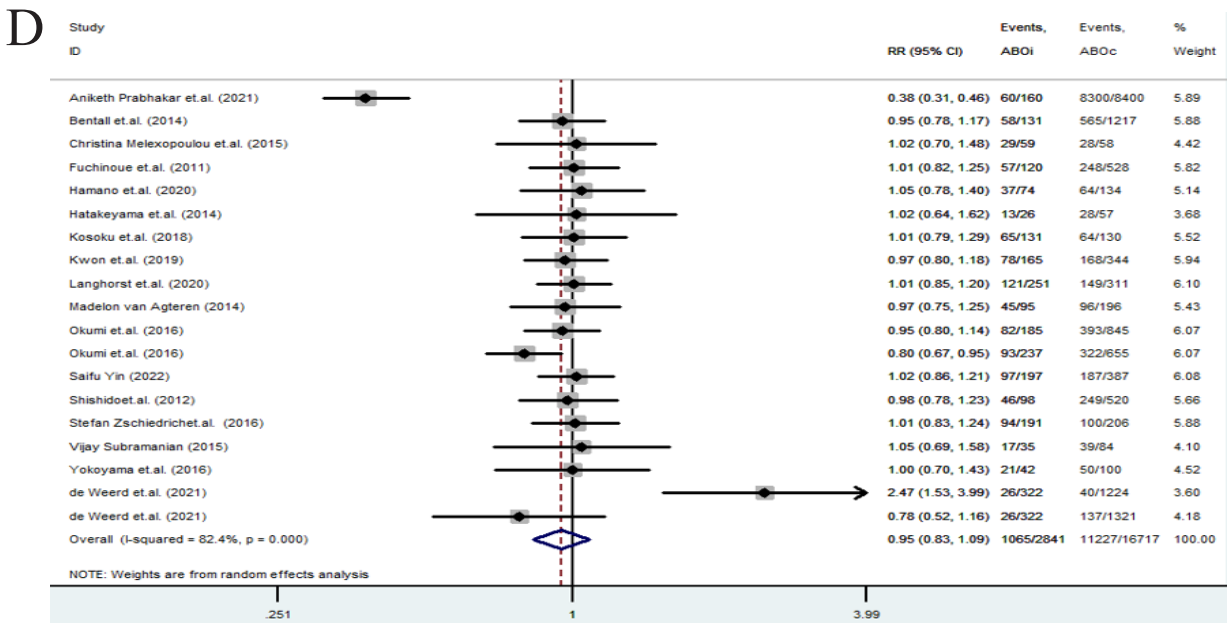
1.51



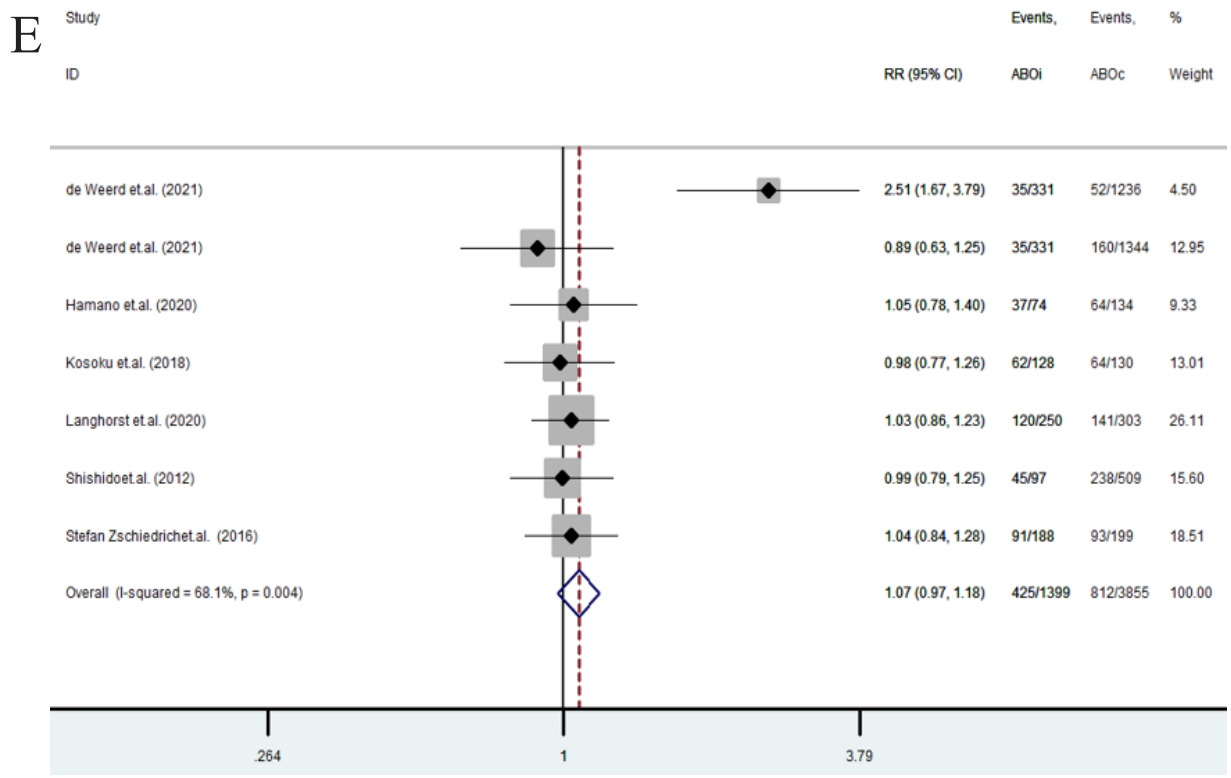


Figure 4. Forest plots of death-censored graft survival comparing ABO-incompatible (ABOi) versus ABO-compatible (ABOc) kidney transplantation: overall graft survival **(A)**, at 1 year **(B)**, 3 years **(C)**, 5 years **(D)**, and 10 years **(E)** after transplantation.

Search Flow and Study Characteristics

The systematic search strategy initially retrieved 544 records. Following duplicate removal and title/abstract screening, 127 full-text articles were evaluated for eligibility. Ultimately, 63 observational studies met the explicit inclusion criteria and were included in the quantitative meta-analysis (the completed PRISMA 2020 flowchart and screening counts are shown in **Figure 1**).

The pooled population comprised 53,802 patients (5,852 ABOi and 47,950 ABOc recipients). The baseline characteristics, including study design type (single-center, multicenter, or registry), donor type (living or deceased allografts), transplant era, pediatric/adult classification, and center desensitization features (rituximab and splenectomy use), are extensively detailed within **Table 1**. All 63 studies achieved an NOS score $\geq$ 5 (**Supplemental Table 5**).

Allograft Rejection Endpoints

Overall Rejection: Evaluated across 39 studies (15,261 participants). The pooled analysis demonstrated that ABOi was associated with an increased point estimate for all-cause rejection (RR = 1.28, 95% CI: 1.17–1.40,

$P < 0.001$, $I^2 = 0.0\%$; **Figure 2A**).
Antibody-Mediated Rejection (AMR): Synthesized from 35 studies (10,680 participants). ABOi cohorts showed a markedly higher point estimate for AMR (RR = 2.14, 95% CI: 1.48–3.09, $P < 0.001$, $I^2 = 65.5\%$; **Figure 2B**).
T-Cell-Mediated Rejection (TCMR): Evaluated across 24 studies (4,982 participants). The pooled estimate showed wide compatibility with the null hypothesis between the two groups (RR = 0.86, 95% CI: 0.72–1.04, $P = 0.12$, I2 = 0.0%; **Figure 2C**).

Patient and Graft Survival

Patient Survival: At 1 year (28 studies, 30,103 participants; RR = 1.00, 95% CI: 0.97–1.04, $P = 0.83$; **Figure 3B**), 3 years (16 studies, 72,656 participants; RR = 1.00, 95% CI: 0.97–1.04, $P = 0.87$; **Figure 3C**), and 10 years (6 studies, 12,928 participants; RR = 1.01, 95% CI: 0.95–1.07, $P = 0.82$; Figure 3E), survival estimates were highly comparable and compatible with the null between ABOi and ABOc groups under the random-effects framework ($I^2 = 0.0\%$). However, 5-year patient survival (20 studies, 15,904 participants) demonstrated lower compatibility with the null, indicating a higher risk of death for the ABOi cohort (RR = 1.62, 95% CI: 1.13–2.32, $P = 0.008$, $I^2 = 97.8\%$; **Figure 3D**). Overall patient survival also remained comparable across cohorts (**Figure 3A**).
Graft Survival: Synthesized across fixed intervals. No substantial point deviations from the null were observed for overall graft survival (RR = 1.01, 95% CI: 0.93–1.09, $P = 0.83$, $I^2 = 0.0\%$; **Figure 4A**), 1-year graft survival (RR = 0.99, 95% CI: 0.95–1.03, $P = 0.58$, $I^2 = 0.0\%$; **Figure 4B**), 3-year graft survival (RR = 0.98, 95% CI: 0.94–1.03, $P = 0.50$, $I^2 = 0.0\%$; **Figure 4C**), 5-year graft survival (RR = 0.95, 95% CI: 0.83–1.09, $P = 0.46$, $I^2 = 82.4\%$; **Figure 4D**), or 10-year graft survival (RR = 1.09, 95% CI: 0.92–1.30, $P = 0.31$, $I^2 = 68.0\%$; **Figure 4E**).

Secondary Infectious and Surgical Complications

Infectious events were more frequent among ABOi recipients (10 studies, 5,788 participants; RR = 1.31, 95% CI: 1.01–1.70, $P = 0.045$, $I^2 = 73.4\%$). Stratified estimates showed higher compatibility with increased risk in ABOi for sepsis (RR = 1.62, 95% CI: 1.07–2.46, $P = 0.022$), pneumonia (RR = 1.41, 95% CI: 1.09–1.84, $P = 0.010$), and BKV (RR = 1.95, 95% CI: 1.47–2.58, $P < 0.001$). Conversely, risks for UTI, CMV, and EBV showed wide compatibility with the null (**Supplementary Figure 1**).
Surgical complications differed substantially, with ABOi patients exhibiting higher complication rates than ABOc controls across 10 studies (RR = 1.78, 95% CI: 1.37–2.30, $P < 0.001$, $I^2 = 0.0\%$). Postoperative bleeding was notably more common in the ABOi group (14 studies, 4,089 participants; RR = 1.65, 95% CI: 1.27–2.16, $P < 0.001$, $I^2 = 0.0\%$; **Supplementary Figure 2**).

DISCUSSION

This updated systematic review and meta-analysis synthesized evidence from 63 observational studies to clarify the comparative safety and efficacy of ABOi versus ABOc kidney transplantation. By transitioning primary analyses to a random-effects model and strictly avoiding statistical significance dichotomy, our results present a nuanced clinical picture.
The findings demonstrate a higher estimated risk of overall allograft rejection and AMR among ABOi recipients, aligning directly with previous data from registry networks.[4,5,54,72] Interestingly, T-cell-mediated rejection rates did not differ significantly, suggesting that the observed excess risk is largely driven by antibody-related mechanisms, which remain incompletely mitigated by current desensitization strategies. The lack of a clear divergence in TCMR suggests that the immunological barrier in ABOi remains predominantly humoral, driven by rebound anti-A/B isoagglutinins that bypass standard induction regimens.[53]
Regarding survival outcomes, our pooled estimates for 1-, 3-, and 10-year fixed endpoints demonstrate close proximity to the null, suggesting that comparable long-term outcomes are achievable in selected settings. However, a significant divergence was captured at the 5-year patient survival interval, where the pooled point estimate indicated an elevated mortality risk for the ABOi cohort. This finding contrasts with claims of uniform long-term noninferiority and must be interpreted cautiously. Because time-to-event data were extracted as fixed-point RRs rather than hazard ratios (HRs) due to reporting variations in primary studies, this estimate does not account for individual censoring patterns and represents a critical methodological limitation. This medium-term survival gap may reflect the cumulative clinical toll of enhanced maintenance immunosuppression, plasmapheresis-related tissue vulnerabilities, or subclinical humoral injury over time.[4]
Unadjusted confounding represents the primary limitation of the observational literature summarized here. Primary studies varied greatly regarding donor type (living vs. deceased), baseline isoagglutinin titers, and desensitization choices (such as rituximab dosing variations or splenectomy), all of which confound survival and complication risks. The higher frequencies of sepsis, pneumonia, BKV, and postoperative bleeding observed in the ABOi group clearly reflect the therapeutic trade-offs of aggressive perioperative desensitization and plasma exchange protocols.[4,64]

Study Limitations

First, the protocol was not prospectively registered in PROSPERO. Second, the exclusion of non-English publications may omit relevant cohorts, particularly from East Asia, where ABOi programs are highly active. Third, the reliance on crude unadjusted RRs extracted at fixed intervals instead of adjusted hazard ratios (HRs) from Kaplan-Meier curves prevents adequate control for residual confounding elements such as recipient age, HLA-sensitization status, and center volumes. Finally, high statistical heterogeneity ($I^2 > 50\%$) in the AMR, 5-year patient survival, and overall infection analyses limits the precision of those specific pooled metrics.

CONCLUSIONS

ABOi kidney transplantation constitutes a valuable strategy to expand the living donor pool, demonstrating comparable patient and graft survival estimates at 1, 3, and 10 years. However, it is accompanied by higher risks of antibody-mediated rejection, perioperative bleeding, and severe infections, alongside a noted divergence in 5-year patient survival. Future registry and prospective studies should utilize standardized, adjust-

ed time-to-event data to refine recipient selection and close the medium-term survival gap.

SUMMARY

ABO-incompatible kidney transplants expand donor options with comparable 1-, 3-, and 10-year survival. However, they carry higher risks of rejection, bleeding, and infection, along with lower 5-year survival compared to compatible transplants.

DATA AVAILABILITY

All data generated during the current study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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