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Impact of Intrapatient Immunosuppression Variability in Liver Transplantation Outcomes: A Systematic Review and Meta-analysis

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Background. To investigate the impact of intrapatient variability (IPV) in the levels of immunosuppressant drugs on health outcomes after liver transplantation. **Methods.** A comprehensive systematic review and meta-analysis were conducted, examining literature from MEDLINE/PubMed, Embase, Web of Science, Cochrane Reviews, and Cochrane CENTRAL. **Results.** The analysis focused on acute rejection, graft survival, acute kidney injury, and cancer risk as health outcomes. Of 2901 articles screened, 10 met the inclusion criteria. The results indicate a 19% reduction in the risk of acute rejection in patients with lower IPV (RR = 0.81; 95% confidence interval, 0.66-0.99), although 6 studies found no significant association between high IPV and acute rejection. Contrasting results were observed for graft survival, with 1 study indicating worse outcomes for high IPV, whereas another reported no significant difference. High IPV was consistently associated with acute kidney injury across 3 studies. One study suggested a link between high IPV and hepatocellular carcinoma, although a meta-analysis for these outcomes was not feasible. **Conclusions.** These findings point to a marginal but statistically significant association between high IPV and an increased risk of acute rejection, highlighting the importance of precise management of immunosuppressive drugs in liver transplant recipients to enhance patient outcomes.

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The disparity between the demand for organ transplants and their availability is a critical issue, with more than 100,000 people on the transplant waiting list, according to the United Network for Organ Sharing, including more than 10,000 awaiting liver transplantation.[1] This gap, a global challenge, is only expected to widen with increases in health risk factors and an aging population, highlighting the necessity of maximizing transplant efficacy.[1,2]

Genetic differences between donor and recipient in transplantation can trigger an immune response, risking graft rejection and loss.[3] Therefore, immunosuppressive therapy is essential to transplant management.[4] The appropriate titration of immunosuppression is vital, as either insufficient or excessive immunosuppression can lead alternately to graft rejection or increased risk of toxicity and infection.[5]

Dosing of the immunosuppressive drugs used for solid organ transplantation is complex because of the variability of their pharmacokinetics.[2] Many of these drugs, such as calcineurin inhibitors (tacrolimus and cyclosporine) and sirolimus, have narrow therapeutic windows, resulting in the need

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The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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for routine drug monitoring.[6,7] Although many studies have evaluated interpatient variability in the pharmacokinetics of these drugs, very few have focused on intrapatient variability.[8] Intrapatient variability (IPV) is defined as the variation in the concentration of a given drug within a single individual during a set period of time in which the dosage is unchanged. Therapeutic drug monitoring for drugs with high IPV is complicated, as the concentration of the drug is often outside of the therapeutic window, putting the patient at risk of rejection if it is too low and toxicity if it is too high.[8] Therefore, consideration of IPV for patients receiving immunosuppressive therapeutic for transplantation is essential when studying patient outcomes. Studies, primarily in renal transplant contexts, have linked high IPV to worse clinical outcomes, such as increases in acute rejection and graft loss.[8] However, the impact of IPV in liver transplantation remains less clearly defined.

The aim of this study was to conduct a systematic review and meta-analysis to examine the relationship between IPV and clinical outcomes in liver transplant recipients, aiming to clarify the effect of IPV on liver transplant outcomes.

MATERIAL AND METHODS

Design

This study was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines and was registered on PROSPERO (CRD42023437992) with preestablished methods before conducting the review.

Data Source and Search Strategy

A comprehensive search was conducted across MEDLINE/PubMed, Embase, Web of Science, Cochrane Reviews, and Cochrane CENTRAL Register of Controlled Trials using keywords related to liver transplantation, kidney transplantation, immunosuppressive agents, over/under immunosuppressed, and variability. When available, relevant controlled vocabulary was applied, including Medical Subject Headings for PubMed and Emtree Terms for Embase. Publication bias was addressed with the searches in CENTRAL for registered scientific trials and in Embase for conference proceedings. Language was restricted to English as our team was not capable of handling studies published in other languages, and publication date was limited to 1994 to present to reflect the US Food and Drug Administration approval of tacrolimus. No additional manual or hand searching was used or use of unpublished manuscripts. Authors were not contacted for additional information in our study. The literature search was completed on June 7, 2023, and all identified studies were imported into Covidence for screening, with expert librarian (A.P.) assistance for database searches. An update search was conducted on January 17, 2024, to ensure all current articles that meet the criteria are included in the review. The updated search included articles published from June 2023 to January 17, 2024. Full search strategies for each database are available in **Table S1** (**SDC**, http://links.lww.com/TXD/A693).

Study Screening

The screening of titles and abstracts for inclusion involved 2 independent coders (S.L., I.A.P.) using Covidence. Conflicts for this section were resolved by a third reviewer (B.E.). Criteria for exclusion were articles published before 1983, non-English publications, conference abstracts, case reports, literature reviews, systematic reviews, and studies not discussing IPV in relation to immunosuppressive agents. Full-text review was performed by 2 coders (A.C., S.L.) before moving on to data extraction.

Data Extraction

Data extraction was conducted by 2 authors (S.L., A.S.), focusing on studied characteristics, patient demographics, and outcome measurements. Extracted outcomes included biopsy-proven acute rejection, chronic rejection, and allograft loss. Discrepancies in data extraction were resolved through consensus.

Quality Assessment

Two authors (S.L., A.S.) assessed the quality of each study using the Joanna Briggs Institute checklist for cohort studies.[9] This assessment focused on selection bias, validity, reliability of methods, confounding factors, and statistical analysis.[10] Analysis of confounding factors included considerations such as patient demographics, comorbid conditions, and variations in clinical practice. Studies with 3 or more "no" or "unclear" responses in the quality assessment were excluded.

Data Synthesis and Statistical Analysis

Data synthesis and statistical analysis were performed using R Studio (Posit PBC, Boston, MA), version 2023.9.1.494[11] and the "metafor" package.[12] A random-effects meta-analysis was conducted, with studies weighted by the reciprocal of the sampling variance.[13] A pooled meta-analytic logarithmic risk ratio was calculated, and a forest plot was generated. Further analysis included publication bias testing by generating a funnel plot and computing Egger's test of the intercept.[14] Cook's distance and sensitivity analysis were performed to look for outliers. Statistical significance was set at $P < 0.05$.

RESULTS

Study Selection

The literature search yielded 5210 studies, from which 2211 duplicates were removed automatically by Covidence. A total of 2999 studies underwent title and abstract screening; 2639 of these studies were excluded due to irrelevance based on their titles and abstracts. The remaining 360 studies were assessed for inclusion during the full-text review; of these, 51 were chosen for data extraction. Given the variation in organ systems studies, the sample was split into liver and kidney transplant studies, resulting in 10 liver transplant studies pertinent to our objective; the remaining 41 focused on kidney transplants. This distribution is detailed in the PRISMA flowchart (Figure 1).

Characteristics of Included Studies

Among the 10 liver transplant studies included (Table 1), 1 (10%) addressed IPV in pediatric patients, whereas the other 9 (90%) focused on adult patients. Despite the search encompassing all immunosuppression, all selected studies exclusively examined tacrolimus. These studies varied in the way their outcomes were statistically measured. The majority of the studies calculated a coefficient of variation (CV) to

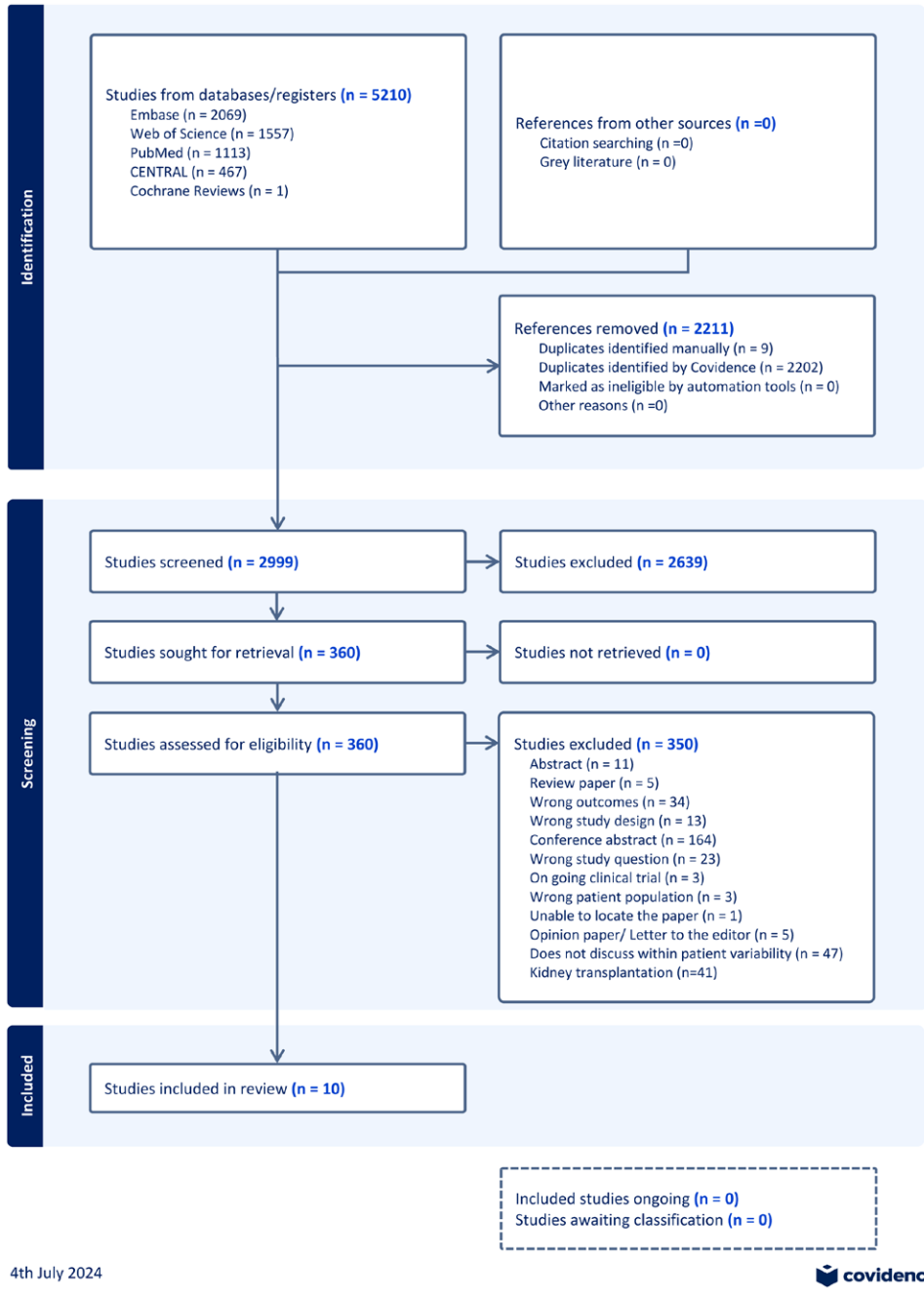

FIGURE 1. PRISMA flowchart. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

determine the cutoff percentage for their study population. In contrast, 2 studies used different methods: 1 used a median value, and another used values above and below 2 standard deviations to determine their cutoff points. The studies originated from a diverse range of countries, with none from the United States. There were 2 studies each from investigators in Brazil, Spain, and France. The other 5 studies came from Belgium, Australia, the Netherlands, the Republic of Korea, and China. All selected studies were cohort in design.

Outcomes Analyzed in Systematic Review

The studies analyzed various outcomes, including acute rejection, acute kidney injury (AKI), genetic polymorphisms, and hepatocellular carcinoma (HCC) recurrence.

Acute Rejection

Eight of the 10 in our review specifically examined the relationship between tacrolimus IPV and acute rejection in liver transplant patients. Two studies did not discuss acute rejection.[18,21] Six of the remaining 8 studies (75%) found no significant correlation between high tacrolimus IPV and an increased risk of acute rejection events. The CV, the measure of relative variability (the ratio of the SD to the mean expressed as a percentage), was calculated for each study.[16] It was common to see a CV percentage of at least 28% and as high as 40% being associated with biopsy-proven rejection. One study found statistically significant evidence of high tacrolimus IPV being associated with acute rejection ($P = 0.04$).[16] An additional study supported these findings. In their study

TABLE 1.

Articles included in the systematic review (n = 10)

Study	Title of study	Total number of participants	Immunosuppressant
de Oliveira et al[3]	Variability index of tacrolimus serum levels in pediatric liver transplant recipients younger than 12 y: Nonadherence or risk of nonadherence?	50	Tacrolimus
Rayar et al[15]	High intrapatient variability of tacrolimus exposure in the early period after liver transplantation is associated with poorer outcomes.	812	Tacrolimus
Del Bello et al[16]	High tacrolimus intrapatient variability is associated with graft rejection and de novo donor-specific antibodies occurrence after liver transplantation.	116	Tacrolimus
Defrancq et al[5]	Intrapatient variability in tacrolimus exposure in pediatric liver transplant recipients: evolution, risk factors, and impact on patient outcomes.	41	Tacrolimus
van der Veer et al[17]	High intrapatient variability in tacrolimus exposure is not associated with immune-mediated graft injury after liver transplantation.	326	Tacrolimus
Di Maira et al[18]	Posttransplant calcineurin inhibitors levels and intrapatient variability are not associated with long-term outcomes after liver transplantation.	432	Tacrolimus
Maciel et al[4]	Liver transplantation: tacrolimus blood levels variation and survival, rejection and death outcomes.	127	Tacrolimus
Dopazo et al[19]	High intrapatient variability of tacrolimus exposure associated with poorer outcomes in liver transplantation.	140	Tacrolimus
Kim et al[20]	Clinical association between tacrolimus intrapatient variability and liver transplantation outcomes in patients with and without hepatocellular carcinoma.	636	Tacrolimus
Song et al[21]	Lower tacrolimus time in therapeutic range is associated with inferior outcomes in adult liver transplant recipients.	207	Tacrolimus

population, higher time in therapeutic range (TTR) was associated with a significantly lower risk of developing acute rejection ($P < 0.001$); that is, the low TTR group (equivalent to the high IPV group) had an increased risk of developing AR.[21]

Acute Kidney Injury

Three studies (30%) explored the impact of tacrolimus IPV on renal function. All 3 found a higher incidence of AKI in the group that had high IPV/low TTR. Song et al[21] found that 20.8% of patients with a low TTR had an increased association with AKI compared with the high TTR group ($P < 0.001$). This finding was supported by the additional 2 studies that reported outcomes on AKI. There was a significantly impaired renal function in the high tacrolimus IPV "dose corrected concentration (C_0/D) CV at the third and sixth month group" (C_0/D CV 3–6 mo) postliver transplantation group at 1 y; this was observed in 12 of 35 patients (34%).[19] Van der Veer et al[17] found that at 6 mo, there was no difference in estimated glomerular filtration rate between low and high tacrolimus IPV groups if renal function was at least 60mL/min; however, if patients had impaired renal function at 6 months (estimated glomerular filtration rate <40 mL/min), a higher tacrolimus IPV was associated with greater loss of renal function.

Allograft Survival

Two studies evaluated graft survival.[15,18] Rayar et al analyzed the correlation between tacrolimus CV (high or low) and 3-mo and 1-y graft survival rates. The difference in 3-month graft survival was not statistically significant (94.9% in the high CV group versus 97.4% in the low CV group; $P = 0.108$). The study did find worse graft survival rates in the high CV group for 1-y graft survival with 88% in the high CV group versus 92.7% in the low CV group ($P = 0.043$).[15] Di Maira et al[18] conducted a Cox regression analysis and found no significant difference between high versus low CV groups with a hazard ratio of 1.022 (95% confidence interval [CI], 0.628-1.662).

Cancer Risk

Even though HCC is a common indication for liver transplantation, the effects of high tacrolimus IPV on HCC recurrence have not been studied extensively. One study, however, found that high tacrolimus IPV was significantly associated with an increased risk of HCC recurrence. The recurrence-free survival rates at 1, 2, and 5 y were worse in the high tacrolimus IPV group compared with the low IPV group (84.7%, 76.9%, and 74.5% versus 93.8%, 90.1%, and 86.6%, respectively; $P = 0.001$).[20]

Meta-analysis

Acute Rejection and Tacrolimus IPV

Six studies were included in the meta-analysis (Figure 2), excluding 2 studies originally discussed in the systematic review. These studies—Del Bello et al[16] and Defrancq et al[5]—were omitted from the analysis due to the heterogeneity of their data compared with the 6 included studies. The 2 omitted studies indicated no association between high IPV and acute rejection.

The summative log risk ratio was –0.21 (95% CI, –0.42 to 0.00) with an associated P value of 0.04, corresponding to a pooled risk ratio of 0.81 (95% CI, 0.66-0.99), indicating a 19% lower risk of acute rejection. This suggests a marginally reduced likelihood of acute rejection in patients with lower IPV compared with those with higher IPV. The studies exhibited negligible heterogeneity, indicated by $I^2 = 0.00\%$, $\tau^2 = 0$, and $Q = 3.0$ ($P = 0.70$).

Publication Bias and Outliers Test

The evaluation for publication bias involved analyzing the funnel plot (Figure 3), which indicated little to no asymmetry among the 6 studies, suggesting an absence of publication bias.[22] Further assessment using Egger's test corroborated this, revealing no significant publication bias ($P = 0.40$).[14] Additionally, Cook's distance test was applied to identify

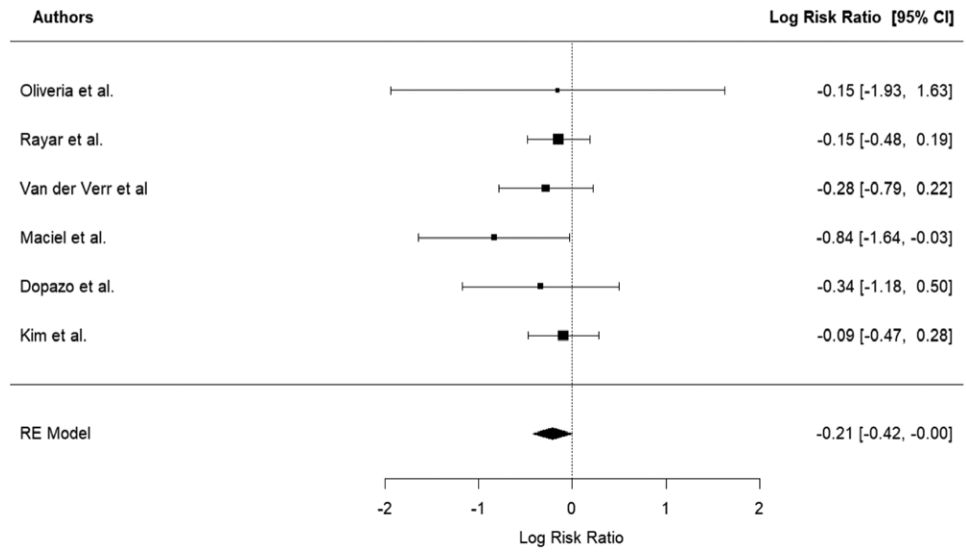

FIGURE 2. Meta-analysis Forest plot: study characteristics (n = 6). RE, regression model.

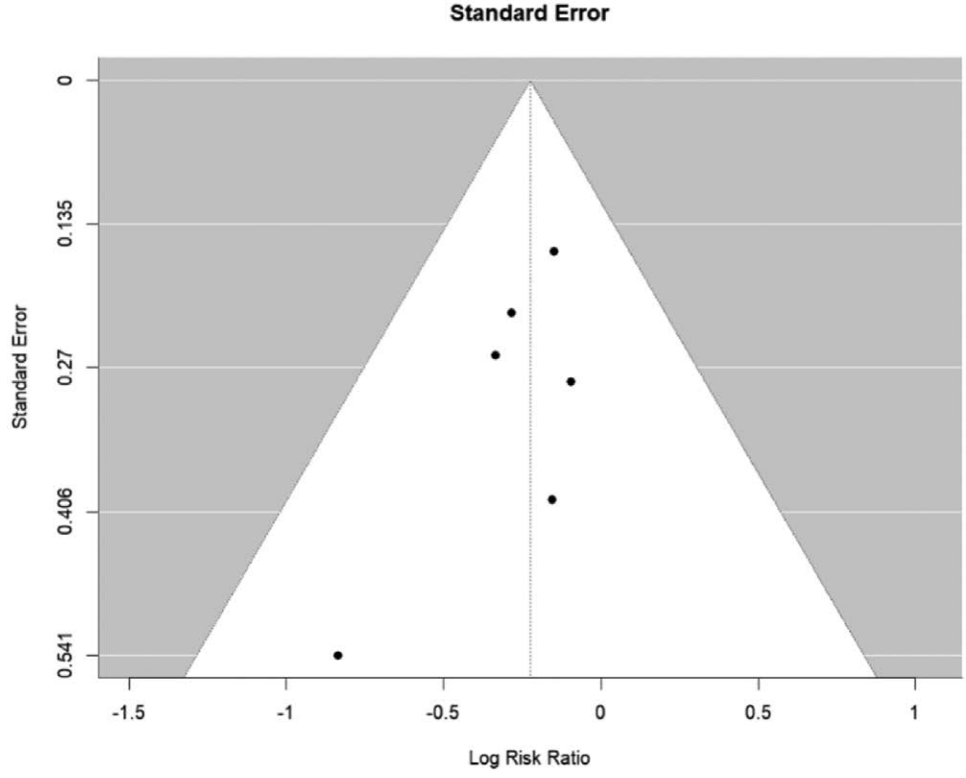

FIGURE 3. SE Funnel plot for publication bias.

potential outliers that may skew the data. This test revealed no significant outliers, with Cook's d values ranging from –0.22 to 0.049, indicating that no single study had a disproportionate effect on the meta-analysis outcomes. This conclusion was reinforced by a sensitivity analysis, which showed that the exclusion of any 1 study did not significantly alter the resulting summary effect size.

Quality Assessment

The Joanna Briggs Institute checklist for cohort studies was used to assess bias within the 10 selected studies. All studies met the inclusion criteria, with none exceeding the threshold of 3 or more "no or unclear" responses to checklist questions. However, because of the nature of the studies all being retrospective cohorts, some checklist items are inapplicable, as detailed in Table 2.

DISCUSSION

This work demonstrates a potential link between high tacrolimus IPV in liver transplant recipients and an elevated risk of acute rejection. This systematic review reveals an emerging

TABLE 2.

Quality assessment using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies

Study	de Oliveira et al[3]	Rayar et al[15]	DelBello et al[16]	Defrancq et al[5]	van der Veer et al[17]	Di Maira et al[18]	Maciel et al[4]	Dopazo et al[19]	Kim et al[20]	Song et al[21]
1. Were the two groups similar and recruited from the same population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were confounding factors identified?	N	N	Y	Y	Y	Y	Y	Y	Y	Y
5. Were strategies to deal with confounding factors stated?	N	N	Y	Y	Y	Y	Y	Y	Y	Y
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7. Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9. Was follow-up complete, and if not, were the reasons for loss of follow-up described and explored?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
10. Were strategies to address incomplete follow-up used?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
11. Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall appraisal	Include	Include	Include	Include	Include	Include	Include	Include	Include	Include

N, no; NA, not applicable; Y, yes.

body of literature on this correlation, presenting mixed evidence. Our systematic review and meta-analysis contribute to this emerging field, highlighting the need for further investigation to solidify the observed trends and their clinical implications.

The challenge of managing immunosuppression, particularly in the context of calcineurin inhibitors like tacrolimus, is well-recognized.[23] Optimal management of these drugs is critical to reducing adverse outcomes, including acute rejection, and prolonging allograft survival, thereby enhancing allograft longevity and patient quality of life.[24] Understanding the current evidence is crucial to advancing immunosuppression management.

Our meta-analysis provides evidence that high tacrolimus IPV in liver transplant recipients is associated with an increased risk of acute rejection. The pooled risk ratio from the meta-analysis indicates a 19% lower rejection risk in the low-IPV group. Our analysis, with a small sample size of 6 studies, found a pooled log risk ratio of –0.21 with an unrounded 95% CI of –0.4196 to –0.0044. Although this CI does not technically exist, it is very close to the threshold of nonsignificance. In addition, the unrounded P value of 0.045 meets the pre-designated significance threshold of $P < 0.05$. Given that the results are on the cusp of statistical significance, more research in the area is warranted to determine if the findings will be borne out by additional studies.

More research has focused on studying the effects of IPV on rejection than on AKI, allograft survival, and cancer risk. With regard to the observed effect on renal function, high IPV in tacrolimus levels can be the result of both overdosing and underdosing, whether because of patient physiology or the dosing strategy. This variability may prompt clinicians to compensate for unpredictable drug levels by administering higher-than-needed doses of tacrolimus, either inadvertently or intentionally. Overdosing tacrolimus can lead to nephrotoxicity, which negatively impacts renal function. As a result, high IPV can contribute to renal function deterioration because of the increased likelihood of excessive tacrolimus exposure in these patients.

Two studies evaluated allograft survival, showing mixed results; 1 found no significant difference in short-term survival but worse 1-year survival rates in the high IPV group, while another found no significant difference between high and low IPV groups. Additionally, 1 study linked high tacrolimus IPV with an increased risk of HCC recurrence, with significantly worse recurrence-free survival rates in the high IPV group.

Future studies should explore these areas to build a more comprehensive knowledge base. Another factor affecting IPV, which is not adequately addressed by these studies, is medication adherence. Variability in tacrolimus levels in the immediate posttransplant setting was a predictor of nonadherence and is significantly associated with graft failure.[25] The creation of the Medication Level Variability Index is another tool to screen patient who may have adherence issues and to assess their risk for poor outcomes.[26,27] Additional research in this area can help medical professionals address nonmedical factors that contribute to poor outcomes such as rejection.

This study had several limitations. First, from over 5 thousand initially identified studies, only 10 liver transplant studies met the criteria for inclusion in the review, with 6 suitable for meta-analysis. Data on outcomes beyond rejection are limited even further. The 4 articles that were not used in the meta-analysis were excluded due to data inconsistencies, such as not reporting acute rejection or lacking uniformity with the data in the included studies. It should be noted, however, that 2 of the excluded studies[5,16] both concluded that high IPV is associated with acute rejection. This highlights the predominance of research on kidney transplantation and IPV. As such, the sample size was limited due to the small number

of articles included, and therefore, the systematic review yielded mixed results on AKI. In addition, the use of induction therapy or other concomitant immunosuppressants was also not consistently reported. Although non-CNI medication adjustments are protocolized and made gradually, and these medications have minimal drug-drug interactions affecting tacrolimus IPV, it is possible that there exist some systematic differences between the high and low IPV groups. Last, the limited number of studies in the meta-analysis restricts the reliability of the heterogeneity assessment. The methodology of each research team, although similar, varied with regard to the values and cutoffs used for IPV, and the studies did not all examine the same outcomes, which affects the heterogeneity of the study. Inherent variability in study outcomes is a common challenge in systematic reviews, particularly when no established standard exists for the specific research area. Despite these differences, the analysis synthesizes available data to provide comprehensive insights into the impact of tacrolimus IPV.

The systematic review revealed inconsistent evidence for the effect of tacrolimus IPV on acute rejection and AKI. There was not enough literature available to provide a clear statement on cancer risk and allograft survival rates. However, the meta-analysis suggests an association between high tacrolimus IPV and an increased risk of acute rejection. Despite the limited sample size of the literature on tacrolimus IPV in liver transplantation, these findings support the importance of close monitoring of this immunosuppressant. The potential impact of tacrolimus IPV on allograft survival is clinically significant because this will help providers make informed decisions about treatment strategies. Early identification of subjects at risk for or affected by high IPV, as well as implementing clinical protocols such as using computational methodologies to improve tacrolimus dosing,[28] may be able to mitigate negative outcomes. Understanding the side effects and potential outcomes of these agents is crucial in optimizing patient care. This study contributes to the ongoing discourse on optimal immunosuppression management. We anticipate that these insights will stimulate further research in the field, enhancing the evidence and ultimately improving patient outcomes in liver transplantation.

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