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Predictive Efficacy of the Index of Microcirculatory Resistance for Acute Allograft Rejection and Cardiac Events After Heart Transplantation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: In patients treated by heart transplantation, the index of microcirculatory resistance (IMR) has been found to have predictive potential for subsequent acute allograft rejection (AAR) and long-time cardiac events. When consulting related literature, the studies mostly were single-center with small sample sizes. The question of whether IMR can be utilized as a predictive biomarker is becoming increasingly contentious. To confirm the predictive efficacy of IMR, researchers did a systematic review and meta-analysis.

Method: From inception to April 2022, PubMed, EMBASE, Cochrane Library, Web of Science, Ovid, ProQuest, and Scopus systematically were searched. The results were presented as pooled ratio rate (RR) with 95% confidence intervals (CI). Assessment of the quality, heterogeneity analyses, and publication bias analysis also were performed.

Results: A total of 616 patients were studied in five trials. There were significant differences in subsequent AAR (RR = 4.08; 95% CI: 2.69~6.17; P = 0.000) or long-time cardiac events (RR=2.14; 95% CI: 1.44~3.19; P = 0.000) between IMR-high and IMR-low patients in the forest plots. Patients treated with heart transplantation in the high IMR group had better predictive efficacy than the low IMR group.

Conclusions: High IMR could predict the events of subsequent AAR and cardiac events after heart transplantation. This will help reduce the occurrence of adverse events and personalize treatment for patients.

INTRODUCTION

Heart transplantation has attracted increasing attention from clinical cardiologists in recent years as a revolutionary therapy [Zhang 2022]. Currently, however, the acute allograft rejection (AAR) has been a major barrier to favorable outcomes after heart transplantation [Ahn 2021]. Heart transplantation for patients with end-stage heart failure as the only curative treatment have been shown to be more effective than conservative therapies [Lee 2021]. Advances in immunosuppression, donor heart procurement, surgical techniques, and post-transplantation care can decrease acute allograft rejection rates and improve survival after heart transplantation [Lee 2021]. Nevertheless, 13% to 30% of patients with heart transplant experience acute allograft rejection within the first year after transplantation, and it remains as one of the leading causes of late cardiac allograft vasculopathy, graft loss, and mortality [Ahn 2021; Lee 2021]. As a result, identifying predictive index to identify AAR is critical. What's more, earlier prediction of subsequent AAR could allow for pre-emptive modification in immunosuppression and surveillance, which might improve outcomes [Ahn 2021]. Previous studies used the index of microcirculatory resistance (IMR) to assess microvascular dysfunction, but a history of acute rejection was identified as a risk factor for microvascular dysfunction [Haddad 2012]. Recent research found that higher IMR predicts better subsequent AAR and long-term cardiac events [Ahn 2021]. There currently is no unified standard for the optimal cutoff value of IMR. The index of microcirculatory resistance (IMR) is an invasive physiological index that measures minimal coronary microvascular resistance and is predictive of cardiac events in various clinical settings associated with microvascular dysfunction [Fearon 2017].

However, it is unfortunate that obtaining adequate samples is frequently clinically impossible. Furthermore, because of its invasiveness, IMR poses technical and ethical challenges. Because of the presence of various flaws, the predictive efficacy of the IMR has been questioned [Zhang 2022]. As a result, it is becoming increasingly urgent and important to investigate the true role of IMR in patients with heart transplantation. In summary, we conducted a systematic review and meta-analysis to assess the value of IMR to better understand the predictive efficacy of IMR in patients with heart transplantation.

MATERIALS AND METHODS

Literature search and study selection: A comprehensive systematic review and meta-analysis were carried out

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in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [Moher 2009]. PubMed, EMBASE, Cochrane Library, Web of Science, Ovid, ProQuest, and Scopus systematically were searched to identify relevant studies published between inception and April 2022, without any restriction of countries. The databases independently were searched by two investigators. The following were the key search terms: "Microcirculation" OR "Microvascular Blood Flow" OR "Blood Flow, Microvascular" OR "Flow, Microvascular Blood" OR "Microvascular Blood Flows" OR "Microvascular Circulation" OR "Circulation, Microvascular" OR "Microvascular Circulations" AND "Resistance." Initially, articles were screened using the title and abstract; then, eligible articles were evaluated using the full text. We also looked through the reference lists of the included articles to find any missing literature. Initially, articles were screened using the title and abstract; then, eligible articles were evaluated using the full text. We also looked through the reference lists of the included articles to find any missing literature. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The meta-analysis was registered in the PROSPERO database (CRD42022326162).

To identify eligible studies, the following inclusion criteria were used: (1) patients who accepted heart transplantation treatment; (2) the IMR is precisely defined as an invasive physiological index that measures minimal coronary microvascular resistance; (3) at least one or more main evaluation indicators (acute allograft rejection (AAR) within 1 year after transplantation, death, re-transplantation and so on) were available comparing low IMR against high IMR; (4) the risk ratio (RR) with 95 percent confidence interval (CI) of AAR and cardiac events could be obtained directly. Due to a lack of information, reviews, guidelines, letters, expert opinion, comments, meeting abstracts, animal studies and so on were excluded.

Data extraction and assessment of the quality of the included studies: Two investigators independently reviewed the included studies and extracted the following data: the surname of the first author, publication year, type of study, sample size, study design, country of origin, and the main reporting outcomes. Number of IMR-high and IMR-low patients in the exposure and control groups, respectively, the value and 95% CI of outcomes (AAR, cardiac events) in the IMR-high and IMR-low groups were extracted for pooled analysis. Inconsistencies were conferred and resolved by consensus among all investigators. The Newcastle–Ottawa Scale (NOS) recommended by the Cochrane Non-Randomized Studies Methods Working Group and Cochrane Collaboration's Tools were used to assess the methodology quality of non-randomized trials and randomized controlled trials for meta-analysis [Stang 2010; Higgins 2011]. The NOS is made up of three quality parameters: selection (0~4 points), comparability (0~2 points), and outcome assessment (0~3 points). The total NOS scores ranged from 0 to 9, with higher scores indicating higher quality. Methodological studies with a score of 6 are of high quality.

Statistical evaluation: The primary endpoint was the difference of events of AAR and cardiac events measured by RR between the exposure and control groups. The Q test and I2 value, which is a quantitative measure of inconsistency across studies, were used to assess study heterogeneity. The fixed effect model (Mantel–Haenszel method) was used if P <0.10 in the Q test or I2 was <50%. Otherwise, a random effect model analysis was carried out [Higgins 2003]. $P < 0.05$ was defined as a statistically significant outcome. Sensitivity analysis was not assessed because that the I2< 50% and $P >$ 0.1 were considered to indicate not significant heterogeneity. Sensitivity analyses were used to investigate the source of heterogeneity. Prespecified subgroup analysis was performed, according to the sample size (take the sample size of 100 as the critical line). Publication bias also was performed with the funnel chart, Begg's Test and Egger's Test to test the stability of the results in this study. STATA software (version 16.0; Stata Corporation, College Station, TX) was used for all statistical analyses.

RESULTS

Literature search and study characteristics: Figure 1 depicts the process of conducting a literature search. (Figure 1) A total of 11 records were included in the initial assessment by searching the literature database and references of relevant studies. After excluding duplication, four papers were left out. Following that, we carefully reviewed the remaining seven publications. One paper was not related to the topic and one paper failed to meet the criteria among them. The meta-analysis eventually included five articles published between 2012 and 2021 [Ahn 2021; Lee 2021; Haddad 2012; Okada 2019; Yang 2016]. Table 1 lists the main characteristics of the included studies. (Table 1) Five studies were cohort studies, involving 616 patients with heart transplantation. One multicenter study was conducted: United States, Norway, Sweden, and the Republic of Korea. The outcome included AAR within 1 year after transplantation and long-time cardiac events. Cardiac events, a key secondary outcome, included death, re-transplantation, failed-transplantation and so on.

Evaluation of quality: All five studies were evaluated using the NOS. The results in Table 2 shows that all of the included studies were high quality. (Table 2)

The definitions of high and low IMR varied across studies. The cutoff value for IMR ranged from 12 to 20. Exposure group and control group were defined by high and low IMR, respectively. Appendix 3 and Appendix 4 list the number of IMR and cardiac events in exposure group and control group. (Appendix 3) (Appendix 4) Clinical indicators, such as AAR and cardiac events, were compared between low IMR and high IMR patients.

As shown in Figure 2, five studies were conducted to assess the predictive efficacy of the IMR for AAR [Ahn 2021; Lee 2021; Haddad 2012; Okada 2019; Yang 2016], and meta-analysis revealed significant difference between heart transplant patients with low IMR and those with high IMR. (Figure 2) The pooled RR was 4.08 (95% confidence interval (CI)

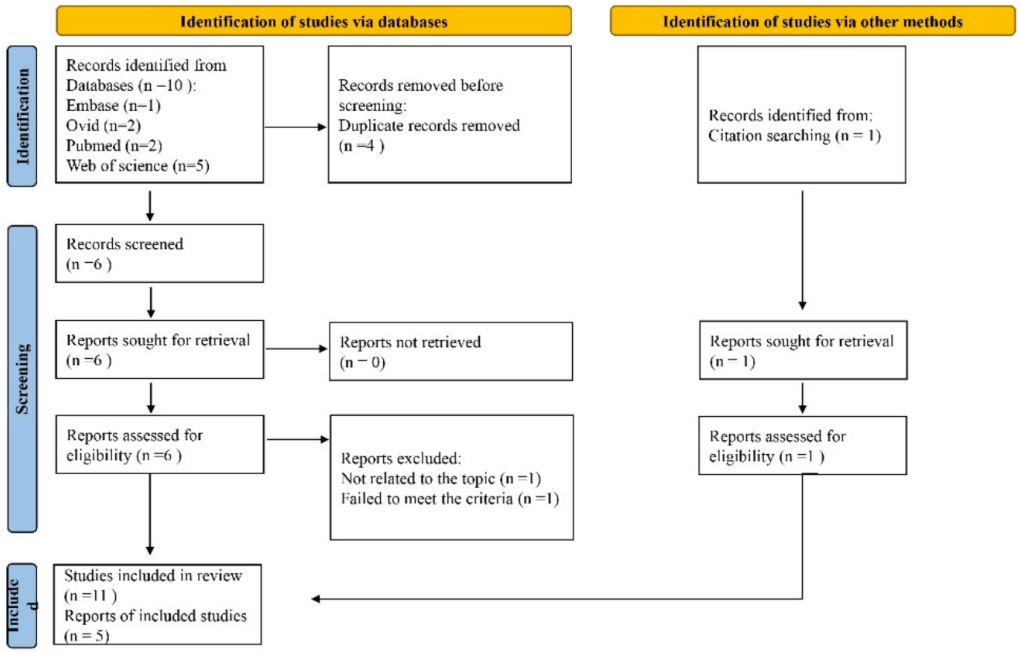


Figure 1.

Table 1. The main feature of the studies included in the meta-analysis

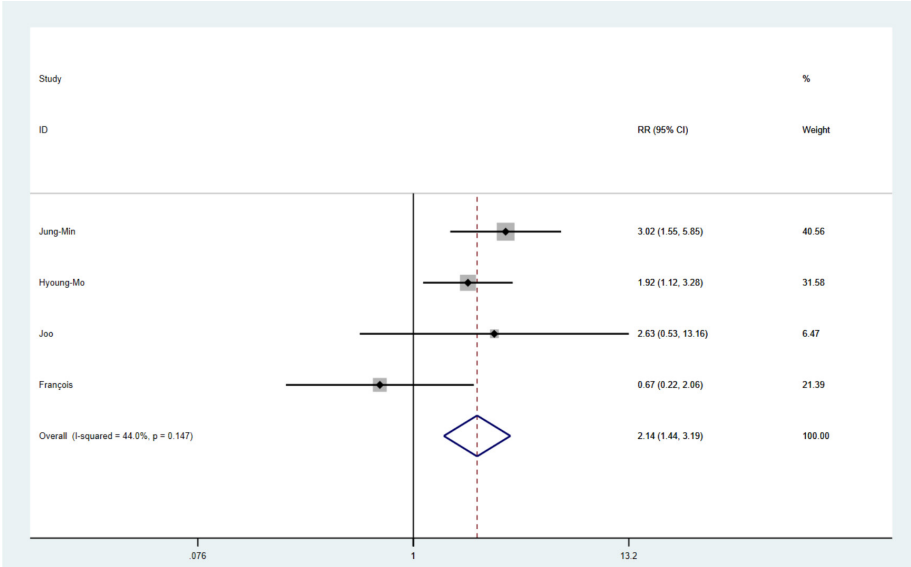
Study	Region	Type of study	*N*	Outcomes
Jung-Min, 2021	Multiple areas	Cohorts study, Unblinded	237	AAR, MACE
Hyoung-Mo, 2016	USA	Cohorts study, Unblinded	74	Death, re-transplantation
Kozo, 2019	USA	Cohorts study, Unblinded	88	AAR
Joo, 2021	Republic of Korea	Cohorts study, Unblinded	154	AAR, death
François, 2012	USA	Cohorts study, Unblinded	63	AAR, death, failed-transplantation

AAR: The primary outcome was acute allograft rejection (AAR) within 1 year after transplantation. MACE: A key secondary outcome was major adverse cardiac events (MACE) (the composite of death, re-transplantation, myocardial infarction, stroke, graft dysfunction, and readmission) at 10 years.

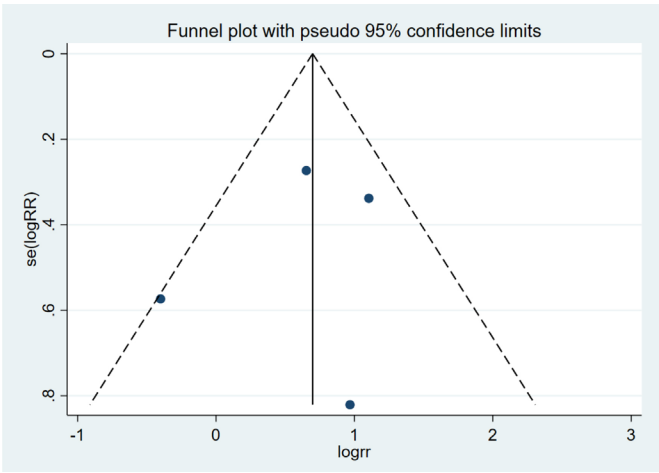
Table 2. The Newcastle–Ottawa Scale (NOS) assessment of the included studies' risk of bias

Study	Selection	Comparability	Outcome	Total score
Jung-Min, 2021	XXXX	XX	XXX	9
Hyoung-Mo, 2016	XXXX	XX	XX	8
Kozo, 2019	XXXX	XX	XX	8
Joo, 2021	XXXX	XX	XX	8
François, 2012	XXXX	XX	XX	8

NOS points: 0 to 3: very high risk of bias; 4 to 6: high risk of bias; 7 to 9: low risk of bias



Appendix 1. Forest plot of clinical events' comparison for long-time cardiac events between the exposure group and control group.



Appendix 2. Funnel plot for the analysis of publication bias about long-time cardiac events.

Appendix 3. Number of IMR in the exposure group and control group

Study	Year	AAR in exposure group	Total in exposure group	AAR in control group	Total in control group
Jung-Min	2021	26	110	8	127
Hyoung-Mo	2016	9	22	9	52
Kozo	2019	21	58	1	30
Joo	2021	24	75	3	79
François	2012	15	29	7	34

exposure group: IMR-high patients; control groups: IMR-low patients

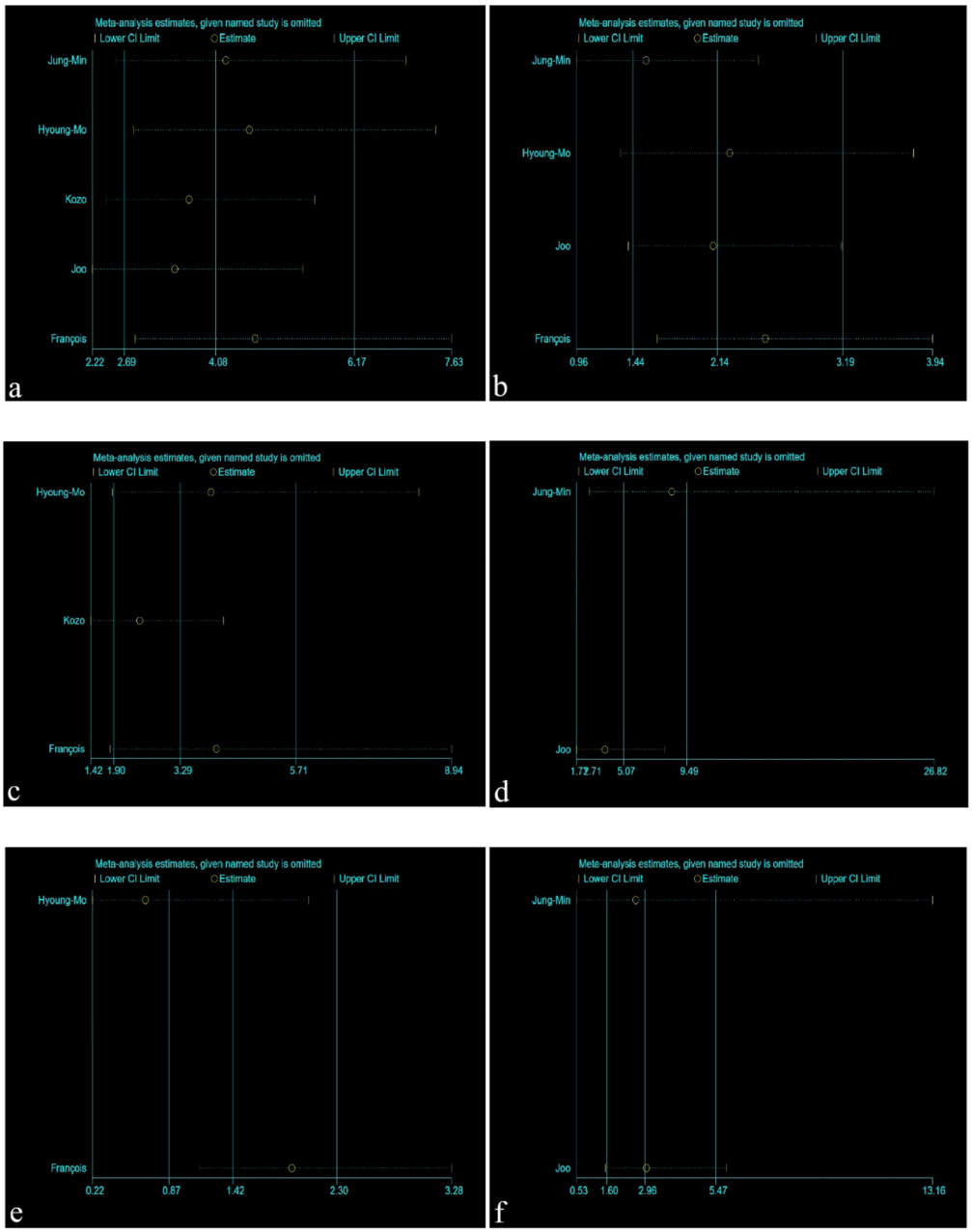
Appendix 4. Number of cardiac events in exposure group and control group

Study	Year	Cardiac events in exposure group	Total in exposure group	Cardiac events in control group	Total in control group
Jung-Min	2021	78	181	8	56
Hyoung-Mo	2016	13	22	16	52
Joo	2021	5	75	2	79
François	2012	4	29	7	34

2.69~6.17; P = 0.000). It was suggested that high IMR was better than the control group in predicting AAR after heart transplantation. Because there was no significant heterogeneity between the studies (I2 = 33.5%, P = 0.198), a fixed-effects model was used. The pooled RR was 4.08 (95% CI 2.69~6.17; P = 0.000), as seen in the forest plot (Figure 2). Eventually, statistically significant differences were found between IMR-high and IMR-low patients. As a result, high IMR appeared to be effective in predicting AAR.

Similarly, to assess the predictive efficacy of the IMR for cardiac events, we performed a pooled analysis based on four studies [Ahn 2021; Lee 2021; Haddad 2012; Yang 2016]. There was no significant heterogeneity between the studies (I2 = 44%, P = 0.147), so a fixed-effects model was used. The pooled RR was 2.14 (95% CI 1.44~3.19; P = 0.000), as seen in the forest plot. (Appendix 1) It revealed significant difference between heart transplant patients with low IMR and those with high IMR. The pooled outcome for IMR suggested that high IMR can significantly predict long-term cardiac events.

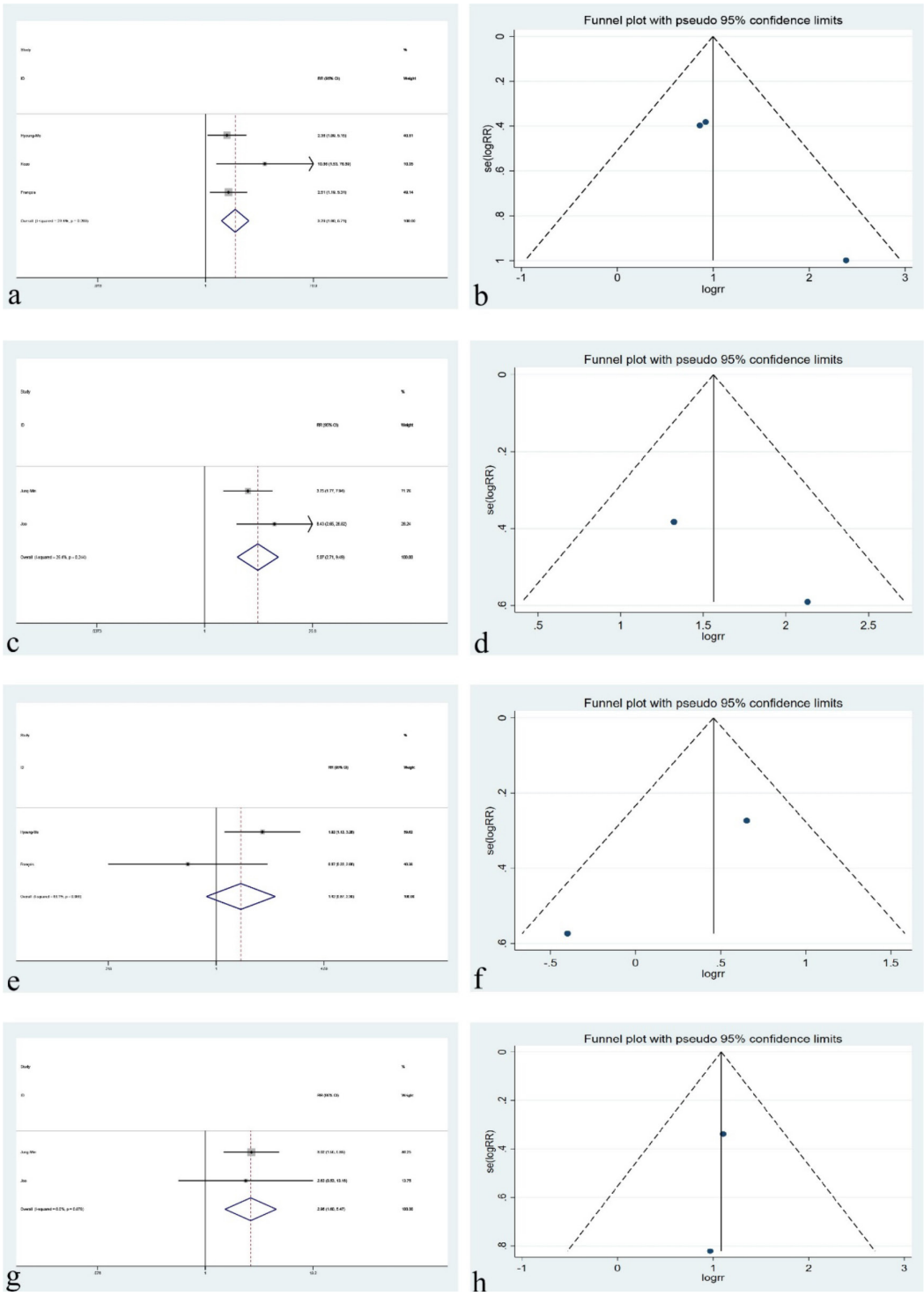
Subgroup analysis: Among the patients treated by heart transplantation, high IMR was better than the control group in predicting AAR after heart transplantation in the studies of large sample size [Ahn 2021; Lee 2021]. The pooled RR



Appendix 5. Sensitivity analysis of the potential impact of individual studies on outcomes. Sensitivity analysis of clinical events' comparison for AAR (5A) and long-time cardiac events (5B) between the exposure group and control group. Sensitivity analysis of clinical events' comparison for AAR (5C and 5D) and long-time cardiac events (5E and 5F) between the exposure group and control group (5C and 5E: small sample size; 5D and 5F: large sample size).

was 5.07 (95% CI 2.71~9.49; P = 0.000), as seen in the forest plot (Appendix 6C). (Appendix 6) Because there was no significant heterogeneity between the studies (I2 = 26.4%, P = 0.244), a fixed-effects model was used. Similarly, high IMR also was better in studies of small sample size [Haddad 2012; Okada 2019; Yang 2016] (RR=3.29, 95% CI 1.90~5.71; P = 0.000) (Appendix 6A). There was no significant heterogeneity between the studies (I2 = 23.8%, P = 0. 269). The pooling analysis indicated that high IMR can significantly predict long-term cardiac events in studies of large sample size [Ahn 2021; Lee 2021] (RR=2.96, 95% CI 1.61~5.47, P = 0.001) (Appendix 6G). What's more, there was no significant heterogeneity between the studies (I2 = 0.0%, P = 0. 878). However, in the studies of small sample size [Haddad 2012; Yang 2016], there was no significant difference between the two groups in predicting long-term cardiac events (RR=1.42, 95% CI 0.87~2.30, P = 0.161) (Appendix 6E). There was mildly significant heterogeneity between the studies (I2 = 66.1%, P = 0. 09).

Sensitivity analysis: The potential impact of individual studies on the pooled RR was assessed in a sensitivity analysis.



Appendix 6. Forest plot and funnel plot of subgroup analysis for AAR and long-time cardiac events between the exposure group and control group. Forest plot and funnel plot of clinical events' comparison for AAR between the exposure group and control group (6A and 6B: small sample size; 6C and 6D: large sample size). Forest plot and funnel plot of clinical events' comparison for long-time cardiac events between the exposure group and control group (6E and 6F: small sample size; 6G and 6H: large sample size).

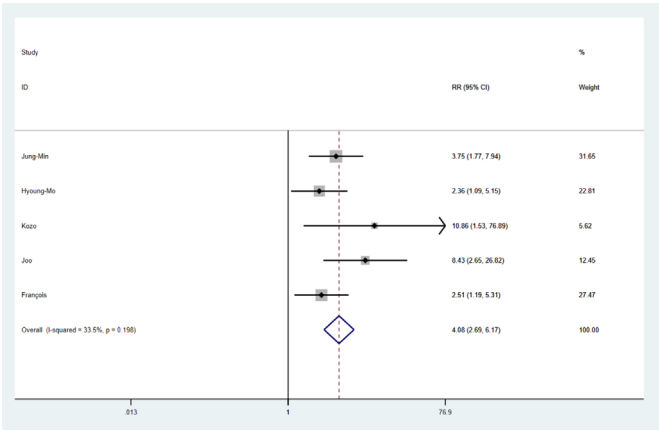


Figure 2. Forest plot of clinical events' comparison for AAR between exposure group and control group. RR, relative risk

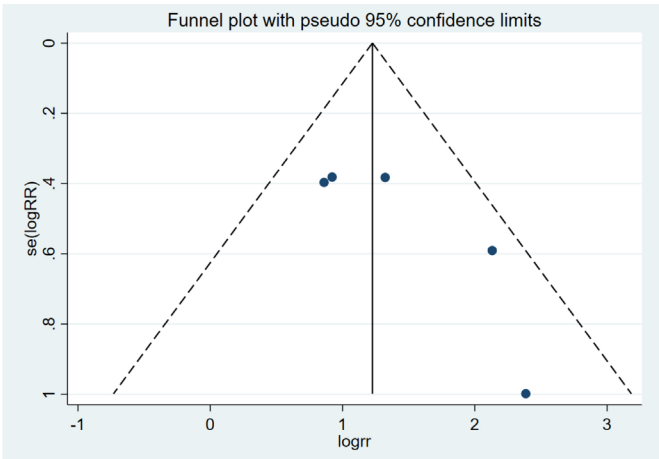


Figure 3. Funnel plot for the analysis of publication bias about AAR. se, standard error

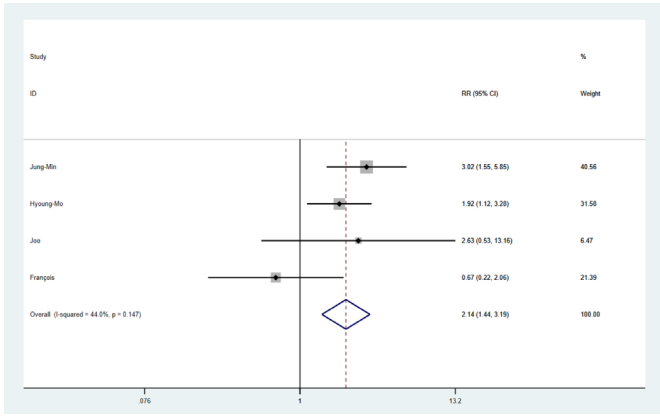


Figure 4. Forest plot of clinical events' comparison for long-time cardiac events between the exposure group and control group.

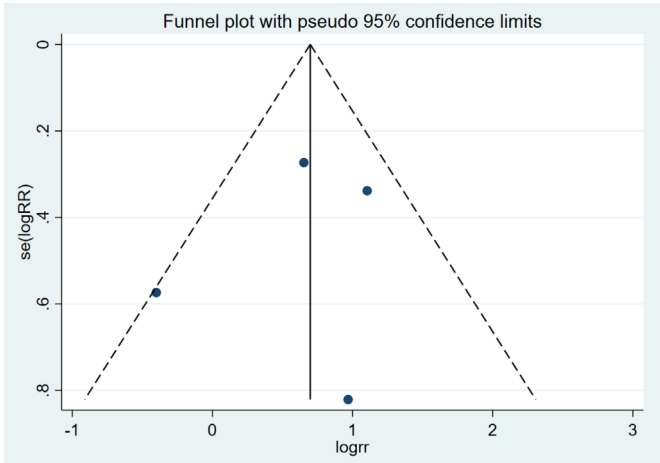


Figure 5. Funnel plot for the analysis of publication bias about long-time cardiac events.

There were no significant changes in any of the outcomes, indicating that the analysis was stable. (Appendix 5)

Analysis of bias: We performed publication bias with the funnel chart, Begg's Test and Egger's Test and funnel plot to test the stability of the results in this study. The funnel plots were symmetrical, as seen in the Figure 3, Appendix 2 and Appendix 6B, 6D, 6F, 6H. (Figure 3) (Appendix 2) Furthermore, publication bias was assessed with Begg's and Egger's tests ($P > 0.05$). They revealed no significant publication bias. Lastly, we could conclude there was no significant publication bias in the literatures of this study.

DISCUSSION

Previously, a number of risk factors, such as age, sex, race, circulating anti-human leukocyte antigen antibodies, induction therapy, human leukocyte antigen mismatch, and genetic polymorphisms, were used to predict AAR [Kilic 2012]. In theory, immune reaction plays a key role in graft failure, including AAR, and pathological evaluation has revealed that myocyte damage and structural distortion of microvasculature and interstitial tissues are common phenotypes of AAR [Lee 2021]. The underlying mechanism for the association between IMR and subsequent AAR may be that microvascular dysfunction early after transplantation develops due to an immune response before the adverse effects of the immune response actually manifest as acute rejection [Ahn 2021]. In this regard, the potential associations between microcirculatory dysfunction and adverse outcomes after heart transplantation, including AAR, were evaluated in previous studies [Haddad 2012; Okada 2019; Yang 2016]. High IMR showed a very high negative predictive value for AAR. In addition, using a lower cutoff value resulted in an even higher negative predictive value, as IMR and the incidence of subsequent AAR were proportional; the incidence of AAR was only 5.4% in patients with the lowest quartile of IMR [Ahn 2021]. There was no uniform cutoff value in the selected literature for our study. Most cutoff values in the literature were close to the optimal value (IMR ≥16) defined in a previous study [Okada 2019].

Table 3. Number of IMR in the exposure group and control group

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exposure group: IMR-high patients; control groups: IMR-low patients

Table 4. Number of cardiac events in the exposure group and control group

Study	Year	Cardiac events in exposure group	Total in exposure group	Cardiac events in control group	Total in control group
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Hyoung-Mo	2016	13	22	16	52
Joo	2021	5	75	2	79
François	2012	4	29	7	34

As a result, this meta-analysis focused on the clinical utility of IMR as a predictive biomarker of subsequent AAR and long-time cardiac events after heart transplantation. In our study, we collected data from five reports with a total of 616 patients to assess the predictive efficacy of IMR. A few studies and patients were included in this study because of the small number of patients with heart transplantation totally. Furthermore, many of the previous studies were not randomized controlled trials and blinded, which were difficult to do. But in the latest multicenter study, three prospective randomized trials were conducted [Ahn 2021]. A comparison of high IMR versus low IMR was performed in the Forest plots. The pooled results revealed there was significant difference in high IMR or low IMR. This finding was not surprising, implying that high IMR did appear to be effective in predicting subsequent AAR after heart transplantation. These findings are consistent with previous research with a relatively larger sample size. A previous study showed that the recurrent rejection after 1 year could be influenced by the presence of rejection during the first year. Therefore, we think the IMR should be measured at an early time point after transplantation to predict subsequent AAR. According to Jung-Min and Joo, the IMR measured at 4 and 7 weeks after transplantation in the latest research.

Another major finding is the association of IMR early after transplantation and the risk of long-term cardiac events. Microvascular dysfunction assessed using index of microcirculatory resistances at 1 year was associated with worse graft function and possibly worse clinical outcomes [Haddad 2012]. What's more, several studies confirmed that an episode of acute rejection during the first year is associated with cardiac allograft vasculopathy, graft dysfunction, and late mortality [Raichlin 2009; López-Sainz 2018; Carl 2014]. In our study, the pooled results confirmed the above association between high IMR and long-time cardiac events. We can predict the long-time outcomes by measuring the IMR early with a relatively larger sample size. In addition, an increased IMR was associated with the subsequent progression of cardiac allograft vasculopathy [Yang 2016; Lee 2017].

Limitations: Our meta-analysis had some limitations. First and foremost, there were fewer trials included in this analysis, and the sample size varied among the included studies. Second, the majority of the studies included in the analysis are retrospective in nature, which may introduce selection bias and other uncontrolled variables into the assessment of IMR and associated clinical outcomes. Third, given the foregoing, we ran funnel chart, Begg's Test and Egger's Test to evaluate the publication bias. Although the outcome is stable, its impact on the final conclusion is objective and cannot be overlooked. In a word, the finding of the study should be interpreted with caution, and additional validation trails are required.

CONCLUSIONS

High IMR measured early after heart transplantation is a feasible and reliable predictive biomarker for identifying subsequent AAR and long-time cardiac events after heart transplantation. Although increased IMR had the potential to predict the cardiac events, its role at this stage is limited. More literature is required. Future studies will need to focus on whether IMR measurement allows a more personalized post-transplantation management strategy [Saraiva 2011; Vecchiati 2014].

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