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SYSTEMATIC REVIEW

Once-Daily versus Twice-Daily Tacrolimus in Kidney Transplantation: A Systematic Review and Meta-analysis of Observational Studies

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Abstract

Background Tacrolimus is the most commonly prescribed medication in initial immunosuppressive regimens to prevent acute rejection in kidney transplant recipients (KTRs). Tacrolimus was originally available as an immediate-release formulation (IR-Tac) given twice daily. Extended-release tacrolimus (ER-Tac) given once daily was later developed with the expectation of improved medication adherence. Data from observational studies, which compared outcomes between ER-Tac and IR-Tac in different populations of KTRs including those who are unlikely to be enrolled in randomized clinical trials, have been reported.

Purpose To evaluate the incidence of biopsy-proven acute rejection (BPAR) at 12 months together with other outcomes reported in observational studies among adult KTRs who received ER-Tac compared to IR-Tac.

Methods In accordance with the recommendations of the Cochrane Collaboration and the Meta-analysis of Observational Studies in Epidemiology, we systematically reviewed all observational studies that compared clinical outcomes between ER-Tac and IR-Tac in KTRs. The systematic searches were conducted on PubMed, EMBASE, Scopus, and Web of Science without language restriction. Reference lists were also searched and reviewed. Data were extracted for BPAR, graft survival, patient survival, estimated glomerular filtration rate (eGFR), serum creatinine (Scr), creatinine clearance (CrCl), at different times after kidney transplantation (KT). A meta-analysis was performed to integrate the results from the eligible studies. This study is registered with PROSPERO, number CRD42019135705.

Results From the 1401 articles screened, 10 observational studies in KTRs who received tacrolimus were included. The pooled results showed significantly lower BPAR with ER-Tac than with IR-Tac at 12 months post-KT (5 studies, $n=659$; RR, 0.69; 95% CI 0.51–0.95; $p=0.02$; $I^2=0\%$). No significant differences in BPAR at other time points after KT were found. Graft survival, patient survival, Scr, and eGFR were comparable between groups at different times over approximately 1 year after transplantation.

Conclusions Based upon currently available evidence in observational studies, 30% lower risk of BPAR was observed in ER-Tac group compared with IR-Tac group at 12 months post-KT, while there was no significant difference in BPAR risk at any other studied time points. No differences in graft- and patient-survival rates and kidney function were found. Given the limitations of observational studies to make causal inference, as well as quality limitations among the included studies, caution should be exercised in interpreting these findings.

1 Introduction

Tacrolimus, a calcineurin inhibitor (CNI) with potent immunosuppressive activity in inhibiting T-lymphocyte activation and proliferation, as well as T-helper-cell-dependent B cell response, has been widely used as a preferred CNI for prophylaxis of acute rejection after kidney transplantation (KT) [1]. Tacrolimus is available in innovator and non-innovator immediate-release, twice-daily formulations (IR-Tac), and two different extended-release, once-daily formulations (ER-Tac) produced using different technologies: MR-4 formulation [2, 3], and Meltdose formulation [4].

Different pharmacokinetic properties and dosage requirements to achieve similar blood concentrations have been observed among these tacrolimus formulations. In comparison with IR-Tac, a higher dosage of MR-4 ER-Tac is often required to maintain a similar tacrolimus trough concentration [5–7], whereas a lower dosage requirement of

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Key Points

Similar clinical outcomes of extended-release tacrolimus and immediate-release tacrolimus were found from the pooled results of well-designed randomized controlled studies, in which most of the included kidney transplant recipients were at low immunologic risk, while little is known about clinical outcomes of extended-release tacrolimus in comparison with immediate-release tacrolimus among high immunologic risk recipients.

One-third lower risk of rejection at 1-year post-kidney transplant was observed among recipients who received extended-release tacrolimus compared to immediate-release tacrolimus when data were pooled from available observational studies in which wide spectrum of kidney recipients actually using tacrolimus therapy in routine clinical care were included.

The quality of currently available observational reports is considered sub-optimal; well-designed studies with longer time follow-up would be useful for optimizing tacrolimus therapy in kidney transplant recipients.

the Meltdose ER-Tac formulation has been demonstrated [8]. ER-Tac has been reported to provide less intra-patient variability of exposure [9] and increase convenience and self-reported adherence among kidney transplant recipients (KTRs) when compared to IR-Tac [10]. These advantageous properties of ER-Tac have garnered much interest since it was found that high intra-patient variability in tacrolimus exposure and nonadherence to tacrolimus treatment have been associated with poor long-term transplant outcomes [11–13]. However, a decrease in tacrolimus systemic exposure was observed following the conversion from IR-Tac to MR-4 ER-Tac (1:1 mg) in stable KTRs and a delay in reaching the target therapeutic range has been reported in de novo KTRs [14]. Underexposure to tacrolimus during the very early period post-transplantation, when the highest risk of allograft rejection is generally expected, is a clinical concern.

Based upon the evidence from randomized controlled trials (RCTs) comparing the efficacy and toxicity across different formulations in de novo KTRs, the impact on kidney allograft function appears to be comparable between ER-Tac and IR-Tac [15]. Of note, most of the studied KTRs were at low immunologic risk, possibly for ethical reasons. High-risk KTRs such as re-transplant KTRs, ABO blood group incompatible (ABOi) kidney recipients, and pre-sensitized recipients were not included in most of the RCTs, in which inclusion and exclusion criteria are generally more stringent than patient characteristics normally seen in clinical practice. Observational studies may provide information on patients who are not likely to be enrolled in RCTs. Meta-analysis techniques, originally designed to combine data from RCTs, have been used to summarize evidence on an association from multiple observational studies in some KTR populations such as obesity KTRs and ABOi recipients [16–18].

Given that various induction therapies, potent maintenance immunosuppressive regimens with different steroid dosing strategies, and desensitization protocols together with newer, more subtle immunology tests are currently available, immunosuppressive regimens can be tailored to specific needs according to the immunological risk status of individual KTRs. In many transplant institutions, early immunosuppression options and long-term regimens are selected based upon a pre-transplant risk assessment and the post-transplant clinical course of each recipient.

Data from published observational studies comparing the effects of different formulations of tacrolimus may provide further insights into treatment patterns and outcomes for a more heterogenous patient population than those participating in RCTs. Inclusion of high risk KTRs, who are usually excluded from RCTs that are designed to evaluate the effects of tacrolimus formulations, may better reflect the wide spectrum of patients actually using the treatment in routine clinical care. In addition to filling the critical knowledge gaps, the results of appropriately designed observational studies should also be used for augmenting the information from RCTs and to evaluate the generalizability of the RCT findings.

The objective of this systematic review and meta-analysis is to evaluate the incidence of biopsy-proven acute rejection (BPAR) at 12 months post-KT, together with other outcomes of de novo KTRs who received ER-Tac compared to those who received IR-Tac after transplantation based on currently available evidence from reported observational studies.

2 Methods

2.1 Data Sources and Search Strategy

This systematic review and meta-analysis was conducted according to the recommendations of the Cochrane Collaboration and the Meta-analysis of Observational Studies in Epidemiology study [19, 20]. The study protocol is available in the International Prospective Register of Systematic Review (PROSPERO): CRD42019135705. To identify potentially eligible studies, the electronic databases PubMed, EMBASE, Scopus, and Web of Science were systematically searched from inception to 15 May 2019. No language restrictions were applied. The following search terms were used: [kidney transplant* or renal transplant*] AND [extended-release tacrolimus or prolonged-release

tacrolimus or once-daily tacrolimus or FK506E] AND [immediate-release tacrolimus or twice-daily tacrolimus or tacrolimus or FK506]. A historical search of relevant articles was undertaken, reference lists of reports were reviewed for potential additional studies, and personal contact with correspondents of the articles was made, if necessary.

2.2 Eligibility Criteria

The studies searched were included in this study if they: (a) were observational studies in de novo KTRs, including recipients undergoing re-transplantation, that reported clinical outcomes after ER-Tac and included an IR-Tac control group, and (b) reported one or more of the following measures: BPAR, graft survival and patient survival, estimated glomerular filtration (eGFR), creatinine clearance (CrCl), and serum creatinine (Scr). Studies conducted with pediatric populations and those reported in abstract only, editorials, conference proceedings, and letters were excluded.

2.3 Study Selection

All identified studies in our literature search were screened for eligibility by two reviewers (WS, AP) independently. If either reviewer identified a citation as potentially relevant, the full text of the article was also obtained. The reviewers independently assessed the full texts of the selected studies to determine the appropriateness for inclusion. Any disagreement was resolved by consensus between the reviewers or adjudication with a third party (SV), if necessary. The reasons for exclusion were recorded at the full-text screening stage.

2.4 Outcome Measures

The primary outcome was the identification of studies reporting BPAR at 12 months after transplantation. The secondary outcomes comprised studies reporting BPAR within 6 months and after 12 months post-KT; graft survival and patient survival within 6 months, at 12 months and after 12 months post-KT; eGFR at 6, 12 and after 12 months after transplantation, calculated from serum creatinine with the use of MDRD equation [21] or another method if eGFR estimated by the MDRD equation was not available; CrCl calculated by the Cockcroft-Gault equation [22] or measured by a 24-h urine collection at 6 and 12 months and after 12 months post-KT; and Scr reported in mg/dL (Scr values reported in μmol/L were converted to mg/dL before pooling the results). Data reported in a graphic format were used only when the numerical data of the outcome of interest were not reported in the included studies.

2.5 Data Extraction

Using a standardized extraction form, two investigators (WS, AP) independently extracted the following data from each included study: demographic and clinical information, study design, eligibility criteria, and treatment outcomes. When duplicate reports of the same study or population were identified, the latest complete publication was selected. Any disagreement was resolved through discussion, or with consultation of a third party (SV or WC). When studies presented different estimates of the outcome of interest, the most precise or adjusted measures were extracted.

2.6 Assessment of Risk of Bias

The quality of each study was independently assessed by two investigators (WS, AP) using the ROBINS-I tool, assessing the following 7 domains: confounding, selection of participants, classification of intervention, deviations from intervention, missing data, measurement of outcome, and selection of reported results [23]. These domains were qualitatively classified as being at critical, serious, moderate or low risk of bias. A "no information" category was used only when insufficient data were reported to permit an assessment. The overall risk of bias of each study was considered as low if the risk of bias was low in all domains, as moderate if the risk of bias was low or moderate for all domains, as serious if the risk of bias was serious in at least one domain, as critical if the risk of bias was critical in at least one domain, or as no information when there was no clear indication as to whether the study was at serious or critical risk of bias and/or there was a lack of information in one or more domains. Disagreement was resolved by discussion and consensus or by the decision of a third party (SV).

2.7 Statistical Analysis

Statistical heterogeneity between studies was determined using Cochrane's Q test. The Q statistic at a level of 0.1 was considered as significant. The degree of heterogeneity was quantified using I^2 statistic. The I^2 index is the percentage of total variation across studies due to heterogeneity, which can be quantified as low ($<25\%$), moderate (25–75%), and high ($>75\%$) [24].

The treatment effects from multiple studies that reported the same outcomes were pooled to integrate the findings and provide combined estimates. For continuous data, the mean difference (MD) was calculated to estimate the amount by which ER-Tac changes the outcome on average compared with IR-Tac. The pooled estimates of discrete data were expressed as relative risk (RR) to compare the probability of an outcome occurring in KTRs who received ER-Tac as compared to those who received IR-Tac. The results were

depicted by forest plots with a 95% CI. The inverse variance-weighted method was used for the pooling of MD and RR. A random effects model was used to estimate the effect size for each outcome measure.

To evaluate publication bias, a funnel plot was constructed by plotting the RR of the primary outcome against the standard error (SE) of the logarithm of RR. Egger's test was used for detecting asymmetry in a funnel plot [25]. Sensitivity analysis was performed to assess whether the difference of ER-Tac starting techniques between early conversion to ER-Tac from IR-Tac within 10 days post-KT and de novo ER-Tac initiation affected BPAR incidence at 12 months after KT.

All analyses were performed using the Review Manager (RevMan) program, version 5.3 Copenhagen (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Unless otherwise stated, a p value of < 0.05 was considered statistically significant.

3 Results

3.1 Literature Search Results

The initial electronic database search captured 1401 potential articles. After the exclusion of 568 duplicates, 833 titles and abstracts were screened. Then, 801 reports were further excluded, leaving 32 studies for eligibility evaluation. The majority of exclusions were made due to the articles being abstract-only publication, as described in Fig. 1. A total of 10 observational studies, with a total number of 1176 adult de novo KTRs, were included in this meta-analysis [26–35].

3.2 Study Characteristics

The characteristics of the included studies are summarized in Table 1. Mean age of studied populations, type of kidney transplantation and other characteristics of KTRs in each of these studies are presented in Table 2. All 10 studies reported the clinical outcomes of the MR-4 formulation of ER-Tac in comparison with IR-Tac in de novo KTRs. Almost all of the included KTRs received tacrolimus in combination with either mycophenolate mofetil (MMF) or mycophenolate sodium (MPS) and corticosteroids (CS) together with or without the use of anti-T lymphocyte globulin, alemtuzumab, or basiliximab for induction therapy. The use of intravenous immunoglobulins, rituximab with plasmapheresis or splenectomy were also reported in some studies [29–31, 33, 35], as provided in Table 3. The reported outcomes of interest are shown in Table 4.

3.3 Risk of Bias

Of the 10 included observational studies in the review, only one [29] was considered of moderate quality when assessed using the ROBINS-I quality assessment tool. The other nine studies had serious overall risk of bias. Three studies were assessed as having serious risk of bias in both domains of confounding and of selection of participants into the studies. Six studies had a serious risk of bias due to either confounding or selection of participants for the studies, as presented in Fig. 2. The level of available evidence is currently sub-optimal.

3.4 Biopsy-proven Acute Rejection Incidence at 12 Months after Kidney Transplantation

There were 5 included studies that reported BPAR incidences in KTRs who received ER-Tac and IR-Tac at 12 months post-KT [29–31, 33, 35]. Based on the pooled results of these studies, the BPAR incidence was 15.7% in the ER-Tac group and 23.7% in the IR-Tac group. The calculated absolute risk difference was 8%. A significant difference in BPAR was found between ER-Tac and IR-Tac at 12 months post-KT with the pooled RR of 0.69 (5 studies, $n = 659$; 95% CI 0.51–0.95; $p = 0.02$). A RR reduction of 31% was estimated. The results among these studies were homogenous (Q statistic, $p = 0.61$; $I^2 = 0\%$), as presented in Fig. 3. The Egger's test detected no evidence of publication bias (bias, − 0.62; 95% CI − 3.74 to 2.48; $p = 0.478$; 4 studies, excluding 1 study with a zero rate in total). When the study in which KTRs received treatment conversion to ER-Tac from IR-Tac within 10 days post-KT [35] was excluded in the sensitivity analysis, no substantive change to the difference was observed (4 studies, $n = 585$; RR, 0.70; 95% CI 0.51–0.95; $p = 0.02$; $I^2 = 0\%$).

3.5 Biopsy-proven Acute Rejection Incidence at Other Time Points after Kidney Transplantation

Two included studies reported comparable BPAR within the first 6 months post-KT [30, 31]. One reported BPAR at 3 weeks [30], and the other at 3 months [31]. No significant difference in BPAR was observed among those who received the ER-Tac formulation in comparison with the IR-Tac within 6 months post-KT (2 studies, $n = 164$; RR, 1.25; 95% CI 0.33–4.80; $p = 0.75$; $I^2 = 0\%$), as presented in Fig. 3. There was only one study which reported BPAR at 24 months post-KT [34]. With a 16.6% (28 of 168 patients) conversion from IR-Tac to ER-Tac and 7.3% (6 of 82 patients) conversion from ER-Tac to IR-Tac, BPAR incidences of 10.6% (11 of 104 patients) and 11.6% (17 of 146

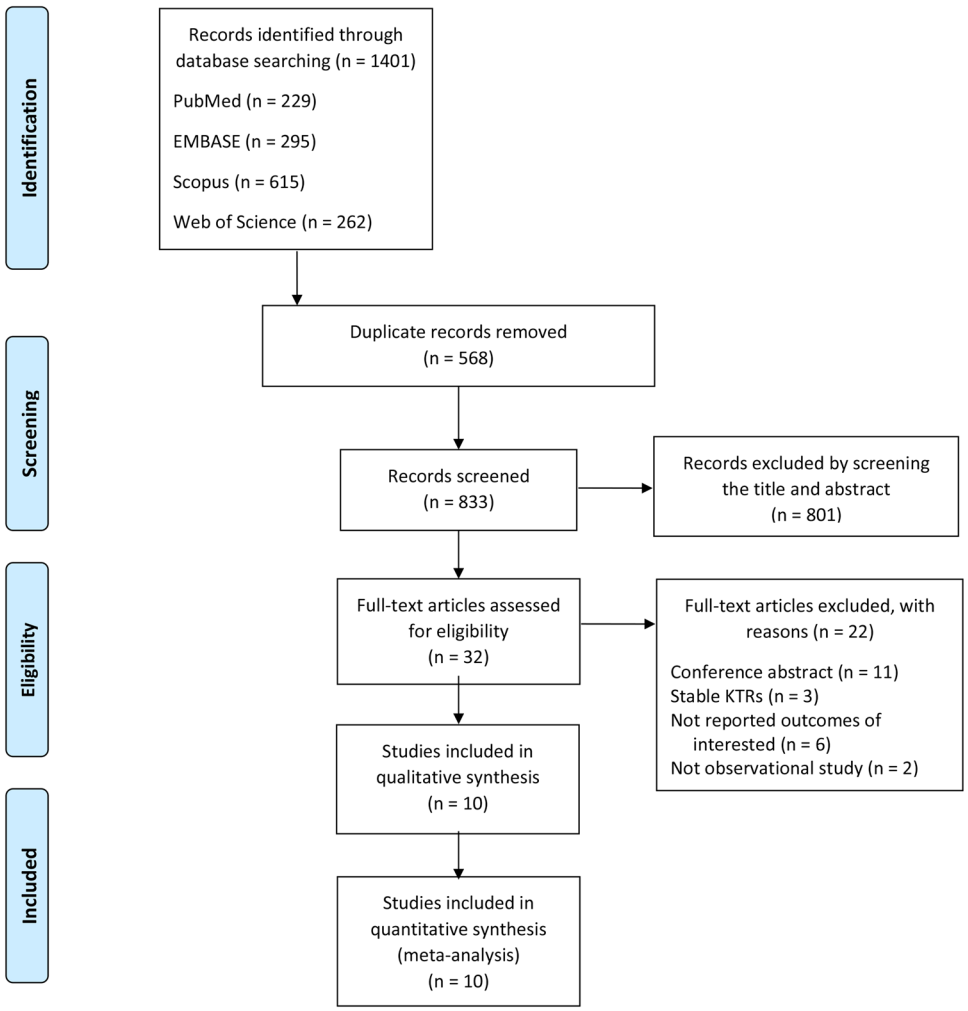

Fig. 1 Study selection process

patients) were observed in those who received ER-Tac and IR-Tac at 24-month follow-up, respectively ($p = 0.84$) [34].

3.6 Graft Survival

Three included studies reported graft survival rates within the first 6 months post-KT [26–28]. Two studies reported graft survival at different follow-up times during the first 6 months post-KT [27, 28] and the other reported no graft loss at 6 months [26]. The reported graft survival rate within 6 months post-KT among KTRs who received ER-Tac was not significantly different from those who received IR-Tac (3 studies, $n = 161$; RR, 1.01; 95% CI 0.96–1.07; $p = 0.68$; $I^2 = 0\%$), as shown in Fig. 4. Graft survival rates at 12 months were reported in 4 included studies with an overall 1-year graft survival rate of 97.4% [29, 30, 32, 35]. The 1-year graft survival rate of KTRs who received ER-Tac was comparable to those who received IR-Tac (4 studies, $n = 426$; RR, 1.01; 95% CI 0.98–1.04; $p = 0.50$; $I^2 = 0\%$), as shown in Fig. 4. The graft survival rate after 12 months post-KT was reported in the only one small study in which a 100% graft survival rate was observed in both ER-Tac and IR-Tac groups at 15.7 months after transplantation [30].

3.7 Patient Survival

Two included studies reported patient survival rates within the first 6 months post-KT between KTRs who received ER-Tac and IR-Tac [27, 35]. The reported patient survival rate within the first 6 months post-KT of KTRs who received ER-Tac was comparable with those who received IR-Tac (2 studies, $n = 153$; RR, 0.99; 95% CI 0.94–1.04; $p = 0.75$; $I^2 = 0\%$), as shown in Fig. 4. Of the 4 included studies that reported the patient survival rate at 12 months [29, 30, 32, 35], the overall patient survival rate at 12 months post-KT was 98.6% and the pooled RR was 1.00 (4 studies, $n = 426$; 95% CI 0.97–1.03; $p = 0.94$; $I^2 = 0\%$), as shown in Fig. 4. A patient survival rate of 100% was also reported at 15.7 months after transplantation in one study [30].

Table 1 Characteristics of the included observational studies

Study ID	Country	Number of participants			Study design	Observational period		Follow-up duration
		Total	ER-Tac	IR-Tac		ER-Tac	IR-Tac	
Crespo et al. (2009) [26]	Spain	52	26	26	Retro	N/A	Immediately before ER-Tac group	6 months
Andrés et al. (2010) [27]	Spain	79	49	30	Retro	N/A	N/A	ER-Tac, 3.5 ± 25 months IR-Tac, 4 ± 2.6 months
Jelassi et al. (2011) [28]	France	30	12	18	Retro	June 2007–March 2010[a]		ER-Tac, 45 ± 60 days IR-Tac, 37 ± 26 days
Fanous et al. (2013) [29]	Canada	201	106	95	Retro	July 2009–July 2010	July 2008–July 2009	12 months
Ishida et al. (2013) [30]	Japan	45	10	35	Retro	After February 2009	Before February 2009	Mean 15.7 months (range 12.9–18.5 months)
Masutani et al. (2014) [31]	Japan	119	90	29	Retro	August 2008–April 2011[a]		12 months
Fan et al. (2017) [32]	China	106	45	61	Retro	May 2013–June 2014[a]		12 months
Niioka et al. (2017) [33]	Japan	220	80	140	Retro	June 2001–August 2014[a]		12 months
Hage et al. (2019) [34]	France	250	82	168	Retro	January 2009–December 2013[a]		24 months
Ho et al. (2019) [35]	USA	74	19	55	Retro	January 2012–June 2016[a]		12 months

ER-Tac extended-release tacrolimus, *IR-Tac* immediate-release tacrolimus, *N/A* no available information, *Retro* retrospective study

[a]Information was reported only for the overall population

3.8 Serum Creatinine

Five studies reported Scr within 6 months post-KT [26–28, 31, 33]. One study reported comparable Scr in ER-Tac and IR-Tac groups of 1.25 (IQR 0.96–1.51) and 1.22 (IQR, 1.00–1.57) at 1-month post-KT [33]. Another study reported comparable Scr evolution at 6 months post-KT [28]. Based on the pooled results of the other studies, which reported mean and SD of Scr [26, 27, 31], there was no significant difference in Scr between ER-Tac and IR-Tac during the 6 months post-KT (3 studies, $n = 246$; MD, − 0.05 mg/dL; 95% CI − 0.25 to 0.15; $p = 0.62$; $I^2 = 58\%$), as shown in Fig. 5. Of 2 studies which reported Scr at 12 months post-KT [31, 33], one reported similar Scr during the follow-up period ($p = 0.1$) [31] and the other reported comparable median Scr at 12 months post-KT of 1.27 (IQR 0.86–1.53) and 1.14 (IQR 0.85–1.33) in those who received ER-Tac and IR-Tac, respectively [33].

3.9 Estimated Glomerular Filtration Rate

Comparable means of GFR between the ER-Tac and IR-Tac groups at Day 3 and at Months 3, 6, 12, and 24 were reported in one included study in which eGFR of KTRs in the ER-Tac group was 57.97 ± 21.74 mL/min and those in the IR-Tac group was 58.26 ± 21.01 mL/min at 24 months post-KT [34]. No significant difference of eGFR between KTRs who received ER-Tac and those who received IR-Tac within 6 months post-KT was graphically reported [29]. Two included studies reported means of eGFR at 12 months post-KT [29, 32]. One study reported eGFR of 58.8 ± 17 mL/min/1.73 m^2 in KTRs who received ER-Tac versus 59.2 ± 18 mL/min/1.73 m^2 in those who received IR-Tac at 12 months post-KT ($p = 0.307$) [29]; whereas the other reported eGFR of 68.4 ± 12.8 mL/min/1.73 m^2 in KTRs who received ER-Tac and 70.8 ± 12.4 mL/min/1.73 m^2 in those who received IR-Tac at 12 months post-KT [32]. Based on the pooled results of these studies, there was no significant difference in eGFR between ER-Tac and IR-Tac at 12 months post-KT (2 studies, $n = 307$; MD, − 1.37 mL/min/1.73 m^2 [95% CI − 4.80 to 2.07]; $p = 0.44$; $I^2 = 0\%$), as presented in Fig. 5.

None of the included studies reported creatinine clearance.

4 Discussion

This is a systematic review and meta-analysis of the current available evidence from observational studies comparing ER-Tac and IR-Tac based on BPAR in de novo KTRs at

Table 2 Characteristics of kidney transplant recipients among the included studies

Study ID	Type of kidney transplantation[a]			Recipient age (years)[b]		Recipient gender (male %)		Others
		ER-Tac	IR-Tac	ER-Tac	IR-Tac	ER-Tac	IR-Tac	
Crespo et al. (2009) [26]	Living donor	0%	8%	48.7 ± 16.7	49.1 ± 13.1	69	69	Peak PRA: ER-Tac, 0.7 ± 3.5%; IR-Tac, 3.5 ± 9.1%
	Deceased donor	100%	92%					
	Re-transplant	19%	19%					Caucasians 88%
	Non-heart-beating donor	4%	12%					Exclude: KTRs who received ATG or had not reached 3 months post-KT[c]
Andrés et al. (2010) [27]	N/A	N/A	N/A	54.0 ± 18.0	49.0 ± 12.0	N/A	N/A	
Jelassi et al. (2011) [28]	N/A	N/A	N/A	51.0 ± 12.0	54.0 ± 10.0	67	72	
Fanous et al. (2013) [29]	Living donor	33%	37%	53.4 ± 14.0	52.6 ± 13.2	60	55	Peak PRA: ER-Tac, 21.7 ± 32.2%; IR-Tac, 27.9 ± 35.1%
	Deceased donor	67%	63%					
	Re-transplant	8%	7%					Caucasians/Black/Asian/other: ER-Tac, 55/11/28/5%; IR-Tac, 54/5/36/5%
Ishida et al. (2013) [30]	Living donor	100%	100%	Mean 37.8;	Mean 47.0;	70	80	Japanese
	ABOi	30%	40%	Range 17–62	Range 19–67			HLA mismatch, mean (range): ER-Tac, 2.5 (1–5); IR-Tac, 2.9 (0–6)
								Exclude: re-transplantation, KTRs who had not reached 1-year post-KT
Masutani et al. (2014) [31]	Living donor	100%	100%	42 ± 15	34 ± 5	76	57	Flow cytometric PRA: ER-Tac, 12.2%; IR-Tac, 10.3%
	ABOi	32%	21%					HLA mismatch: ER-Tac, 2.8 ± 1.4; IR-Tac, 2.6 ± 1.6
Fan et al. (2017) [32]	Living donor	31%[d]		Median, 42.0;	Median, 39.6;	67	70	DSA negative
	Deceased donor	69%[d]		Range 21–59	Range 24–57			Reach 1-month post-KT
								CYP3A5 nonexpressers: ER-Tac, 33%; IR-Tac, 41%
								Exclusion: usage of medication or food significantly influent tacrolimus concentration
Niioka et al. (2017) [33]	N/A	N/A	N/A	Median, 53;	Median, 45;	61	61	Japanese
				Range 40–60	Range 35–55	(64)[e]		Absence of pretransplant DSA
								Exclusion: non-adherence, drug interaction obviously affected CYP and ABCB1
Hage et al. (2019) [34]	Living donor	21%	22%	55 ± 13	52 ± 14	70	68	Non-HLA sensitized
	Deceased donor	79%	78%					No re-transplantation
								No ABOi
Ho et al. (2019) [35]	Re-transplant	0%	6%	49.5 ± 16.3	N/A	63	62	ER-Tac group must continue the regimen for ≥ 3 months.
								Propensity score matched[f]
								PRA < 20/20-80/> 80%: ER-Tac, 73.7/15.8/10.5%; IR-Tac, 72.7/20.0/7.3%
								Non-Hispanic white/Non-Hispanic black/Hispanic/Asians: ER-Tac, 52.6/5.3/31.6/10.5%; IR-Tac, 38.2/25.5/27.3/9.1%
								No steroid after 3 months post-KT: ER-Tac, 52.6%; IR-Tac, 67.3%

Table 2 (continued)

ABCB1 adenosine triphosphate (ATP)-binding cassette sub-family B member 1, *ABOi* ABO blood group incompatible, *CYP* cytochrome P450, *DSA* donor-specific antibodies, *ER-Tac* extended-release tacrolimus, *IR-Tac* immediate-release tacrolimus, *HLA* human leukocyte antigen, *KT* kidney transplantation, *KTRs* kidney transplant recipients, *N/A* no available information, *PRA* panel reactive antibody

[a]All were de novo kidney recipients

[b]Data presented in mean ± standard deviation or median (interquartile range) unless otherwise stated

[c]Four KTRs who had not reached 6 months post-KT were also excluded

[d]Data were reported only for the overall population

[e]When 14 kidney recipients who were given ER-Tac and treated with everolimus were not included

[f]KTRs in IR-Tac group were propensity score matched for 15 demographic and clinical characteristics present at the time of their first transplantation

12 months after transplantation. The effects on other clinical outcomes at different times after transplantation were also evaluated. A comprehensive search was performed to identify all eligible studies published as of May 15th, 2019. Based on a thorough, systematic and recent review of the literature, 10 studies with a total number of 1176 KTRs were included. The pooled results of 5 included studies showed significant lower incidence of BPAR at 12 months post-KT in kidney recipients who received ER-Tac therapy compared with those who received IR-Tac (5 studies, $n=659$; RR 0.69, 95% CI 0.51–0.95; $p=0.02$) with no heterogeneity ($I^2=0\%$) and no evidence of publication bias (Egger's test, $p=0.478$). There were no significant differences between the ER-Tac and IR-Tac groups with respect to incidence of BPAR at other time points after KT. Graft survival, patient survival, Scr and eGFR were comparable between the groups at different times over approximately 1 year after transplantation.

The various populations included in this current study reflect the wide spectrum of KTRs actually using tacrolimus for prophylaxis of allograft rejection in routine clinical care, including high immunologic risk patients, who are unlikely to be studied in an RCT, such as re-transplant KTRs, ABOi kidney recipients, and pre-sensitized recipients. Almost all of the KTRs in this study used a potent maintenance immunosuppressive regimen comprised of tacrolimus, mycophenolate and steroids. Strategies to reduce the risk of underexposure with ER-Tac during the early period post-KT, such as initiating tacrolimus therapy before transplantation, increasing the initial dose of ER-Tac, and early conversion from IR-Tac to ER-Tac when tacrolimus blood concentration is stable within the target range before hospital discharge, were applied in some of the studies, given that a lower trough blood concentration and/or higher dosage requirement to achieve the same concentration was observed among KTRs who received ER-Tac than among those who received IR-Tac in a Phase III noninferiority study [36]. Different induction therapies, pre-transplant desensitization strategies, and clinical and therapeutic drug monitoring approaches were also reported among the included studies.

Our finding of significant lower BPAR in ER-Tac (5 studies, $n=659$; RR 0.69, 95% CI 0.51–0.95; $p=0.02$; $I^2=0\%$) compared with IR-Tac at 12 months post-KT is inconsistent with our previous meta-analysis of RCTs, in which no significant difference in BPAR at 12 months post-transplant was found between the 2 groups among low-to-moderate risk KTRs (4 trials, $n=1738$; RR 1.11; 95% CI 0.88–1.44; $p=0.40$; $I^2=0\%$) [15]. The difference in these findings may partly be explained by one or more of potential reasons, including a favorable impact of the ER-Tac formulation, a broader range of immunological risk, individualization in selection of induction therapy and pre-/peri-conditioning strategies, refinement in clinical and drug monitoring together with immunosuppressive drug dosage adjustment, and/or plausible bias in patient selection and uncontrolled confounders in the included observational studies.

Similar to the result of our previous meta-analysis [15], a significant difference in BPAR incidences within 6 months was not found in this current study. The impact of induction therapy, close monitoring during this high-risk period post-KT, and/or strategies of initiating ER-Tac therapy would at least in part explain the finding.

Even though the proportion of patients with BPAR at 1 year was significantly lower with ER-Tac, no significant differences in the patient- or graft-survival rate were observed between the 2 groups. Indeed, the current study showed comparable outcomes in both patient- and graft-survival rates between ER-Tac and IR-Tac groups within 6 months, at 12 months and after 12 months post-KT. It has been reported that KTRs with acute rejection episodes had reductions in the estimated half-life of graft survival compared with those with no rejection episode (6.6 and 12.5 years, respectively) [37]. However, not all rejection episodes have the same impact on long-term kidney allograft function. Prompt recognition and evaluation of allograft dysfunction and timely intervention for acute rejection are the most important milestones for the recovery of graft function. If renal function completely returns to the baseline after treatment, the effects of the acute rejection would no longer have an impact on long-term graft survival [38, 39]. Of note, the 1-year patient- and graft-survival rates reported in all of the included studies were 95–100%. The window of opportunity to improve these outcomes appears rather small.

Table 3 Immunosuppressive regimen usage among the included studies

Study ID	Tacrolimus formulation/starting regimen		Target tacrolimus trough concentration (ng/mL)	Immunosuppressive regimen		
	ER-Tac	IR-Tac		CS	Antiproliferative agents	Induction therapy and conditioning treatment
Crespo et al. (2009) [26]	MR-4; 0.2 mg/kg OD from Day 1 post-KT	Innovator; 0.1 mg/kg BID from Day 1 post-KT	N/A	✓	MPA	Anti-CD25 monoclonal antibodies
Andrés et al. (2010) [27]	MR-4	Innovator	Immediate post-KT: 9–12, Maintenance phase: 5–10	✓	MPA	N/A
Jelassi et al. (2011) [28]	MR-4; 0.2 mg/kg OD immediately post-KT (except 1 KTR received 0.4 mg/kg/d)	Innovator; 0.1–0.3 mg/kg/day immediately post-KT	5–15	✓	MPA	IVIG
Fanous et al. (2013) [29]	MR-4; 0.1 mg/kg/day started within 6 h of engraftment	Innovator; 0.1 mg/kg/day started within 6 h of engraftment	5–10	✓	MMF	ATG or basiliximab, ± IVIG
Ishida et al. (2013) [30]	MR-4; 0.15–0.2 mg/kg OD started 7 days prior to KT in ABOc KTRs or 14 days prior to KT in ABOi KTRs	Innovator;; 0.15–0.2 mg/kg/day BI.D started 7 days prior to KT in ABOc KTRs or 14 days prior to KT in ABOi KTRs	First month: 9–12, Month 1–3: 6–8, Thereafter: 5–7	✓	MMF	Basiliximab for ABOc KT Rituximab and DFPP for ABOi KT
Masutani et al. (2014) [31]	MR-4	Innovator	N/A	✓	MMF	Basiliximab for ABOc KT Rituximab and DFPP for ABOi KT, pre-sensitized patients with positive flow cytometric PRA
Fan et al. (2017) [32]	MR-4; 0.1–0.15 mg/kg OD from Day 0 before surgery	Innovator; 0.1–0.15 mg/kg/day given B.I.D. from Day 0 before surgery	First month: 8–12	✓	MMF	Preoperative ATG
Niioka et al. (2017) [33]	MR-4; 0.2 mg/kg OD started 2 days prior to KT[a], or 7 days prior to KT in ABOi KTRs	Innovator; 0.1 mg/kg BID started 2 days prior to KT[a], or 7 days prior to KT in ABOi KTRs	First week: 15–20, Second week: 12, Third week: 10, Thereafter: < 8	✓	MMF[b]	Basiliximab for ABOc KT Rituximab or splenectomy for ABOi KT
Hage et al. (2019) [34]	MR-4	Innovator	N/A	✓	MPA[c]	T-cell depleting agent/basiliximab/no induction therapy: ER-Tac, 4.9/53.6/41.5%; IR-Tac, 9.5/69/21.4%
Ho et al. (2019) [35]	MR-4; started within 10 days of transplantation[d]	Either generic or branded formulations	6–10	✓	N/A	Basiliximab or alemtuzumab or neither

ABOc ABO blood group compatible, *ABOi* ABO blood group incompatible, *ATG* anti-thymocyte globulin, *BID* twice daily, *CS* corticosteroid, *DFPP* double filtration plasmapheresis, *ER-Tac* extended-release tacrolimus, *IR-Tac* immediate-release tacrolimus, *IVIG* intravenous immunoglobulin, *KT,* kidney transplantation, *KTRs,* kidney transplant recipients, *MMF* mycophenolate mofetil, *MPA* mycophenolic acid, *MR-4* MR-4 tacrolimus formulation, *N/A* no available information, *OD* once daily, *PRA* panel reactive antibody

[a]A 24-h continuous IV infusion of 0.05 mg/kg/day of tacrolimus was administered for the first 3 days after surgery. On the fourth postoperative day, intravenous administration was discontinued, and the same dose as initial oral dose was administered orally

[b]Fourteen of 80 KTRs who were given ER-Tac were treated with everolimus

[c]A proportion of patients were converted from mycophenolic acid to mammalian target of rapamycin inhibitor during the follow-up period

[d]IR-Tac was started if tacrolimus therapy was initiated during the initial hospital stay and subsequently, were switched to ER-Tac upon hospital discharge. If the first dose of tacrolimus therapy was initiated after hospital discharge, KTRs were stared and maintained on ER-Tac. The median time between KT and initiation of ER-Tac was 1.5 days [interquartile range (IQR), 1.3–3.0 days]. The median time of receiving ER-Tac was 490 days (IQR, 111–632 days)

Based on the included studies, differences in the renal function effect, evaluated by eGFR or Scr, were not found between the two tacrolimus formulations within 6 months, at 12 months, and after 12 months post-KT. It should be also mentioned that the number of KTRs in the studies reporting these renal function outcomes is quite small and the long-term influence of the different formulations of tacrolimus on kidney allograft function in clinical practice is still questionable.

Consistent and homogenous results were observed in almost all of the outcomes studied in this meta-analysis. Only the I^2 of Scr reported within 6 months post-KT was higher than 25% (58%), indicating a moderate variance in the observed Scr among various included studies. Therefore, interpretation of the pooled results of Scr within the first 6 months post-KT should be done with caution. Differences in factors such as donation from brain death donors [26] and marginal donors [26, 27] could have various consequences on kidney function post-KT. The marginal deceased donor kidney affects not only 2-year mean Scr levels [40] but is also considered as a risk factor for acute rejection [41]. Donor characteristics were not reported in a few of the included studies [28, 33, 35].

Although ER-Tac formulations were designed to promote a recipient's adherence to tacrolimus therapy by allowing a single morning dose once daily, Ho et al. [35] reported that there were KTRs who switched from ER-Tac to IR-Tac because of borderline changes on a protocol biopsy, supratherapeutic tacrolimus concentration on ER-Tac, and cost difference between branded ER-Tac and generic IR-Tac. Hage et al. [34] also reported that some KTRs requested to switch from IR-Tac to ER-Tac to improve their quality of life, while others were converted from ER-Tac to IR-Tac because high doses of ER-Tac were required to achieve the target trough level.

The pharmacokinetic profiles of IR-Tac, once-daily MR-4 ER-Tac, and once-daily Meldose ER-Tac differ, and these formulations are not bioequivalent [42]. Of the 10 included studies which reported the outcomes of interest, all included KTRs who received the MR-4 formulation of ER-Tac. Six of these studies reported a lower trough blood concentration or a higher dosage requirement of ER-Tac than IR-Tac to achieve comparable target trough concentrations [26, 27, 30–33]. Due to once-daily Meltdose ER-Tac release becoming more prevalent in more recent years, published data of this formulation regarding outcomes in clinical practice compared with those of the other tacrolimus formulations are still lacking.

Genetic variations in the gene-encoding cytochrome P450 (CYP) 3A5, the principle enzyme responsible for tacrolimus metabolism, significantly impacts tacrolimus exposure in KTRs. Not only are there higher dosage requirements for ER-Tac among heterozygous or homozygous carriers of a *CYP3A5**1 allele (CYP3A5 expressers) compared with homozygous carriers of a *CYP3A5**3 allele (CYP3A5 non-expressers), but also a greater reduction in tacrolimus exposure has been reported in CYP3A5 expressers compared with CYP3A5 non-expressers in the early and stable states after kidney transplantation when the IR-Tac was converted to the once-daily ER-Tac formulation [43–46]. A possible explanation for the greater influence of CYP3A5 expression in the intestinal tract on the pharmacokinetics of ER-Tac than IR-Tac is that the prolonged-release characteristics of ER-Tac lead to more distal intestinal absorption and longer exposure of ER-Tac in the small intestine where the level of CYP3A5 protein expression varies depending on the genotype of *CYP3A5* polymorphism [14, 45, 46]. Inclusion of KTRs with different ethnicities in this current meta-analysis may provide an advantage regarding generalizability to different groups of populations given that the allelic frequencies of the CYP*3A5*3* single nucleotide polymorphism differ among individuals of different ethnicities [47].

Confounding bias is commonly considered as a major concern that can influence the result of observational studies. Among the included studies, tacrolimus therapy provided as part of routine clinical care to the included KTRs was simply observed. Although all of these studies are uniformly lacking randomization, key confounders were reported in most of them. Some studies also compared either measured confounders to report the level of covariate balance or proxy variables to mitigate concerns about unmeasured confounding. Propensity score matching, a confounding adjustment method, was used in the study reported by Ho et al. [35]. Of note, KTRs who did not reach a certain time point after KT were excluded in some studies [26, 30, 32, 35] and diversities in the measurement of the outcomes were found among studies, for instance, type of allograft biopsy (clinical indicated vs protocol biopsy) and version of the BANFF classification of allograft pathology [26, 27, 29].

The results of this study suggest that ER-Tac may provide a significant improvement in BPAR at 12 months post-KT compared with the IR-Tac, given that individualization of immunosuppressive strategy selection and refinement of immunosuppressant dosage regimen should be considered as important components of tacrolimus-based therapeutic intervention. In addition, it would be beneficial to identify characteristics of KTRs who may benefit most from the ER-Tac. However, further studies are needed to evaluate the long-term effects of the ER-Tac in clinical practice.

Our study has several limitations inherent with meta-analysis in observational studies in general and with studies of KT outcomes specifically. First, a few studies with small sample sizes were included in this meta-analysis. Second, the observational periods were no longer than 1 year in most of the included studies and, therefore, very limited information was available for evaluation of long-term outcomes

Table 4 Outcome reported among the included observational studies

Study ID	Outcomes													
	BPAR			Graft survival			Patient survival			eGFR			Scr	
	≤6 months	12 months	>12 months	≤6 months	12 months	>12 months	≤6 months	12 months	>12 months	≤6 months	12 months	>12 months	≤6 months	12 months
Crespo et al. (2009) [26]	–	–	–	✓	–	–	–	–	–	–	–	–	✓	–
Andrés et al. (2010) [27]	–	–	–	✓	–	–	✓	–	–	–	–	–	✓	–
Jelassi et al. (2011) [28]	–	–	–	✓	–	–	–	–	–	–	–	–	✓[a]	–
Fanous et al. (2013) [29]	–	✓ Banff 1997	–	–	✓	–	–	✓	–	✓ MDRD	✓ MDRD	–	–	–
Ishida et al. (2013) [30]	✓[b]	✓[b]	–	–	✓	✓	–	✓	✓	–	–	–	–	–
Masutani et al. (2014) [31]	✓[b] Banff 2009	✓[b] Banff 2009	–	–	–	–	–	–	–	–	–	–	✓	✓
Fan et al. (2017) [32]	–	–	–	–	✓	–	–	✓	–	–	✓ MDRD	–	–	–
Niioka et al. (2017 [33]	–	✓[b]	–	–	–	–	–	–	–	–	–	–	✓[c]	✓[c]
Hage et al. (2019) [34]	–	–	✓ Banff 2013	–	–	–	–	–	–	✓	✓	✓	–	–
Ho et al. (2019) [35]	–	✓	–	–	✓	–	✓	✓	–	✓[c] MDRD	✓[c] MDRD	–	–	–
Total trials	2	5	1	3	4	1	2	4	1	3	4	1	5	2
Total no. of participants	164	659	250	161	426	45	153	426	45	525	631	250	500	339

BPAR biopsy-proven acute rejection, *eGFR* estimated glomerular filtration rate, *MDRD* modification of diet in renal diseases equation for estimated glomerular filtration rate calculation, *Scr* serum creatinine

[a]Standard deviation was not reported, therefore was not included in the meta-analysis

[b]Protocol biopsy was reported

[c]Median value was reported, therefore was not included in the meta-analysis

Study ID	Assessment within ROBINS-I risk of bias domains							Overall risk of bias assessment
	Confounding	Selection of participants into the study	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	
Crespo et al 2009 [26]	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Andres et al 2010 [27]	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious
Jelassi et al 2011 [28]	Serious	Serious	Moderate	Low	Low	Low	Low	Serious
Fanous et al 2013 [29]	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Ishida et al 2013[30]	Moderate	Serious	Moderate	Moderate	Low	Low	Low	Serious
Masutani et al 2014 [31]	Serious	Moderate	Moderate	Low	Low	Low	Low	Serious
Fan et al 2017 [32]	Low	Serious	Moderate	Low	Low	Low	Low	Serious
Niioka et al 2017 [33]	Serious	Low	Moderate	Serious	Moderate	Low	Low	Serious
Hage et al 2019 [34]	Serious	Moderate	Moderate	Serious	Moderate	Low	Low	Serious
Ho et al 2019 [35]	Low	Serious	Moderate	Moderate	Moderate	Moderate	Low	Serious

Categories for risk of bias assessments: Critical | Serious | Moderate | Low | No Information

Fig. 2 Risk of bias of each of the included studies

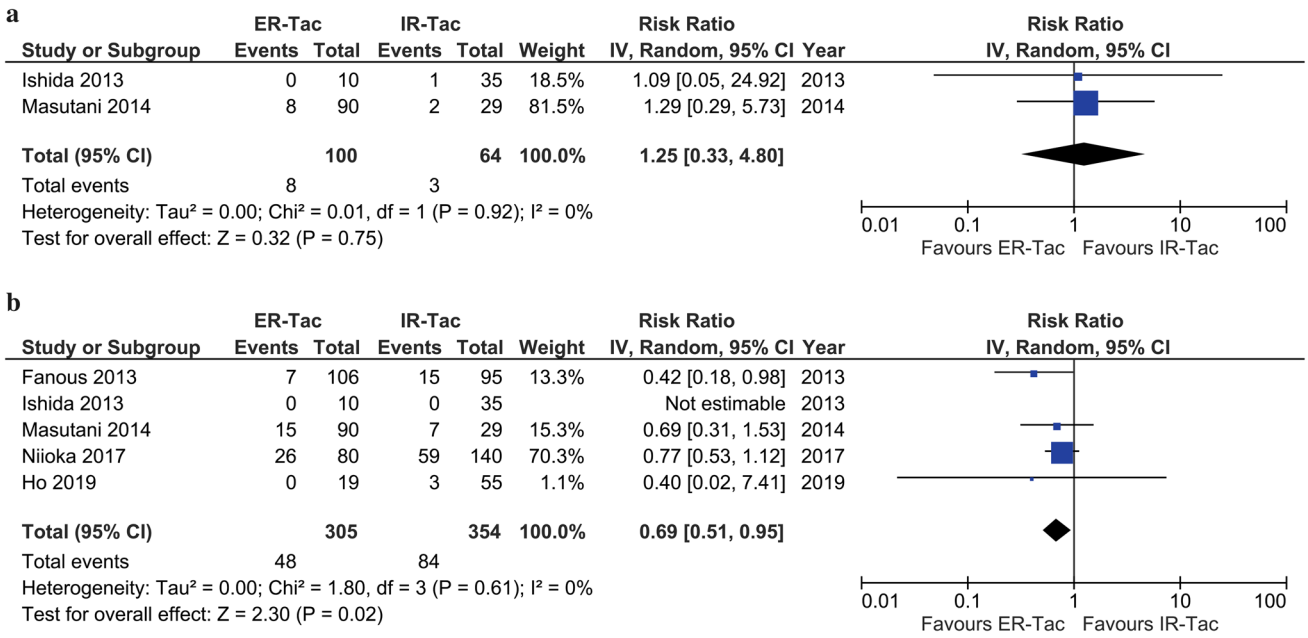

Fig. 3 Meta-analysis of biopsy-proven acute rejection incidence **a** within 6 months and **b** at 12 months post-kidney transplantation

after 1-year post-KT. Third, the study could have been influenced by various biases. For example, although different databases were comprehensively searched and publications in both English and other languages were considered, reporting bias cannot be ruled out. Also, even though all of our studied outcomes are objective parameters, performance bias may possibly exist. Selection bias may have occurred in non-randomized studies. Publication bias, which may lead to an under- or over-estimation of outcomes, also cannot be excluded. Fourth, most of the KTRs in this study received mycophenolate as a concomitant maintenance immunosuppressive agent, whether a combination regimen of tacrolimus

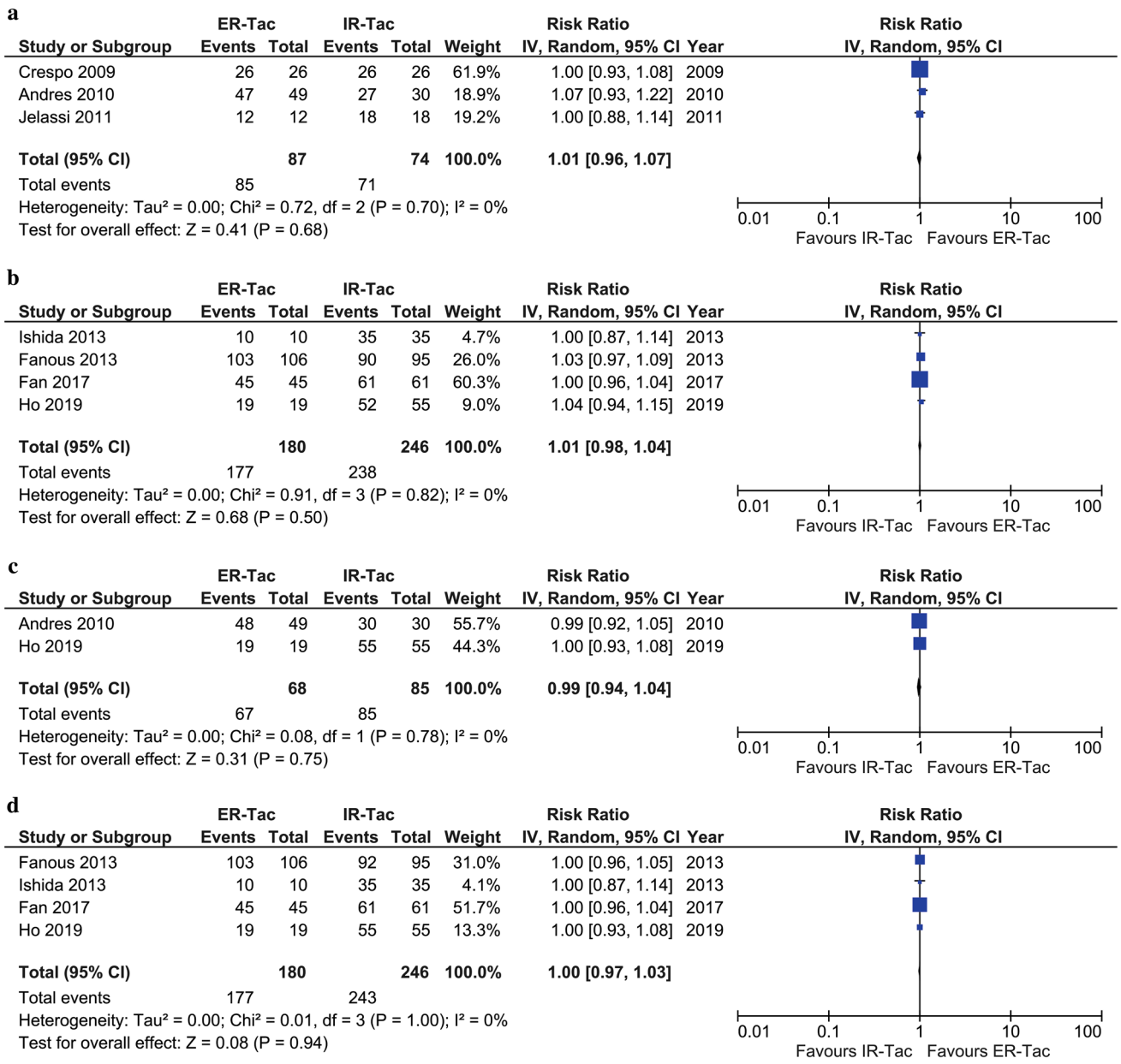

Fig. 4 Meta-analysis of **a** graft survival within 6 months, **b** graft survival at 12 months **c** patient survival within 6 months, and **d** graft survival at 12 months post-kidney transplantation

with other antiproliferative agents would have improved clinical outcomes of KTRs is questionable. Finally, our conclusions are based upon reported observational studies. Whether the different formulations of tacrolimus would impact these outcomes in a long-term follow-up and which populations of KTRs would benefit most from which formulations remain to be further explored.

5 Conclusion

Based upon currently available evidence in observational studies, ER-Tac is associated with a significant lower risk of BPAR at 12 months post-KT compared with IR-Tac, but there was no significant difference in BPAR at any other particular studied time points. No differences in graft- and patient-survival rates and kidney function were observed between the groups. Interpretation of these findings should be regarded with caution given that most of the included studies had serious overall risk of bias. It is plausible that

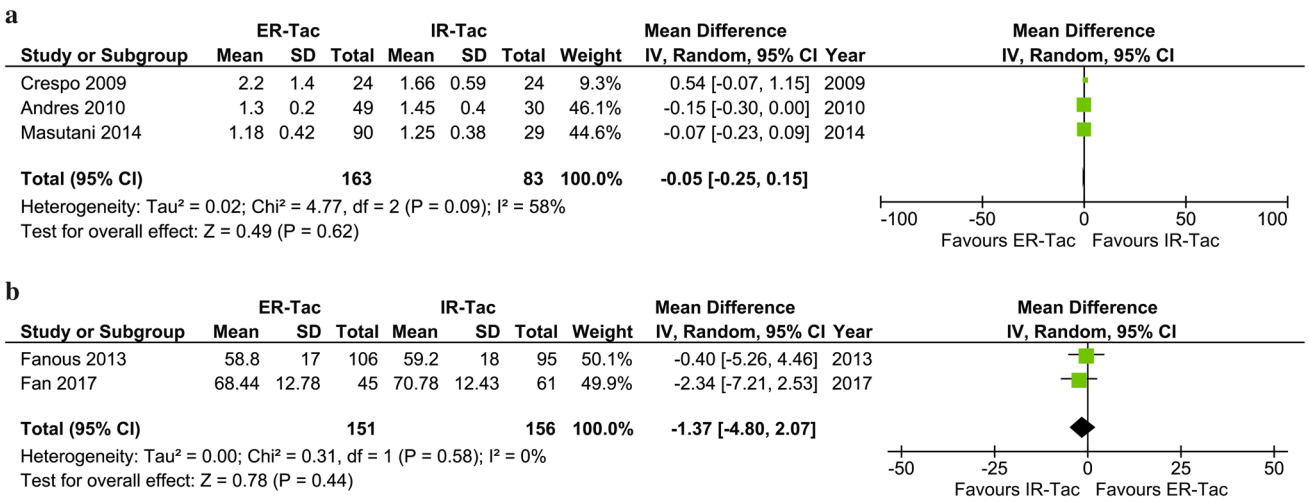

Fig. 5 Meta-analysis of **a** serum creatinine concentration within 6 months and **b** estimated glomerular filtration rate at 12 months post-kidney transplantation

the results could be biased or confounded by unmeasurable or uncontrollable factors. Data from this current study cannot provide convincing evidence of a causal relationship between exposure and outcome. Well-designed observational studies with longer-term follow-up involving high-risk patients could contribute to an improved understanding of the long-term effects of different tacrolimus formulations on allograft clinical outcomes in KTRs.

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Author Contributions SV conducted the selection process, data extraction, data analysis, result interpretation, and wrote the manuscript for submission. WS and AP conducted the literature search, selection process, data extraction, data analysis and results interpretation. All authors participated in the research design, discussions, and approved the manuscript for submission.

Compliance with Ethical Standards

Conflict of interest SV, WS, AP, NP, and WC declare no conflict of interest.

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