Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)

Journal Impact Factor® (2022): 3.4
CiteScore® (2022): 5.3
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SUPPLEMENTAL DATA

Donor-derived cell-free DNA as a diagnostic marker for kidney-allograft rejection: A systematic review and meta-analysis

Table S1. Types of rejection reactions and detailed statistics.

Author	*Year*	*Rejection type*	*Detailed information*
Dauber	2020	Acute rejection	ABMR: 3; TCMR: 5
Huang	2019	Any rejection	TCMR: 10; ABMR: 22; Mixed rejection: 2
Sigdel	2018	Active rejection	ABMR: 16; TCMR: 10; Mixed rejection: 12
Oellerich[a]	2019	Any rejection	Active ABMR: 6; Chronic active ABMR: 1; Mixed acute TCMR and active ABMR: 4; Acute TCMR: 4
Bloom	2017	Active rejection	Acute/active ABMR: 6 (including mixed TCMR); Chronic, active ABMR: 10 (including mixed TCMR); TCMR: 11
Bunnapradist	2021	Active rejection	ABMR: 1; TCMR: 5; Mixed rejection: 3
Park	2021	Acute rejection	ABMR: 42; TCMR:3 8; Mixed rejection: 23
Halloran	2022	Any rejection	ABMR: 58; TCMR: 15; Mixed rejection: 10

Puliyanda	2022	Acute rejection	ABMR: 17; TCMR: 3; Mixed rejection: 9
Obrișcă	2022	Any rejection	ABMR: 12; TCMR: 12; Mixed rejection: 6
Chang	2022	Any rejection	Borderline TCMR: 21; TCMR grade 1A or higher: 21; Acute ABMR: 5; Chronic ABMR: 13; Chronic TCMR: 1; Mixed rejection: 6
Ranch	2023	Any rejection	ABMR: 10; TCMR: 18; Mixed rejection: 7
Dandamudi[b]	2022	Acute rejection	Biopsy-proven acute rejection: 27
Rizvi	2023	Any rejection	ABMR: 28; Mixed rejection: 17
Gupta	2022	Any rejection	Acute ABMR: 22; Chronic active ABMR: 21; Borderline TCMR: 8; 1A TCMR: 13; 1B TCMR: 6
Bu	2022	Any rejection	ABMR: 75; TCMR: 38

[a]The data provided in the literature is in terms of the number of individuals, not the quantity of plasma samples. [b]The literature did not provide estimates for the types of rejection or the number of individuals affected. ABMR: Antibody-mediated rejection; TCMR: T cell-mediated rejection.

Table S2. Summary estimates of the diagnostic accuracy of dd-cfDNA for diagnosis of any rejection according to the cutoff value, age group and biopsy reasons.

Subgroup	Number of studies	SEN (95% CI)	SPE (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC
Overall	9	0.59 (0.48-0.69)	0.83 (0.76-0.88)	3.5 (2.8-4.5)	0.49 (0.40-0.61)	7 (5-10)	0.80
Cutoff							
1%	8	0.57 (0.46-0.68)	0.85 (0.79-0.89)	3.8 (3.0-4.8)	0.51 (0.41-0.63)	8 (5-10)	0.84
0.5%	3	0.78 (0.72-0.84)	0.66 (0.58-0.73)	2.1 (1.6-2.8)	0.34 (0.26-0.46)	7 (4-10)	0.79
Biopsy design							
For-cause	5	0.64 (0.59-0.68)	0.77 (0.74-0.80)	2.8 (2.2-3.7)	0.42 (0.30-0.58)	8 (5-10)	0.79
Protocol-contained	4	0.63 (0.52-0.73)	0.82 (0.76-0.87)	3.5 (2.8-4.3)	0.45 (0.35-0.58)	8 (6-11)	0.82
Age group							
Adults	8	0.59(0.46-0.70)	0.83(0.75-0.88)	3.4(2.6-4.3)	0.50(0.40-0.63)	7(5-9)	0.79
Children	1	ND	ND	ND	ND	ND	ND

SEN: Sensitivity; SPE: Specificity; CI: Confidence interval; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio; AUC: Area under the curve; ND: No data; dd-cfDNA: Donor-derived cell-free DNA.

Table S3. Summary estimates of the diagnostic accuracy of dd-cfDNA for diagnosis of antibody-mediated rejection according to the study type and biopsy reasons.

Subgroup	Number of studies	SEN (95% CI)	SPE (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC
Overall	12	0.81 (0.72-0.87)	0.80 (0.73-0.85)	4.0 (3.0-5.3)	0.24 (0.17-0.35)	17 (10-28)	0.87
Study type							
Prospective	6	0.76 (0.66-0.84)	0.79 (0.74-0.83)	3.6 (2.8-4.7)	0.30 (0.20-0.45)	12 (6-23)	0.83
Retrospective or no clear	6	0.84 (0.71-0.92)	0.81 (0.68-0.90)	4.5 (2.6-7.9)	0.20 (0.11-0.36)	23 (10-51)	0.90
Biopsy design							
For-cause	10	0.83 (0.74-0.89)	0.80 (0.72-0.86)	4.1 (3.0-5.6)	0.22 (0.15-0.32)	19 (11-31)	0.88
Protocol-contained	2	ND	ND	ND	ND	ND	ND

SEN: Sensitivity; SPE: Specificity; CI: Confidence interval; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio; AUC: Area under the curve; ND: No data; dd-cfDNA: Donor-derived cell-free DNA.

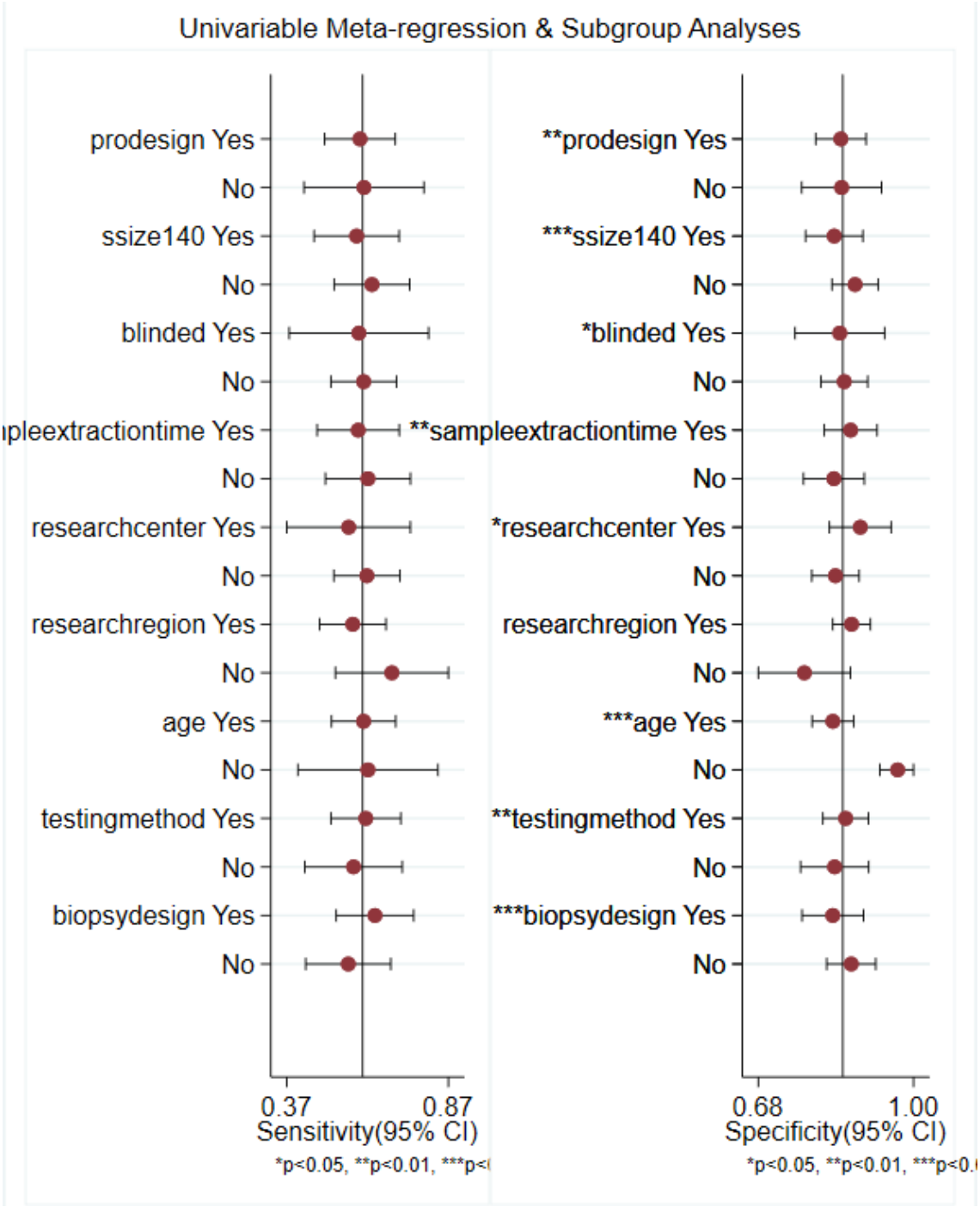

Figure S1. Univariate meta-regression of dd-cfDNA for diagnosis of AR. This includes: study type (YES: Prospective; NO: Retrospective or no clear), sample size (YES: More than 140; NO: Fewer than 140); blind design (YES: Adopted; NO: Not adopted or no clear); sample extraction time (YES: At the same time as biopsy; NO: Not or unclear); research center (YES: Multicenter; NO: Single-center or not clear), research region (YES: United States; NO: Countries other than the United States), age group (YES: Adults; NO: Children), test method (YES: NGS; NO: Others), biopsy design (YES: For-cause ; NO: Protocol contained). * for $P < 0.05$; ** for $P < 0.01$; *** for $P < 0.001$. dd-cfDNA: Donor-derived cell-free DNA; CI: Confidence interval; AR: Any rejection.

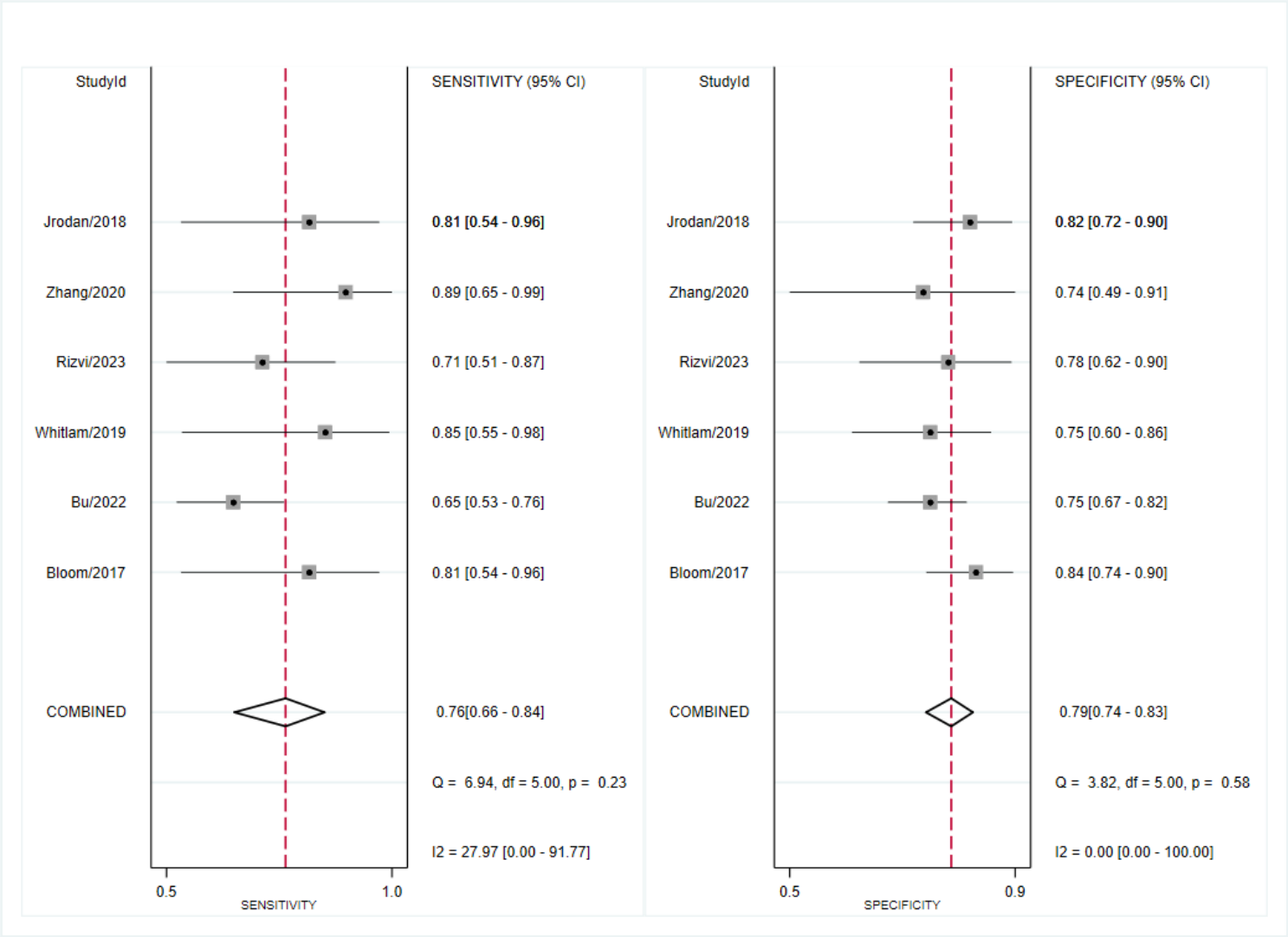

Figure S2. The pooled sensitivity and specificity in prospective studies. CI: Confidence interval.

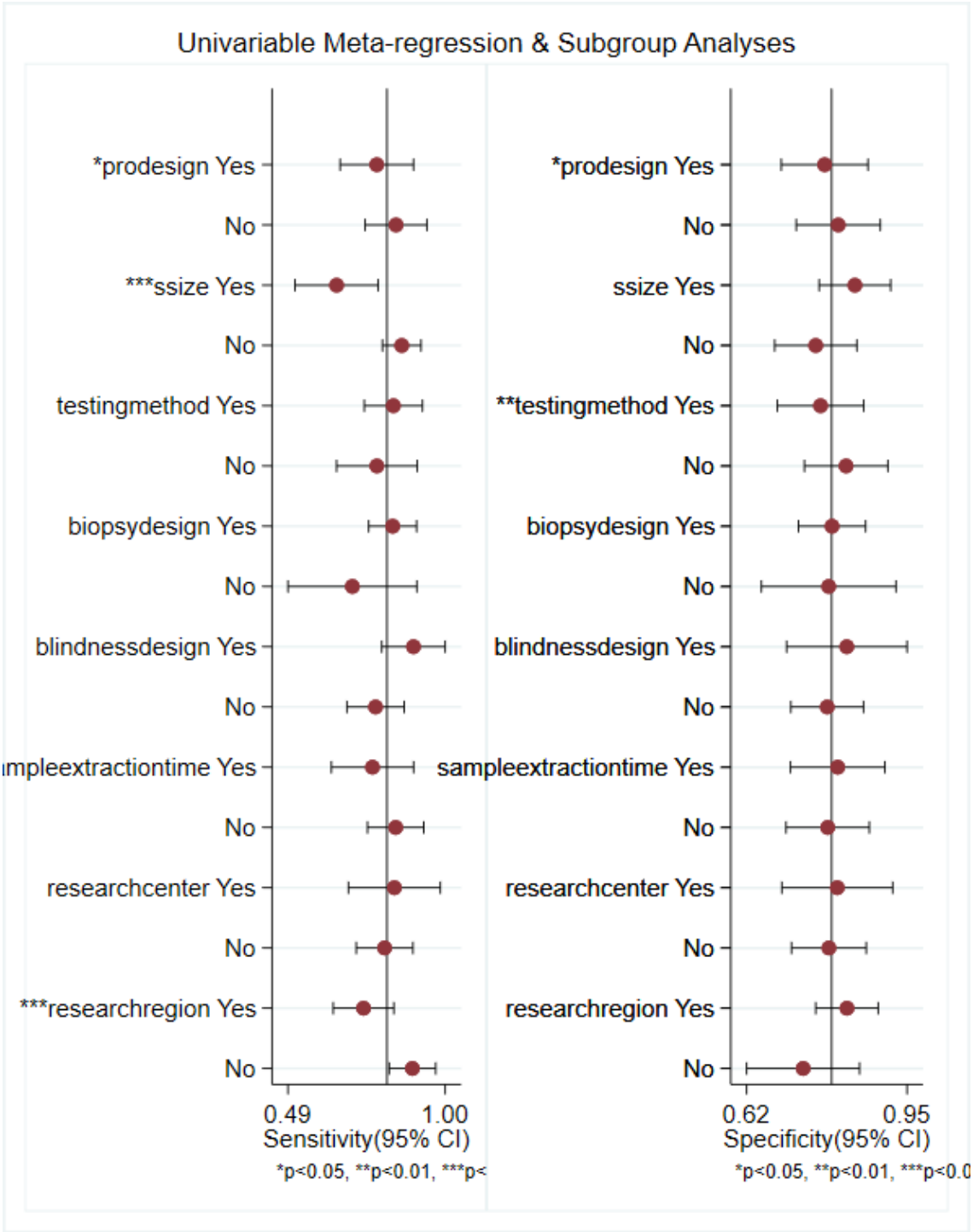

Figure S3. Univariate meta-regression of dd-cfDNA for diagnosis of antibody-mediated rejection. This included: Study type (YES: Prospective; NO: Retrospective or not clear), sample size (YES: More than 140; NO: Fewer than 140), blind design (YES: Adopted; NO: Not adopted or not clear), sample extraction time (YES: At the same time as biopsy; NO: Not or unclear), research center (YES: Multicenter; NO: Single-center or not clear), research region (YES: United States; NO: Countries other than the United States), test method (YES: NGS; NO: Others), biopsy design (YES: For-cause ; NO: Protocol contained).* for $P < 0.05$; ** for $P < 0.01$; *** for $P < 0.001$. dd-cfDNA: Donor-derived cell-free DNA; CI: Confidence interval.

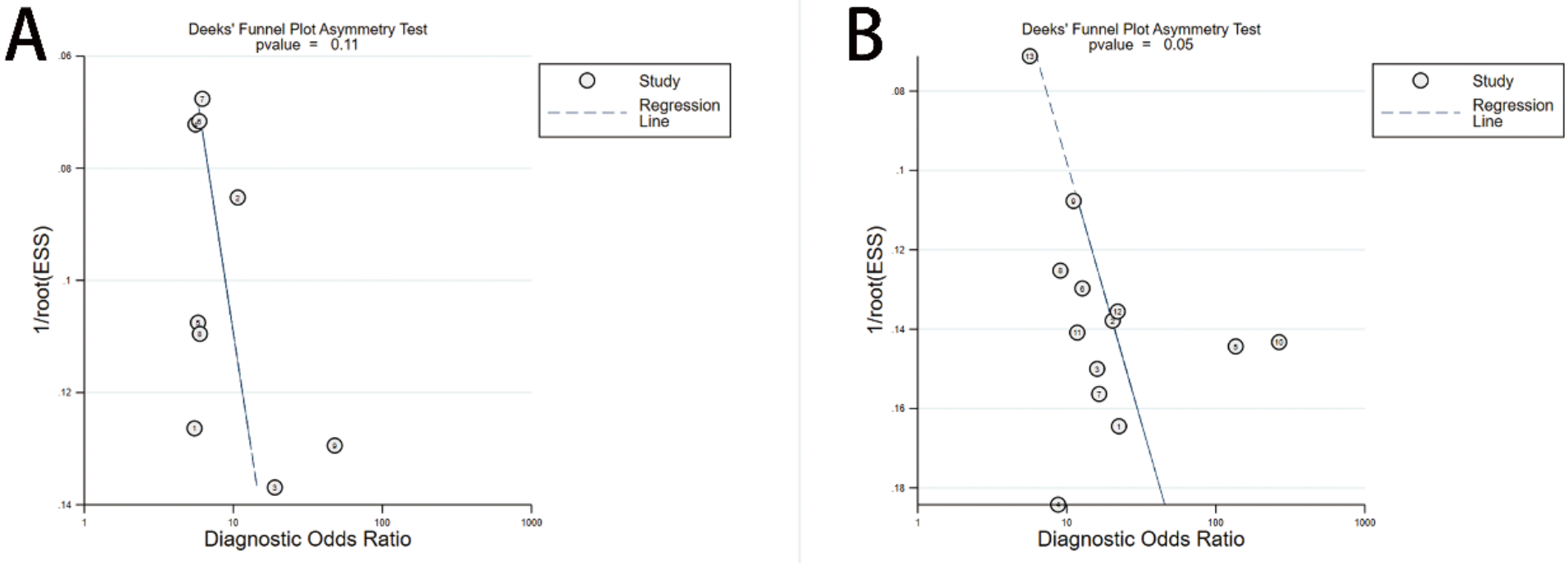

Figure S4. (A) Deeks' funnel plot asymmetry test of dd-cfDNA for diagnosis of AR; (B) Deeks' funnel plot asymmetry test of dd-cfDNA for diagnosis of antibody-mediated rejection. ESS: Effective sample size; dd-cfDNA: Donor-derived cell-free DNA; AR: Any rejection.