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META-ANALYSIS

Risk factors and outcomes of post-transplant erythrocytosis among adult kidney transplant recipients: a systematic review and meta-analysis

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SUMMARY

Post-transplant erythrocytosis (PTE) can occur in up to 10–16% after kidney transplant (KT). However, the post-transplant outcomes of recipients with PTE in the literature were conflicting. We performed systematic review and meta-analysis of published studies to evaluate risk factors of PTE as well as outcomes of recipients who developed PTE compared with controls. A literature search was conducted evaluating all literature from existence through February 2, 2021, using MEDLINE and EMBASE. Data from each study were combined using the random-effects model. (PROSPERO: CRD42021230377). Thirty-nine studies from July 1982 to January 2021 were included (7,099 KT recipients). The following factors were associated with PTE development**:** male gender (pooled RR = 1.62 [1.38, 1.91], I^2 = 39%), deceased-donor KT (pooled RR = 1.18 [1.03, 1.35], I^2 = 32%), history of smoking (pooled RR = 1.36 [1.11, 1.67], I^2 = 13%), underlying polycystic kidney disease (PKD) (pooled RR=1.56 [1.21, 2.01], I^2=44%), and pretransplant dialysis (pooled RR=1.6 [1.02, 2.51], I^2=46%). However, PTE was not associated with outcomes of interest, including overall mortality, death-censored graft failure, and thromboembolism. Our meta-analysis demonstrates that male gender, deceased-donor KT, history of smoking, underlying PKD, and pretransplant dialysis were significantly associated with developing PTE. However, with proper management, PTE has no impact on prognosis of KT patients.

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graft failure, kidney transplantation, overall mortality, post-transplant erythrocytosis, risk factor

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Introduction

Post-transplant erythrocytosis (PTE) is defined by the Kidney Disease Improving Global Outcomes (KDIGO) 2009 as hemoglobin (Hgb) >17 g/dl or a hematocrit (Hct) >51% for both males and females [1]. The rising of Hct must be persistent over a period of 3 to 6 months and independent of other pathological conditions, such as polycythemia vera, tumors associated with increased erythropoetin (EPO), hypoxia, chronic obstructive pulmonary disease, and obstructive sleep apnea [2,3]. PTE is one of the more common post-

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transplant hematologic complications which affect 8–26% of kidney transplant (KT) recipients [4]. The prevalence varies from study to study because of the different levels of Hct used for diagnosis, length persistence of disease, and gender variation of Hct cut-off values [2,5]. Although the cause has remained unclear, several risk factors have been linked to this complication, and the symptoms are similar to other forms of erythrocytosis, including headache, dizziness, fatigue, dizziness, and malaise [5,6].

To understand this hematologic complication better and to recognize it earlier in KT recipients, we aimed to study possible risk factors associated with this complication, including male sex, smoking, pretransplant medical conditions and medications, pre-existing kidney diseases, types of KT, and immunosuppressive regimen.

Spontaneous remission occurs in less than 25% of the patients within 2 years from the onset, with a median time of 13 months [2,4,5]. Thus, early detection and prompt management are necessary. Persistence of the condition causes worsening kidney function because of chronic rejection, which required treatment with angiotensin converting enzymes (ACEI) and angiotensin II receptor blockers (ARB) or phelbotomy [5] with a goal of maintaining Hct below 51% [1]. Several studies have reported thromboembolic events, such as stroke, pulmonary embolism, thrombosis of digital or brachial arteries, and cardiovascular disease, as a sequela of PTE because of an increased blood viscosity [2,5]. However, outcome of PTE is controversial and is also an aim of this study.

Materials and methods

Search strategy

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines [7]. A literature search was performed to identify studies that had investigated the risk factors and outcomes of adult (age $\geq$ 18 years) KT recipients who developed PTE. This was independently conducted by two investigators (P.M. and N.L.) in the MEDLINE and EMBASE, from inception through February 2, 2021; search terms included "erythrocytosis" and "kidney transplant" as described in Data S1. The references of selected articles were also manually searched for additional relevant studies; there were no language restrictions.

Study selection and outcomes

Studies were eligible for inclusion if they met the following criteria: (1) original, published, randomized controlled cohort (either prospective or retrospective), case-control, or cross-sectional studies; (2) studies reporting incidence or prevalence of outcomes of interest including overall mortality, death-censored graft failure (DCGF), and thromboembolism in KT patients with and without PTE; (3) studies where data were stratified for KT patients who developed or did not develop PTE and clearly presented an n (%) for each group with a sample size of more than 10 patients; (4) the odds ratio (OR), relative risk (RR), hazard ratio (HR), and standardized incidence ratio (SIR) with 95% confidence intervals (CI), or sufficient raw data to calculate these ratios, were provided; (5) patients without PTE (controls) were used as comparators in cohort, case-control, and cross-sectional studies.

We excluded editorials, opinions, reviews, case reports, or case series, duplicated or overlapped patient populations, and studies conducted in pediatric populations (<18 years).

Study eligibility was independently assessed by the investigators (P.M. and N.L.); any disagreements were resolved through mutual consensus. The quality of each study was assessed using the Newcastle-Ottawa Quality Scale (NOS) [8]. This scale assesses each study using three categories: (1) the representativeness of the subjects; (2) the comparability between the study groups; and (3) ascertainment of the exposure or outcome of interest, for case-control and cohort studies, respectively. The quality assessment of cross-sectional studies has been adapted from the NOS for cohort studies [9]. Studies with total scores of >6 and <4 were considered to be of high and low quality, respectively. We excluded any studies that the meta-analysis indicated of poor quality.

In this meta-analysis, the primary outcome was the risk of overall mortality, DCGF, and thromboembolism between KT patients with PTE and those without PTE. The secondary outcomes were the risk of developing PTE between KT patients with risk factors of interest and those without.

Review process and data extraction

Two investigators (P.M. and N.L) independently reviewed the titles and abstracts of all retrieved articles. Articles that did not fulfill the inclusion criteria were excluded; only potentially relevant articles underwent

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full-text reviews to determine their eligibility. A standardized data collection form was used to extract the following data: first author's name, year of publication, year of study, country of origin, study design, source of population, number of subjects, baseline characteristics of the subjects, and effect estimates. This data extraction process was performed in duplicate to ensure accuracy.

Statistical analysis

All statistical analyses were performed using RevMan software (version 5.4.1; Cochrane, London, United Kingdom). The pooled risk ratios for various outcomes in the PTE group compared with the control group and risk factors of developing PTE were calculated using a Mantel-Haenszel method. A random effects model was used, given the high likelihood of between-study variance because of differences in underlying population, as well as methodology. The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. An I^2 value of 0–25% represented insignificant heterogeneity, 25–50% represented low heterogeneity, 50–75% represented moderate heterogeneity, and >75% represented high heterogeneity [10].

Results

The initial search yielded 450 articles, all of which underwent both title and abstract reviews. Most were excluded at this step, as they did not fulfill our inclusion criteria; that is, they were irrelevant, case reports, letters to the editor, review articles, or interventional studies. A total of 61 studies underwent full-length article review; 22 were excluded, as they did not include controls or report the outcome of interest. A total of 39 observational studies [4,6,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47], including 7,099 patients, finally met our inclusion criteria and were included in the meta-analysis. Figure 1 outlines our search methodology and selection process; the baseline characteristics of the included studies are summarized in Table 1.

Risk factors for post-transplant erythrocytosis

Table 2 outlines the pooled risk ratio of risk factors evaluated. Male gender and history of smoking were significantly associated with higher risk of PTE with pooled risk ratios of 1.62 (95% CI 1.38–1.91, I^2 = 39%) and 1.36 (95% CI 1.11–1.67, I^2=13%), respectively (Fig. 2). Deceased donor KT recipient status, compared with living-donor KT recipient status, was significantly associated with higher risk of PTE with a pooled risk ratio of 1.18 (95% CI 1.03–1.35, I^2 = 32%). The patients who received dialysis prior to KT were found to have higher risk of PTE with a pooled risk ratio of 1.6 (95% CI 1.02–2.51, I^2 = 46%) (Fig. 3). Pretransplant diabetes, hypertension, and previous transfusion did not show significant association (Figure S1). Previous transplant recipient status and pretransplant ACEI or ARB use were associated with numerically lower risk of PTE, but the effects were not statistically significant (Figure S2).

Among the etiologies of native kidney disease, only polycystic kidney disease (PKD) was found to be significantly associated with higher risk of PTE with a pooled risk ratio of 1.56 (95% CI 1.21–2.01, I^2 = 44%); while glomerulonephritis did not have significant association.

The choice of induction and maintenance immunosuppressive medications did not appear to show any significant associations. Of note, Alemtuzumab and MMF use was associated with a numerically lower risk of PTE, but the effect was not significant (FiguresS3–S4).

Transplant renal artery stenosis also did not have significant association with PTE. Forest plots of nonsignificant risk factors are shown in Figures S1–S3.

Outcomes of Post-transplant Erythrocytosis

Table 3 outlines post-transplant outcomes of KT recipients who developed PTE compared with those who did not. We did not find any significant association between PTE and adverse outcomes, including overall mortality, DCGF, and thromboembolic events. Forest plots are shown in Fig. 4.

Evaluation for publication bias

The funnel plots for the significant risk factors and outcomes of PTE are shown in Figures S5 and S6, respectively. They are symmetrical and do not suggest the presence of publication bias in favor of positive studies.

Discussion

Our meta-analysis found that the risk factors of PTE were recipients with male gender, a history of smoking, underlying PKD, deceased-donor KT status, and pretransplant dialysis.

Currently, the pathogenesis of PTE is not well understood but appears to be multifactorial [5]. Several hormones and growth factors may be involved in the pathogenetic mechanisms of PTE. The main mechanisms

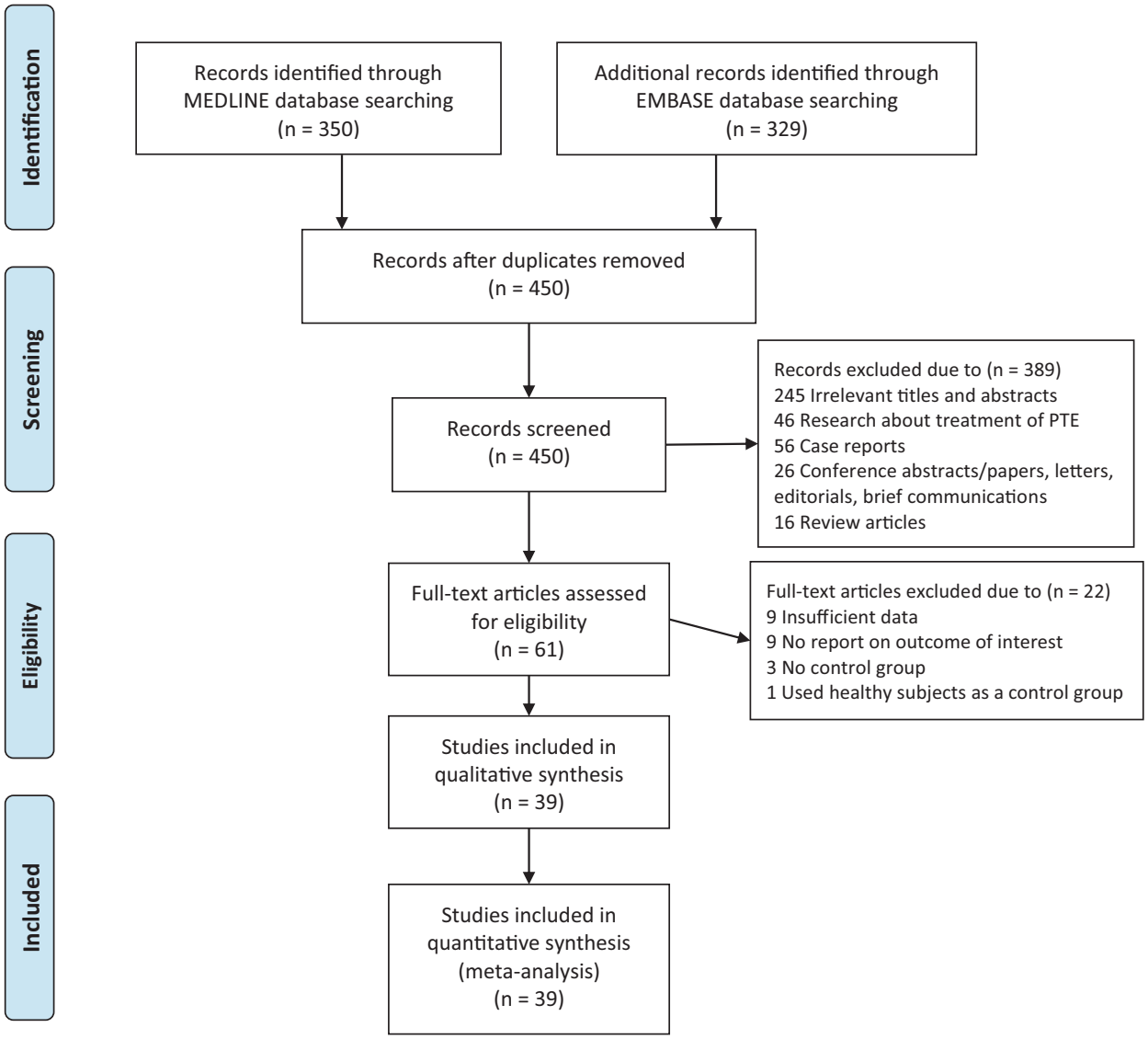

Figure 1 Search methodology and selection process.

are overproduction of EPO, renin-angiotensin system (RAS) activation, increased endogenous androgens, and increased hematopoietic growth factors, such as insulin-like growth factor-1 [5,48].

We confirmed findings from several previous studies that being a male recipient is a risk factor of PTE [4,15,28]. Male gender was the most important risk factor for PTE in our meta-analysis, with a RR of 1.61. This may be explained by endogenous androgens in males, which could promote erythrocytosis directly by stimulating erythroid progenitors that have already been differentiated by EPO [49] or indirectly via RAS [50] or endogenous EPO activation [51].

Smoking has been associated with an increase in the Hgb levels in the general population [52,53], mainly related to increased levels of carboxyhemoglobin in the blood [53]. However, Gaciong *et al*. reported no significant difference in carboxyhemoglobin level between patients with and without PTE [20]. Erythrocytosis among cigarette smokers in the general population is also commonly believed to be because of elevated serum EPO levels; however, a recent study showed an inverse association between erythrocytosis and EPO levels [54]. In addition, there were a few reports showing that PTE was more frequently found in KT recipients with a history of cigarette smoking [46,55]. This could be explained by occult renovascular disease in smokers causing an increase in renin and EPO production [56,57]. Nevertheless, the actual impact of cigarette smoking on PTE is still unknown and needs more

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Table 1. Characteristics of the studies included in the meta-analysis.

First author/ Year	Country	Study design	N	Male (%)	Age (Years)	Duration of follow-up	PTE patients (%)	Definition of PTE	Average level of Hgb or Hct	Timing of PTE diagnosis posttransplant	Main treatment of PTE
Abdelrahman/ 2004	Saudi Arabia	Case-control	47	39 (83)	Mean 44 ± 9	Mean 113 ± 26 months	9 (19)	Hct > 51%	PTE: Mean Hgb 18 ± 1 g/dl	Mean 9.8 ± 9 months	Phlebotomy, ACEI
Abouelenein/ 2018	Egypt	Case-control	348	330 (94.8)	Mean PTE 32 ± 9.1 No PTE 32 ± 9.2	N/A	174 (50)	Hct > 51%	N/A	N/A	Phlebotomy, ACEI, Theophylline
Ahmed/2012	Pakistan	Case-control	200	156 (78)	Mean PTE 29.63 ± 8.78 No PTE 28.69 ± 9.81	N/A	40 (20)	Hct > 51%	PTE: Mean Hgb 16.79 ± 0.75 g/dl	Mean 9.5 ± 2.5 months	Phlebotomy, ACEI
Akcay/2005	Turkey	Case-control	155	119 (76.8)	Mean 34.9 ± 9.7	Mean 53.6 ± 16.1 months	43 (27.7)	Hct > 50%	N/A	N/A	N/A
Alasfar/2021	USA	Prospective cohort	1123	687 (61.2)	Mean PTE 48.3 ± 11.1 No PTE 54.0 ± 13.2	Median (IQR) 4 years (3, 5)	75 (6.7)	Hgb Women > 16 g/ dl Men > 16.5 g/dl	Mean peak Hgb, g/ dl PTE: 17.2 ± 0.77 No PTE: 13.32 ± 1.79	Median (IQR) 4 months (36, 60)	ACEI, ARB
Alzoubi/2020	USA	Retrospective cohort	1249	812 (65)	Median ± IQR 52.2 ± 17.8	N/A	214 (5)	Hct > 51%	PTE: Mean Hct at Dx 52.08 ± 1.26%	Mean 9.92 ± 5.89 months	ACEI/ARB, phlebotomy
Chan/1992	Hong Kong	Cross-sectional	34	28 (82.4)	Mean PTE 34.7 ± 1.7 No PTE 32.9 ± 1.6	N/A	17 (50)	N/A	Mean Hgb, g/dl PTE: Male17.5 ± 0.14, Female 17.1 ± 0.52 No PTE: Male 13.5 ± 0.4, Female 13.4 ± 0.64	Mean 9 ± 2 months	N/A
Charfeddine/ 2008	Tunisia	Case-control	62	49 (79)	Mean PTE 39.57 (Range 27–67) No PTE 36.33 (Range 22–63)	N/A	31 (21.6)	Hct > 52% in male Hct > 50% in female	N/A	Mean 11.3 ± 9.8 months	Phlebotomy, ACEI
Erdem/2011	Turkey	Prospective cohort	96	62 (64.6)	Mean PTE 35.3 ± 8.4 No PTE 32.8 ± 10.6	N/A	15 (15.6)	Hct > 51%	N/A	Mean 7.3 ± 2.8 months	ACEI/ARB
Frei/1982	Canada	Case-control	36	30 (83.3)	Mean PTE 33.1 ± 10.6 No PTE 31.1 ± 11.7	N/A	18 (50)	Hct > 53% in male Hct > 51% in female	N/A	N/A	N/A
Gaciong/1992	USA	Retrospective cohort	159	91 (57.2)	Mean PTE 40 (Range 20–61) No PTE 27	N/A	74 (46.5)	Hct > 55% in male Hct > 50% in female	N/A	Mean (Range) 35.2 months (7–138)	Phlebotomy

Table 1. Continued.

First author/ Year	Country	Study design	N	Male (%)	Age (Years)	Duration of follow-up	PTE patients (%)	Definition of PTE	Average level of Hgb or Hct	Timing of PTE diagnosis posttransplant	Main treatment of PTE
Glicklich/1989	USA	Case-control	180	128 (71.1)	Mean Cyclosporine 42.6 ± 2.7 Non-cyclosporine 42.1 ± 4.3	Mean 40.8 ± 4.4 months	35 (19)	Hct > 51%	Mean Hct, % PTE group: Hct 53.6 ± 0.25 Normal Hct group: Hct 39.9 ± 0.4	Mean, months Cyclosporine 8.3 ± 0.7 Non-cyclosporine 9.7 ± 0.5	Phlebotomy
Glicklich/1999	USA	Cross-sectional	24	9 (37.5)	Mean PTE 51.2 ± 10.9 No PTE 46.9 ± 13	N/A	12 (50)	Hct > 51%	N/A	N/A	ACEI
Gupta/2000	USA	Case-control	25	20 (80)	Mean PTE 48.1 ± 3.1 No PTE 52.6 ± 2.6	N/A	13 (52)	Hct > 51%	N/A	Mean 41.8 ± 15.4 months (Without 2 outlier patient 21.6 ± 8.7)	Phlebotomy
Innes/1991	UK	Case-control	46	PTE group 17 (73.9)	Median 41 (Range 23–60)	N/A	23 (50)	Hct > 50%	N/A	Median 12 months	N/A
Kessler/1996	France	Prospective cohort	36	28 (77.8)	Mean PTE 45.6 ± 13.9 No PTE 13.3 ± 13.9	Mean 22 months (range 9–35)	18 (50)	RBC mass > 120% of the theoretical value	Mean Hgb, g/dl PTE: 16.8 ± 0.9 No PTE: 12.6 ± 1.3	Mean (Range) 247 days (100–500)	Phlebotomy, ACEI
Khan/2021	Parkistan	Prospective cohort	67	57 (85)	Mean 32.6 ± 8.8	Total 12 months	19 (28.4)	Hgb > 17 g/dl	PTE: Mean Hgb 16.79 ± 0.75 g/dl	Mean 5.6 ± 2.5 months	Phlebotomy, ACEI
Khedr/2009	Egypt	Case-control	60	51 (85)	N/A	N/A	N/A	Hct > 51%	N/A	N/A	Phlebotomy
Kiberd/2009	Canada	Retrospective cohort	511	318 (62)	Mean PTE 44 ± 11 No PTE 45 ± 13	Total 8 years	59 (11.5)	Hct > 51% or Hb > 17 g/dl	PTE: Mean peak Hb 18.1 ± 0.9 g/dl	N/A	ACEI, ARB
Kiykim/2009	Turkey	Cross-sectional	97	56 (57.7)	Mean PTE 35.2 ± 2.4 No PTE 34.8 ± 6.1 Healthy control 33 ± 6.7	N/A	13 (13.4)	Hct > 51%	N/A	N/A	N/A
Kolonko/2009	Poland	Prospective cohort	385	247 (64.2)	Mean (Range) PTE 41 (39–44) Non-PTE/PTA 42 (40–43) PTA 40 (38–42)	N/A	71 (18.4)	Hct > 50%	N/A	N/A	N/A
Kurella/2003	USA	Retrospective cohort	283	N/A	N/A	N/A	73 (26)	Hct > 50%	PTE: Mean Hct 54 ± 1%	Median 6 months	ACEI
Lezaic/1997	USA	Case-control	18	10 (55.6)	Mean PTE 31 ± 1.4 No PTE 34.8 ± 2.5	Mean PTE 25 ± 3.9 months No PTE 23.7 ± 3.9 months	9 (50)	Hgb Women > 16 g/dl Men > 18 g/dl	Mean Hgb, g/dl PTE: 17.9 ± 0.3 No PTE: 12.4 ± 0.2	N/A	N/A
Mulhern/1995	USA	Prospective cohort	112	N/A	Mean PTE 45 ± 3.9 No PTE 44 ± 2.9	N/A	8 (6)	Hct > 52%	PTE: Mean Hct 54 ± 0.6%	Mean 25.4 ± 1.6 months	ACEI

Table 1. Continued.

First author/ Year	Country	Study design	N	Male (%)	Age (Years)	Duration of follow-up	PTE patients (%)	Definition of PTE	Average level of Hgb or Hct	Timing of PTE diagnosis posttransplant	Main treatment of PTE
Najoua/2010	Morocco	Retrospective cohort	74	41 (55.4)	Mean PTE 40 ± 11 No PTE 36 ± 13	Mean 37 ± 27 months	11 (14.9)	Hct > 51%	PTE: Mean Hgb 17 ± 0.4 g/dl, Mean Hct 52 ± 0.9%	Mean 9 ± 7 months	Phlebotomy, ACEI
Oymak/1995	Turkey	Case-control	36	25 (69.4)	Mean (Range) PTE 33 (24–40) No PTE 35 (22–55) Healthy control 34 (18–50)	N/A	10 (31.3)	Hct > 51%	PTE: Mean Hgb 17.6 ± 0.2 g/dl	Mean (Range) 10 months (4–22)	Venesection
Pollak/1988	USA	Case-control	42	29 (69)	Mean PTE 37.5 ± 8.8 No PTE 32.3 ± 8.7	Mean 5.5 years (Range 1–15.6)	22 (52.4)	Hct > 50%	PTE: Hct 55.2 ± 4%	Mean 11.4 months	N/A
Qunibi/1991	Saudi Arabia	Case-control	186	140 (75.3)	Median (Range) PTE 34 (13–61) No PTE 33 (12–72)	Median 35 months	93 (50)	Hct > 51%	Median (Range) PTE: Hct 54.6 (51–63.2) %	Median (Range) 9 months (1–99)	Phlebotomy
Rajasekar/2018	India	Cross-sectional	327	261 (79.8)	Mean PTE 30.8 ± 9.08 No PTE 34.6 ± 8.35	Mean 52.9 ± 44.8 months	51 (15.6)	Hgb > 17 and/or Hct > 51%	PTE: Mean Hgb 18.68 ± 0.73 g/dl	Median (Range) 8 months (2–36)	Phlebotomy, ACEI (enalapril)
Razeghi/2008	Iran	Case-control	235	86 (36.6)	Mean PTE 41.5 ± 12.1 No PTE 38.4 ± 14.1	N/A	45 (19)	Hct > 51%	N/A	N/A	N/A
Singh/2002	India	Prospective cohort	150	121 (80.7)	N/A	N/A	11 (7.3)	RBC mas Male > 35 mL/Kg, Female > 30 mL/Kg	N/A	N/A	ARB
Thevenod/ 1983	Germany	Cross-sectional	24	16 (66.7)	Mean PTE 39 ± 10 No PTE 38 ± 11	N/A	12 (50)	N/A	N/A	N/A	Phlebotomy
Usalan/1998	Turkey	Prospective cohort	20	19 (95)	Mean PTE 41 ± 13 No PTE 43 ± 14	N/A	10 (50)	Hct > 51%	PTE: Mean Hgb 17.24 ± 0.53 g/dl	Mean (Range) 13 months (4–26)	Phlebotomy, ACEI (enalapril)
Vedovato/ 1990	Italy	Case-control	31	18 (58.1)	Mean (Range) 41 ± 9 (24–57)	N/A	14 (45)	N/A	PTE: Mean Hct 52 ± 4%	Mean 7 ± 3 months	Phlebotomy
Wang/2002	Hong Kong	Prospective cohort	18	12 (66.7)	Mean PTE 43 ± 18 No PTE 46 ± 8	N/A	8 (44.4)	Hct > 51%	Mean Hgb, g/dl PTE: Losartan group Hgb 17.3 ± 0.8, Enalapril group Hgb 17.1 ± 0.6	N/A	ACEI, ARB
Webb/1987	UK	Case-control	100	PTE 62% No PTE 72%	N/A	N/A	50 (50)	Hgb Women > 15 g/dl Men > 16.5 g/dl	N/A	N/A	Phlebotomy

Table 1. Continued.

First author/ Year	Country	Study design	N	Male (%)	Age (Years)	Duration of follow-up	PTE patients (%)	Definition of PTE	Average level of Hgb or Hct	Timing of PTE diagnosis posttransplant	Main treatment of PTE
Wickre/1983	USA	Case-control	102	56 (54.9)	Mean PTE 35.7 ± 12 No PTE 30.2 ± 13.1	Mean PTE 41.5 ± 27.8 months Control 48.6 ± 18.3 months	53 (52)	Hct > 51%	PTE: Mean Hct 54.8 ± 2.6%	Mean 17 months	Phlebotomy
Yeter/2020	Turkey	Case-control	247	159 (64)	Mean 40 ± 12	N/A	59 (23.9)	Hgb Women > 15 g/dl Men > 16.5 g/dl	N/A	Median (Range) 16 months (8–34)	N/A
Yildiz/2003	Turkey	Case-control	154	106 (68.8)	Mean PTE 32 ± 10 No PTE 31 ± 10	N/A	86 (55.8)	Hgb > 16 g/dl	Mean Hgb, g/dl PTE 18.4 ± 2.3 No PTE 13.6 ± 4.2	Mean 8.8 ± 7.9 months	ACEI, ARB

ACEI, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blocker; Hgb, Hemoglobin; Hct, Hematocrit; PTE, Posttransplant erythrocytosis.

investigation. Moreover, the results could be affected by the fact that more male recipients were smokers than women, which raises the question of whether male gender was a true risk factor [39].

The original cause of end-stage renal disease may also affect the risk of PTE. A study by Razeghi *et al*. revealed that patients with PKD and glomerulonephritis had higher risks of developing PTE [39]. We found in this meta-analysis that underlying PKD is the risk factor of PTE, but we did not find a significant association between underlying glomerulonephritis and PTE. Increased EPO is believed to be one mechanism for developing PTE in patients with PKD. Several studies found that serum EPO levels in patients with PKD are higher than with other renal diseases [58,59]. Normally, EPO is produced by interstitial fibroblast-like cells surrounding the renal tubules and controlled by an oxygen sensor in the epithelial cells of the proximal tubules [60,61]. However, there was a study that found EPO production occurs in the renal cysts of autosomal dominant PKD [62]. Moreover, renal structural changes in PKD may stimulate RAS resulting in the development of PTE [39]. Renin secretion appears to be increasing in PKD patients [63,64], especially with hypertension, and it may be caused by renal ischemia from cyst expansion [64].

We also found that decreased donor KT has higher risk of developing PTE compared with living-donor KT. There have not been many studies assessing this association, but one study reported that the KT recipient with deceased donors had higher plasma renin activity and aldosterone levels than those with living-donor KT [65]. So, RAS activation might explain an association between deceased donor KT and PTE. Pretransplant dialysis was another significant risk factor for PTE in our study, which confirmed the findings in several previous studies [15,18]. Erdem *et al*. reported that all PTE patients in their study had received dialysis prior to KT, but no PTE developed in patients who had direct KT [18]. A longer duration on dialysis was also related to PTE [17]. Moreover, pretransplant dialysis was found to be related to mortality and DCGF in KT patients [15]. However, there is no clear explanation for this relationship.

Transplant renal artery stenosis was believed to be a risk factor for PTE with a possible mechanism of intrarenal hypoxia from renal artery stenosis causing subsequent EPO-dependent erythrocytosis [66]. However, we did not find any association between transplant renal artery stenosis and PTE in our meta-analysis. Pretransplant diabetes, hypertension, dialysis status, previous

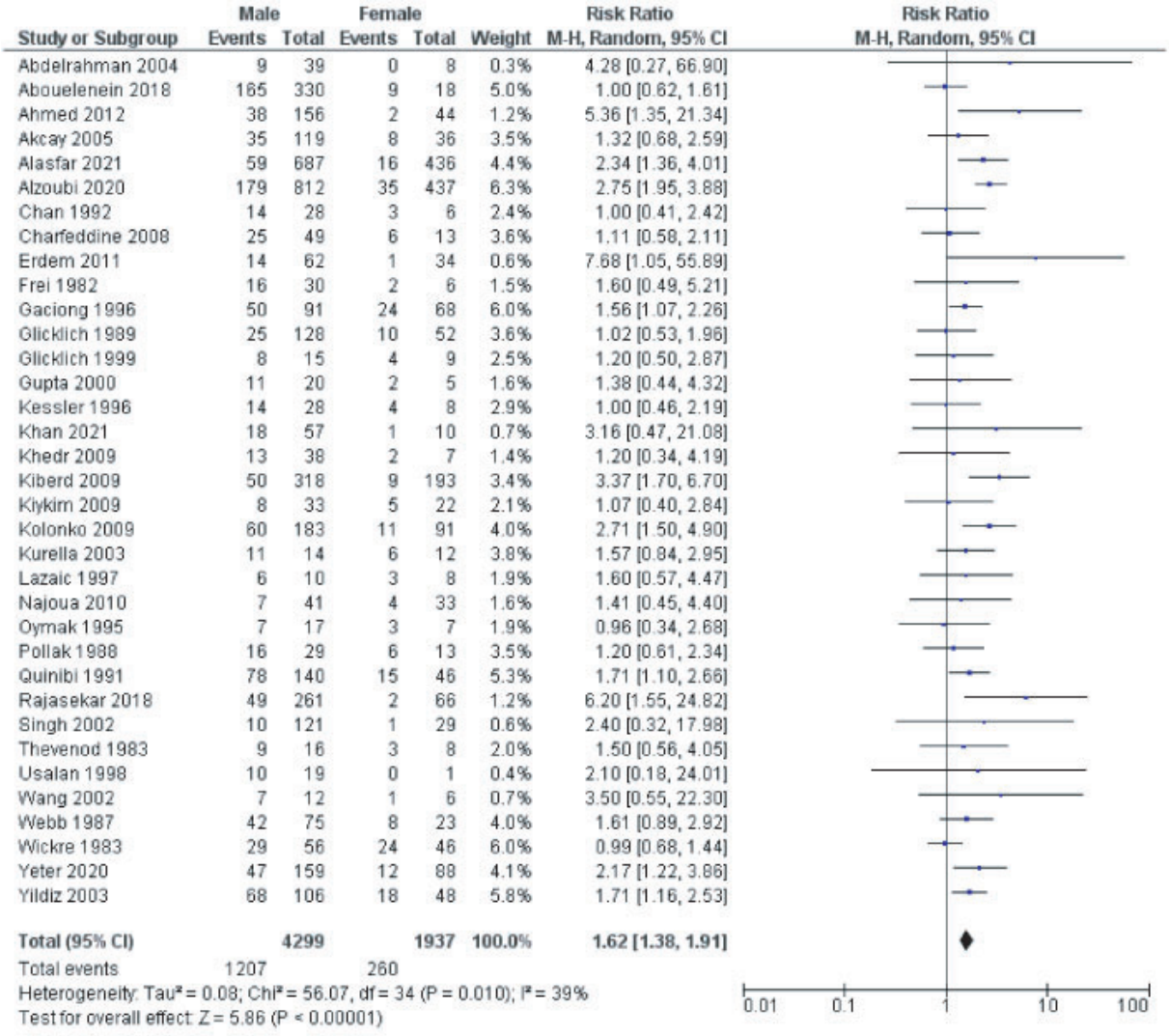
Table 2. Results of pooled risk factors.

Risk factors of interest	Number of studies	Participants	Effect Estimate (M-H, Random)		Study heterogeneity			
			Risk Ratio (95% CI)	*P*-value	$\chi 2$	df	I^2 (%)	*P*-value
Male gender	35	6,236	**1.62 (1.38–1.91)**	**<0.00001**	56.07	34	39	0.01
Decreased-donor KT	17	3,502	**1.18 (1.03–1.35)**	**0.01**	23.44	16	32	0.1
History of smoking	10	1,138	**1.36 (1.11–1.67)**	**0.003**	10.39	9	13	0.32
PKD	16	4,127	**1.56 (1.21–2.01)**	**0.0007**	26.79	15	44	0.03
Glomerulonephritis	19	3,963	1.20 (0.96–1.49)	0.11	34.43	18	48	0.01
Pretransplant DM	11	3,785	1.33 (0.98–1.80)	0.06	17.64	10	43	0.06
Pretransplant hypertension	14	3,865	1.13 (0.88–1.46)	0.34	30.85	13	58	0.004
Pretransplant dialysis	5	1,965	**1.6 (1.02–2.51)**	**0.04**	7.42	4	46	0.12
Pretransplant transfusion	5	697	1.08 (0.79–1.48)	0.62	4.55	4	12	0.34
Previous transplant	4	2,919	0.74 (0.54–1.03)	0.08	1.2	3	0	0.75
Pretransplant ACEI or ARB use	5	792	0.88 (0.54–1.42)	0.6	6.59	4	39	0.16
Alemtuzumab use	3	2,585	0.85 (0.65–1.13)	0.27	1.20	2	0	0.55
Basiliximab use	3	2,585	1.04 (0.87–1.25)	0.68	1.15	2	0	0.56
ATG use	3	2,585	1.14 (0.82–1.57)	0.44	3.67	2	45	0.16
Cyclosporine use	10	3,126	0.90 (0.73–1.11)	0.34	11.17	9	19	0.26
Tacrolimus use	10	3,126	1.11 (0.91–1.36)	0.3	10.56	9	15	0.31
AZA use	5	1,030	1.02 (0.74–1.39)	0.92	4.72	4	15	0.32
MMF use	5	2,133	0.78 (0.54–1.14)	0.2	7.05	4	43	0.13
Transplant RAS	11	839	0.98 (0.67, 1.41)	0.89	4.12	10	0	0.94

ACEI, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blocker; ATG, Anti-Thymocyte Globulin; AZA, Azathioprine; DM, Diabetes mellitus; MMF, Mycophenolate mofetil; PKD, Polycystic kidney disease; RAS, Renal artery stenosis.

Statistically significant values are in bold.

Male Gender



History of Smoking

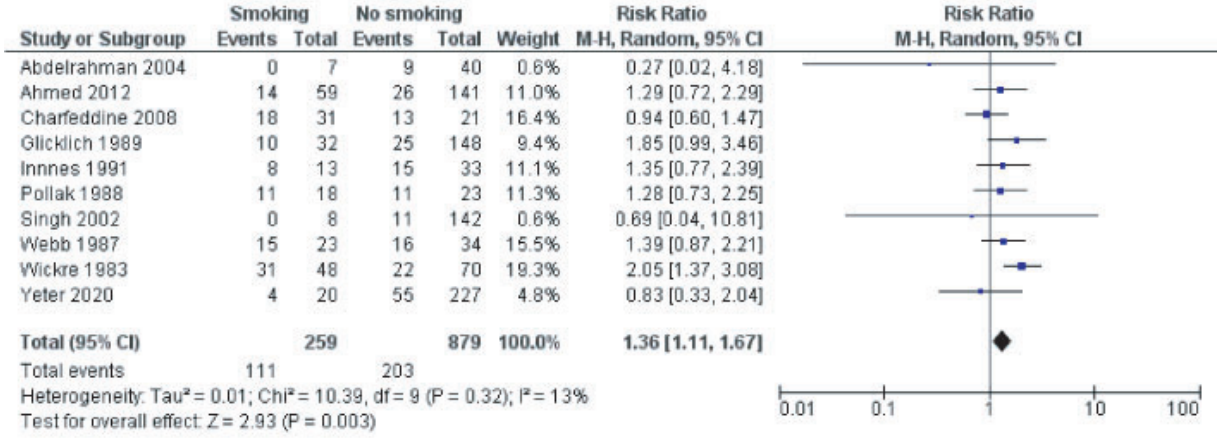


Figure 2 Forest plots of the included studies assessing the association between male gender, history of smoking, and PTE in KT patients.

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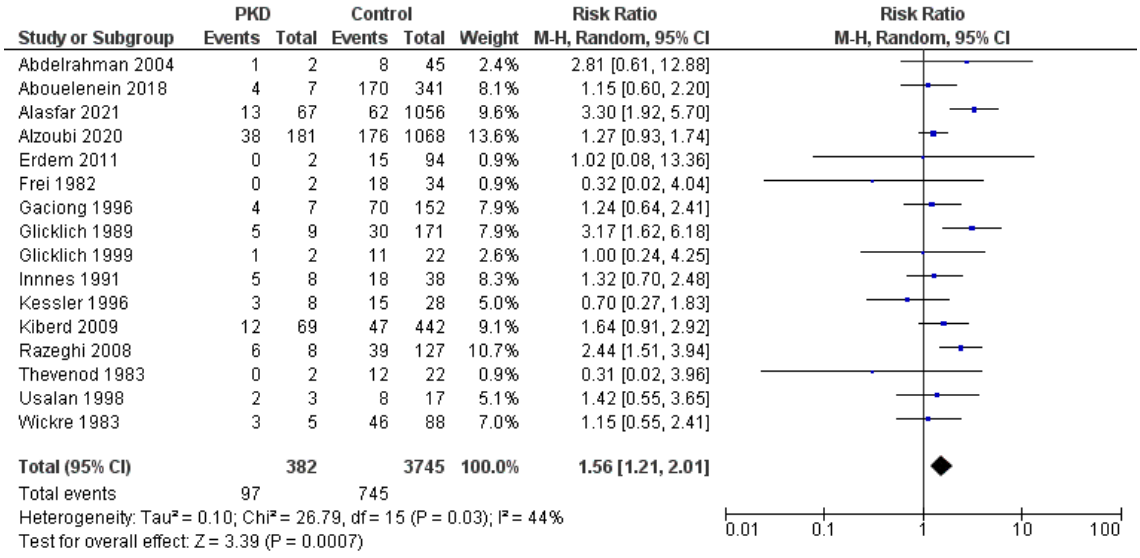
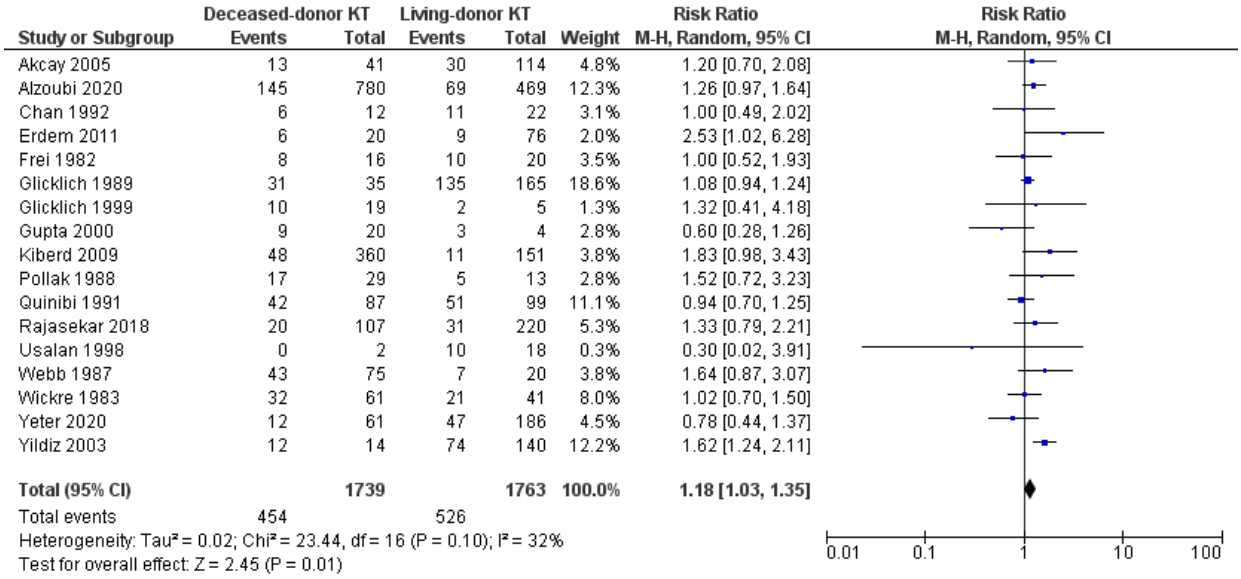
Polycystic Kidney Disease



Deceased Donor Kidney Transplant



Dialysis Prior to Kidney Transplant

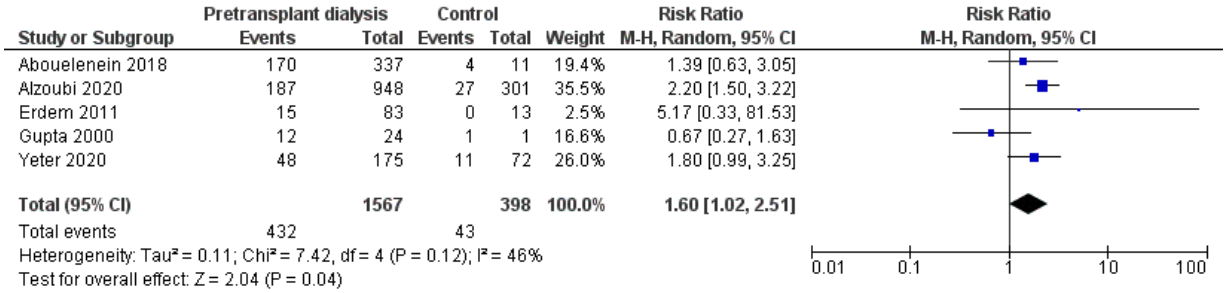


Figure 3 Forest plots of the included studies assessing the association between underlying PKD, deceased donor KT, pretransplant dialysis, and PTE in KT patients.

Table 3. Results of pooled outcomes.

Post-transplant outcomes of interest	Number of studies	Participants	Effect estimate (M-H, Random)		Study heterogeneity			
			Risk Ratio (95% CI)	*P*-value	$\chi 2$	df	I^2 (%)	*P*-value
Thromboembolism	9	2,329	1.65 (0.85–3.19)	0.14	10.68	8	25	0.22
DCGF	4	2,822	0.78 (0.57–1.05)	0.11	4.26	3	30	0.23
Overall mortality	4	2,822	0.79 (0.49–1.26)	0.31	4.4	3	32	0.22

DCGF, Death-censored graft failure.

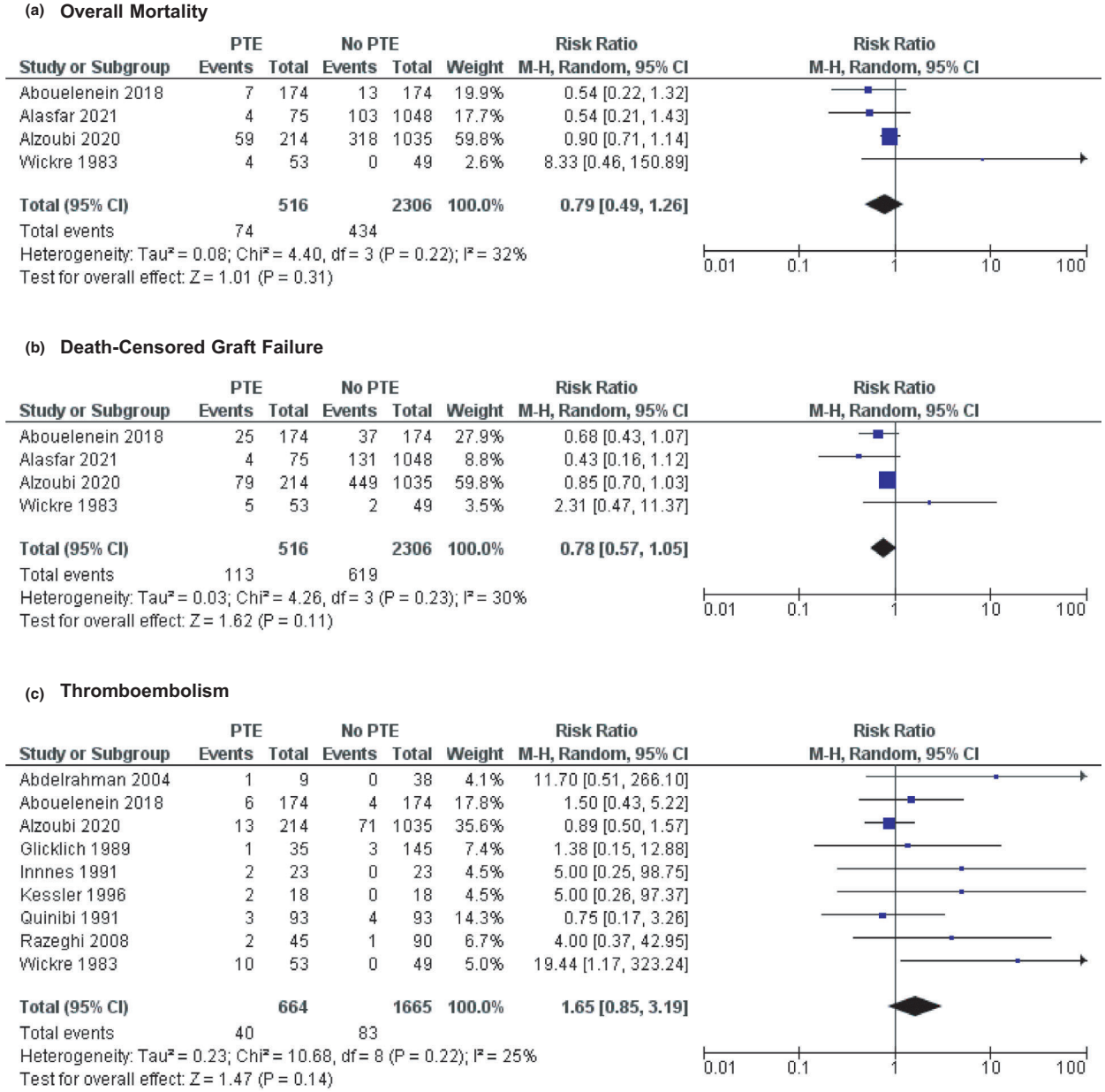


Figure 4 Forest plots of the included studies assessing the association between PTE in KT patients and outcomes of (a) Overall mortality, (b) DCGF, (c) Thromboembolism.

transfusion, and the choice of immunosuppressive medications were also not associated with PTE.

For KT outcomes, there was no statistical significance in the risk of overall mortality, DCGF, and thromboembolism in KT patients with PTE in our analysis. Similar results have been reported in prior studies that PTE did not increase the risk of graft failure and mortality [15,22]. Moreover, a study has even reported improved survival in the patient with PTE [28]. However, there remains some controversy about the risk of thromboembolism among KT patients with PTE, and several studies and case reports showed a significantly higher risk of thromboembolism among PTE patients [46]. However, other studies found that PTE was not associated with venous thromboembolism [6,15,22,37,39]. Gruber *et al.* reported no differences in thromboembolic events between phlebotomized patients and non-phlebotomized patients [55].

The nonsignificant association in the KT outcomes may be because of an excellent response to treatment or good prognosis of PTE in general. As most of the patients included in our studies already received treatment and responded well to treatment with ACEI/ARB [5,67,68], phlebotomy [69], and/or theophylline [70-72]. The other reasons may be because of small sample size or short duration of follow-up.

Up to now, there have not been enough studies of outcomes of untreated patients with PTE. Given good responses and outcomes to treatment in KT recipients with PTE, it is crucial to identify PTE early and treat those patients promptly. Per KIDIGO 2009, they recommend treating all KT recipients with PTE [1]. The target Hgb among patients with PTE is not known but should be less than <17 g/dl (Hct <51%) in both men and women [73]. Initial treatment should be with ACEI or ARB, which can reduce Hct by an absolute value of between 4% and 15% [1,67]. Yildiz *et al.* conducted a randomized study to compare the efficacy of ACEI (enalapril) and ARB (losartan) in the treatment of PTE. They found that enalapril caused a greater decrease but faster relapse in Hgb levels compared with losartan [74]. In the patients with PTE who do not respond to ACEI/ARB or have contraindications or intolerance to ACEI/ARB, second-line therapy such as phlebotomy or theophylline can be considered. Phlebotomy is quite effective for PTE. A study performed by Barenbrock *et al.* showed that phlebotomy could reduce Hct by approximately 10% after two weeks of treatment [69]. Theophylline has also been found to be useful for PTE with absolute reductions in Hct of 8–12% [1]. However, multiple studies have found that theophylline is not as effective as an ACEI [75-77].

Limitations

There are a few limitations in our study. First, this was a meta-analysis of observational studies; we did not demonstrate a causal relationship between risk factors and outcomes in PTE patients. Second, there were heterogeneities in analysis. The heterogeneities were most likely from the difference in demographics, study type, and differences in definitions of PTE in each study. In addition, data on history of malignancy were limited among recipients with PTE and thus future studies are required to assess the impact of history of malignancy on the development of PTE.

Conclusions

In this study, we found that KT recipients with male gender, history of smoking, underlying PKD, deceased-donor KT status, and pretransplant dialysis were more likely to have PTE. However, PTE was not associated with poor KT outcomes, including overall mortality, DGCF, and thromboembolic events. Future research is needed to explore more about the association between PTE and each risk factor.

Authorship

Poemlarp Mekraksakit: Conception design, Data acquisition, Data interpretation, Draft manuscript, Statistic analysis; Boonphiphop Boonpheng: Data acquisition, Draft manuscript, Statistic analysis; Natnicha Leelaviwat: Data acquisition, Draft manuscript; Samapon Duangkham: Draft manuscript; Anasua Deb: Draft manuscript; Jakrin Kewcharoen: Draft manuscript; Kenneth Nugent: Critical reading, Revise manuscript; Wisit Cheungpasitporn: Critical reading, Revise manuscript, Final approval.

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Conflicts of interest

The authors have no conflicts of interest to declare.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Forest plots of the included studies assessing the association between underlying glomerulonephritis,

pretransplant diabetes, pretransplant hypertension and PTE in KT patients.

Figure S2. Forest plots of the included studies assessing the association between transplant RAS, pretransplant transfusion, previous transplant, ACEI or ARB use and PTE in KT patients.

Figure S3. Forest plots of the included studies assessing the association between induction immunosuppressive medications and PTE in KT patients.

Figure S4. Forest plots of the included studies assessing the association between maintenance immunosuppressive medications and PTE in KT patients.

Figure S5. Funnel plots of the significant risk factors of PTE in KT patients. Circles represent observed published studies.

Figure S6. Funnel plots of PTE in KT patients and outcomes of (a) Overall mortality, (b) DCGF, (c) Thromboembolism. Circles represent observed published studies.

Table S1. Newcastle-Ottawa quality assessment scale of included studies in meta-analysis (Cohort Studies).

Table S2. Newcastle-Ottawa quality assessment scale of included studies in meta-analysis (Case-control Studies).

Table S3. Newcastle-Ottawa quality assessment scale of included studies in meta-analysis (Cross-Sectional Studies).

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