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Review article

# Perioperative blood transfusion affects oncologic outcomes after nephrectomy for renal cell carcinoma: A systematic review and meta-analysis

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**Abstract**

*Aim*: To investigate the association of perioperative blood transfusion (PBT) with oncologic outcomes in patients with renal cell carcinoma (RCC), we conducted a systematic review and meta-analysis of the literature to clarify the long-term oncologic effect of PBT in patients undergoing nephrectomy for RCC. *Materials and methods*: We searched the MEDLINE, Web of Science, Cochrane Library and Scopus on 15th April 2018 to identify studies that compared patients who received PBT undergoing radical or partial nephrectomy for RCC to patients who did not with the aim of evaluating its impact on overall mortality (OM), cancer-specific mortality (CSM) and disease recurrence using multivariable cox regression analysis. *Results*: A total of 19,681 patients in 7 studies matched the selection criteria for the systematic review and meta-analysis. All 7 studies were retrospective design and published between 1994 and 2018. **Our study included low quality of eligible studies due to their retrospective design and showed a significant heterogeneity**. PBT was associated with OM (pooled hazard ratio [HR], 1.49, 1.24−1.78), CSM (pooled HR, 1.46, 1.20−1.77), and disease recurrence (pooled HR, 1.80, 1.03−3.12). In a subgroup analysis of 3,664 patients with nonmetastatic RCC, PBT was remained associated with OM (pooled HR, 1.91; 1.06−3.41), but not anymore with CSM (pooled HR, 1.92, 0.94−3.91) or disease recurrence (pooled HR, 2.18, 0.86−5.55). *Conclusions*: PBT in patients undergoing nephrectomy for RCC is associated with worse overall survival. While PBT may be reflective of the underlying aggressiveness of the disease, it could be that its detrimental effect on outcomes is caused by its negative effect on the host's resilience. 

*Keywords:* Blood transfusion; Renal cell carcinoma; Surgery; Clinical outcomes

Key of Definitions for Abbreviations*:* CI, confidence interval; CSM, cancer specific mortality; HR, hazard ratio; PBT, perioperative blood transfusion; RCC, renal cell carcinoma; NOS, Newcastle-Ottawa Scale; OM, overall mortality; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

## 1. Introduction

Renal cell carcinoma (RCC) is associated with approximately 84,400 new cases and leads to 34,700 deaths per year in the European Union countries alone [1]. Standard

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treatment for most RCC is surgical removal of the primary tumor [2]. Despite adequate surgery, 10% to 20% of patients with seemingly localized RCC treated with radical or partial nephrectomy experience local and/or distant recurrence [3,4]. RCC is a highly vascular disease with significant angiogenetic activity leading potentially higher blood loss compared to other diseases [5].

PBT has been associated with worse oncologic outcomes in several malignancies [6-8]. It has been hypothesized that PBT has an immunosuppressive effect, but the definitive mechanism underlying this association has not been uncovered yet [9]. In RCC, Soubra et al. reported, in a population-based study, that PBT was associated with overall mortality (OM) and cancer specific mortality (CSM) in 14,379 patients treated with nephrectomy [10]. Several other studies have provided further evidence on the prognostic value of PBT on RCC outcomes after nephrectomy [11-20]. However, all studies suffer from common limitations such as single center design, small sample size, short follow-up and lack of data regarding confounding factors. No study to date had a prospective controlled design to allow for robust evidence to change clinical practice. We hypothesized that PBT might impact prognosis in patients with RCC after surgical treatment. To elucidate this, we conducted a systematic review and meta-analysis of the literature to survey the association of PBT with oncologic outcomes such as OM, CSM and disease recurrence in patients who had undergone surgical treatment for RCC.

## 2. Materials and methods

A completed PRISMA-P 2015 checklist is shown in the Supplementary table 1 to describe the methodology of our study clearly. The protocol has also been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018096910).

### 2.1. Search strategy

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [21]. We searched the electronic databases MEDLINE, Web of Science, Cochrane Library and Scopus on 15th April 2018 for studies published until March 2018 investigating the impact of PBT on oncologic outcomes in RCC patients treated with nephrectomy. After a first screening based on study title and abstract, all papers were assessed based on full text and excluded with reasons when inappropriate; a further check of the appropriateness of the papers based on full text revision which was performed after data extraction. Two investigators (T.I. and S.K.) carried out this process independently. Disagreements were resolved by a consensus meeting with a third investigator or referring to senior author (SFS). The following keywords were used in our search strategy: ("blood transfusion" OR "perioperative transfusion" OR "blood salvage") and ("renal cell carcinoma" OR "RCC" OR "kidney cancer" OR "renal tumor") and ("radical nephrectomy" OR "partial nephrectomy" OR "RN" OR "PN"). Primary outcomes of our interest were OM, CSM and disease recurrence.

### 2.2. Inclusion and exclusion criteria

Studies were included if they investigated whether patients treated with nephrectomy for RCC (Patients) had received PBT (Intervention) as compared to those who did not (Comparison) to assess the independent predictive value of PBT on OM, CSM and disease recurrence (Outcome) utilizing multivariable Cox regression analysis (Study design) in nonrandomized observational, (or randomize) or cohort studies. We excluded reviews, letters, editorials, meeting abstracts, replies from author, case reports and articles not published in English language. In case of duplicate publications, either the higher quality or the most recent publication was selected.

### 2.3. Data extraction

Two investigators (T.I. and S.K.) independently extracted the information from the included articles. The information contained the following characteristics: first author's name, publication year, recruitment country, period of recruitment, number of patients, age, sex, preoperative hemoglobin, operation type, blood loss, disease stage, follow-up duration, and PBT rate. Subsequently, the hazard ratios (HRs) and 95% confidence intervals (CIs) of PBT associated with each of the outcomes were retrieved. The HRs was extracted from the multivariable analysis. All discrepancies regarding data extraction were resolved by consensus with a third investigator.

### 2.4. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies according to the Cochrane Handbook for systematic reviews of interventions for included non-randomized studies [22]. The scale focuses on 3 factors: Selection (1–4), Comparability (1–2) and Exposure (1–3). The total score ranges from 0 (lowest) to 9 (highest). The main confounders were identified as the important prognostic factors of OM, CSM and disease recurrence after radical or partial nephrectomy. The presence of confounders was determined by consensus and review of the literature. We identified as "high-quality" choices those with scores of more than 6.

### 2.5. Statistical analysis

We performed a forest plot to assess HRs from the multivariable analyses of individual studies and obtained a summary HR of the effect of PBT on mortality and recurrence.

We also performed subgroup analysis in patients with non-metastatic disease only, due to the lack of outcome data in patients with metastatic disease in eligible studies. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated by using Cochrane Q test and $I^2$ statistic. $P < 0.05$ in Cochrane Q test was defined statistically significant. The ratio >50% in $I^2$ statistic, the summary HRs and the 95% CI were calculated with random effects models, whereas these tests were negative for heterogeneity, which led to the use of random-effect models according to the DerSimonian and Laird method. We used fixed effects models for calculation of pooled HRs through the inverse-variance method [23-25]. Publication bias was assessed by funnel plots. Statistical analyses were all performed using Stata/MP 14.2 (Stata Corp., College Station, TX); statistical significance level was set at $P < 0.05$.

## 3. Results

### 3.1. Study selection and characteristics

Our initial search identified 679 records. After removal of duplicates, 450 remained (Fig. 1). After screening the titles and abstracts, 388 articles were excluded. Then, we assessed full texts for selection leaving 7 studies for the qualitative and quantitative evidence synthesis including 19,681 patients.

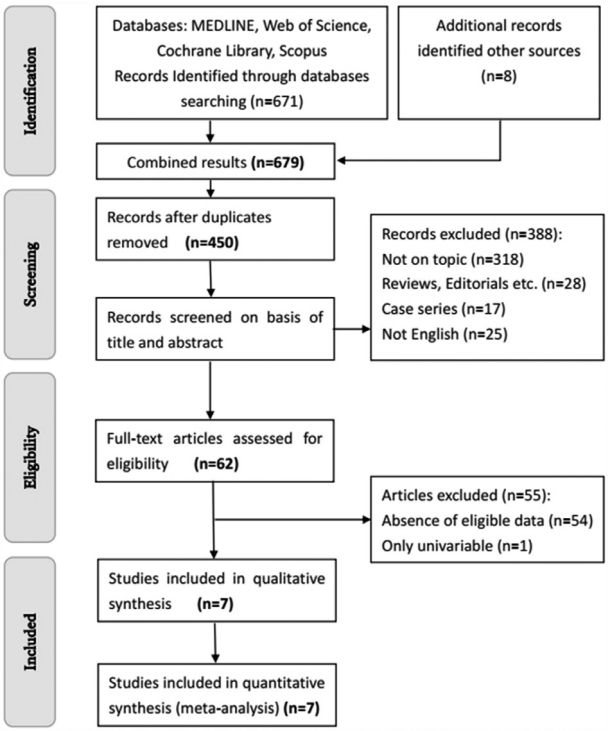


Fig. 1. Flow chart for article selection process to analyze the prognostic significance of perioperative blood transfusion (PBT) on oncologic outcomes in patients with renal cell carcinoma treated with nephrectomy.

The baseline characteristics of the 7 studies are outlined in Table 1. All included studies had a retrospective design and were published between 1994 and 2018 with 3 being from Europe, 3 from North America and 1 from Asia. Overall, 2,866 of the 19,681 (14.6%) patients received PBT. Only one study reported only in patients treated with open radical nephrectomy, the other studies reported in patients treated with RN or partial nephrectomy (PN) by open or minimally invasive approach. Four studies reported PBT rates were 369 of 1671 (22.1%) and 188 of 1064 (17.7%) in RN group and PN group, respectively. Three studies reported PBT rates were 480 of 1611 (29.8%) and 117 of 928 (12.6%) in open group and minimally invasive group, respectively. Preoperative hemoglobin concentration was reported in 2 studies only; in both studies, the preoperative hemoglobin of patients in PBT group was less than those in non-PBT group. Definition of PBT was reported in 3 studies. Two hundred eighty-nine of the 1,638 (17.6%) patients reported preoperative distant metastasis in only 3 studies. The median follow-up duration ranged from 39 to 109 months. Pathological features are summarized in Table 2. Histological subtype was reported in only 3 studies with clear cell histology being present 771 of 926 (83.3%) patients in PBT group and 2,091 of 2,772 (75.4%) in non-PBT group, respectively. Pathological T stage was reported in 5 studies, most studies were likely to more advanced T stage in PBT group. Lymph node metastasis was reported 122 of 1,134 (10.8%) patients in PBT group and 84 of 2,822 (3.0%) patients in non-PBT group, respectively. The NOS in eligible studies ranged from 5 to 8 and its mean number was 6.5, which was relatively low score due to their retrospective design.

### 3.2. Meta-analysis

#### 3.2.1. Association of PBT with OM

Six studies including 19,423 patients provided data on the association of PBT with OM. The forest plot (Fig. 2A) showed that PBT was significantly associated with OM in RCC patients treated with radical or partial nephrectomy (pooled HR, 1.49; 95% CI, 1.24−1.78; z = 4.32). The Cochrane Q test ($Chi^2 = 12.03$; $P = 0.034$) and $I^2$ test ($I^2 = 58.4\%$) showed significant heterogeneity. The funnel plot identified 2 studies over the pseudo 95% CI (Fig. 2A).

#### 3.2.2. Association of PBT with CSM

Seven studies including 19,681 patients provided data on the association of PBT with CSM. The forest plot (Fig. 2B) showed that PBT was significantly associated with CSM in RCC patients treated with radical or partial nephrectomy (pooled HR, 1.46; 95% CI, 1.20−1.77; z = 3.74). The Cochrane Q test ($Chi^2 = 10.46$; $P = 0.107$) and $I^2$ test ($I^2 = 42.6\%$) did not show significant heterogeneity. The funnel plot did not identify any studies over the pseudo 95% CI (Fig. 2B).

Table 1
Characteristics of the eligible studies included in the systematic review.

| Study year | Region | Recruit period | Study design | PBT | N | Age (median) | Sex male (%) | Type of nephrectomy (RN/PN) (%) | Operation approach (Open/Mis) (%) | Preoperative Hb (g/dl) | Blood loss (ml) | Definition of PBT | Preoperative distant metastasis (%) | Follow months (median) | Outcome | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jakobsen 1994 | Denmark | 1977–1988 | R | PBT+ | 208 | 63 | 68.6 | 100/0 | 100/0 | NR | 900 | No | 22.1 | NR | CSM | 5 |
| | | | | PBT− | 50 | 58 | | 100/0 | 100/0 | | 300 | | 18.0 | | | |
| Kopp 2013 | USA | 2002–2012 | R | PBT+ | 33 | NR | 60.0 | 60.6/39.4 | 76.2/33.8 | NR | NR | No | excluded | 41.5 | OM,CSM RFS | 6 |
| | | | | PBT− | 169 | | 69.3 | 60.4/39.6 | | | | | | | | |
| Linder 2014 | USA | 1990–2006 | R | PBT+ | 498 | 67 | 60.0 | 64.4/35.6 | 89.9/20.1 | 11.8 | 878 | Yes | excluded | 109.2 | OM,CSM RFS | 7 |
| | | | | PBT− | 1820 | 63 | 69.3 | | | 14.0 | 200 | | | | | |
| Soubra 2015 | USA | 1992–2009 | R | PBT+ | 1501 | 74 | 53.7 | RN+PN | Open+Mis | NR | NR | No | NR | 39 | OM,CSM | 6 |
| | | | | PBT− | 12878 | | NR | | | | | | | | | |
| Park 2016 | Korea | NR | R | PBT+ | 366 | 59 | 66.9 | 81.2/18.3 | 79.0/21.0 | NR | 800 | No | 19.9 | 42 | OM,CSM RFS | 8 |
| | | | | PBT− | 366 | 59 | 68.3 | 82.5/16.4 | 78.4/21.6 | | 300 | | 18.9 | | | |
| Soria 2017 | Austria | 2004–2014 | R | PBT+ | 62 | 66 | 58.1 | 66.1/33.9 | 75.8/24.2 | NR | NR | Yes | 16.1 | 63 | OM,CSM | 7 |
| | | | | PBT− | 586 | 64 | 67.2 | 56.7/43.3 | 45.4/54.6 | | | | 12.6 | | | |
| Abu−Ghanem 2018 | Israel | 1988–2013 | R | PBT+ | 198 | 68 | 55.1 | 56.1/43.9 | 72.7/27.3 | 12.6 | NR | Yes | excluded | 63.2 | OM,CSM RFS | 7 |
| | | | | PBT− | 961 | 63 | 66.1 | 48.5/51.5 | 60.1/39.9 | 13.8 | | | | | | |

CSM = cancer specific mortality; Hb = hemoglobin; Mis = minimally invasive surgery; NOS = Newcastle-Ottawa score; NR = not reported; OM = overall mortality; PBT = perioperative blood transfusion; PN = partial nephrectomy; RFS = recurrence-free survival; R = retrospective; RN = radical nephrectomy; USA = United States of America.

### 3.2.3. Association of PBT with disease recurrence

Four studies including 4,396 patients provided data on the association of PBT with disease recurrence. The forest plot (Fig. 2C) showed that PBT was significantly associated with disease recurrence in RCC patients treated with radical or partial nephrectomy (pooled HR, 1.80; 95% CI, 1.03−3.12; z = 2.07). The Cochrane Q test ($Chi^2 = 19.24$; $P = 0.000$) and $I^2$ test ($I^2 = 84.4\%$) showed significant heterogeneity. The funnel plot identified one study over the pseudo 95% CI (Fig. 2C).

### 3.2.4. Subgroup analyses

We analyzed studies including exclusively patients with the nonmetastatic RCC; we excluded studies including metastatic RCC patients. Three studies including 3,664 nonmetastatic patients reported the association of PBT with oncologic outcomes. The forest plot (Fig. 3A) showed that PBT was significantly associated with OM in patients with nonmetastatic RCC treated with radical or partial nephrectomy (pooled HR, 1.91; 95% CI, 1.06−3.41; z = 2.17). The Cochrane Q test ($Chi^2 = 10.22$; $P = 0.006$) and $I^2$ test ($I^2 = 80.4\%$) showed significant heterogeneity. The funnel plot identified 2 studies over the pseudo 95% CI (Fig. 3A). The forest plots (Fig. 3B, 3C) did not show any association of PBT with either CSM (pooled HR, 1.92; 95% CI, 0.94 −3.91; z = 1.79) or disease recurrence (pooled HR, 2.18; 95% CI, 0.86−5.55; z = 1.64) in patients with nonmetastatic RCC treated with radical or partial nephrectomy. The Cochrane Q test ($Chi^2 = 7.35$; $P = 0.025$, $Chi^2 = 19.02$; $P = 0.000$) and $I^2$ test ($I^2 = 72.8\%$, $I^2 = 89.5\%$) for CSM and disease recurrence, respectively, showed significant heterogeneity. The funnel plots for the association with CSM did not identify any studies over the pseudo 95% CI (Fig. 3B); for disease recurrence, one study was identified over the pseudo 95% CI (Fig. 3C).

## 4. Discussion

We investigate the association of PBT with oncologic outcomes in RCC patients treated with radical or partial nephrectomy. To the best of our knowledge, our study is the first systematic review and meta-analysis evaluating the association of PBT with oncologic outcomes. We relied on data from 7 published studies with a combined patient population of more than 19,000 patients. PBT was associated with significantly increased risks of OM, CSM and disease recurrence when all RCC patients treated with nephrectomy were evaluated (i.e., both nonmetastatic and metastatic RCC). In our review, only 3 studies reported the rate of patients with distant metastasis and 289 of 1,638 (17.6%) patients had preoperative distant metastasis. In a subgroup analysis of these patients with nonmetastatic RCC, PBT remained associated with an increased risk of OM, but did not retain its association with CSM or disease recurrence. The causes underlying these differential associations are

Table 2
Pathological features of patients of the eligible studies included in the systematic review.

| Study year | PBT | Histological subtype (%) | | | | Stage (%) | | Furman grade (%) | | | | pN1 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Clear cell | Papillary | Chromophobe | Sarcomatoid variant | pT1-2 | pT3-4 | G1 | G2 | G3 | G4 | |
| Jakobsen | PBT+ | | | NR | | 43.3 | 56.7 | | NR | | | 14.8 |
| 1994 | PBT− | | | | | 66.0 | 34.0 | | | | | 14.0 |
| Kopp | PBT+ | 80.7 | 15.5 | 3.7 | 5.9 | 86.6 | 13.4 | 23 | 47.6 | 24.1 | 5.3 | NR |
| 2013 | PBT− | | | | | | | | | | | |
| Linder | PBT+ | 84.9 | 11.2 | 3.8 | 5.2 | 53.8 | 46.2 | 5.8 | 29.7 | 50.0 | 14.7 | 9.4 |
| 2014 | PBT− | 74.5 | 19.2 | 6.3 | 1.1 | 85.9 | 14.1 | 8.5 | 55.5 | 33.0 | 3.0 | 1.5 |
| Soubra | PBT+ | | | NR | | 44.6 | 32.5 | 12.2 | 33.8 | 19.3 | 5.7 | NR |
| 2015 | PBT− | | | | | NR | NR | NR | NR | NR | NR | |
| Park | PBT+ | 82.2 | | NR | 4.7 | 61.2 | 38.8 | 2.9 | 34.3 | 46.3 | 16.5 | 10.4 |
| 2016 | PBT− | 85.0 | | | 4.8 | 62.0 | 38.0 | 2.6 | 34.3 | 46.2 | 16.8 | 9.6 |
| Soria | PBT+ | 75.8 | 14.5 | 9.7 | NR | 51.6 | 48.4 | 6.5 | 64.5 | 24.2 | 4.8 | 3.2 |
| 2017 | PBT− | 72.5 | 18.4 | 9.0 | | 57.8 | 42.2 | 9.7 | 63.0 | 22.0 | 5.3 | 2.6 |
| Abu-Ghanem | PBT+ | | | NR | | 72.2 | 27.8 | 9.7 | 46.0 | 33.5 | 10.8 | NR |
| 2018 | PBT− | | | | | 78.6 | 21.4 | 12.0 | 59.2 | 26.3 | 2.5 | |

NR = not reported; PBT = perioperative blood transfusion.

hypothetical. For example, PBT has been suggested to have detrimental effects on the human immune system such as a suppressive transfusion-related immunomodulation (TRIM). Mechanisms of TRIM include the suppression of cytotoxic cells and monocytes, the inhabitation of interleukin-2 production and increase in suppressor T cell activity [26,27]. In addition, hypoxia-induced factor (HIF), which may be included in preserved allogenic red blood cell products could promote vascular endothelial and platelet-derived growth factors, two powerful modulators of angiogenesis resulting in tumor progression through non-immunogenic mechanisms [28,29]. These explanations for the mechanisms of PBT affecting oncologic outcomes in RCC patients are insufficient, because many studies which proposed these explanations were with animal models and no one mechanism has been identified for this detrimental effect, likely because multiple mechanisms are involved. However, in fact, PBT has been reported to be associated with worse outcomes in other cancers [6,7]. In colorectal cancer, for example, Acheson et al. reported that PBT was associated with significantly higher morbidity and mortality in patients treated with surgery [30]. In bladder cancer, Wang et al. reported that PBT was also significantly associated with OM, CSM and disease recurrence in patients treated with radical cystectomy [31].

Preoperatively identifying patients of an increased risk for PBT may allow optimal prehabilitation with modern blood management strategies. Clinicopathologic characteristics such as performance status, age, preoperative anemia, advanced tumor stage, and pathologic features were shown to predict the need for PBT. Vricella et al. reported that elderly patients and those with comorbidities together with anemia were more likely to receive PBT during radical or partial nephrectomy [32]. Xia et al. reported that preoperative anemia was associated with earlier recurrence and shorter survival after radical or partial nephrectomy for non-metastatic RCC [33]. These and other authors suggested that preoperative anemia predicts tumor aggressiveness [28,33]. Induced HIF from unavoidable PBT can potentially cause an unfavorable prognosis [28,29]. Indeed, Linder et al. found that PBT was significantly related to worse OM after nephrectomy in non-metastatic RCC patients [13]. The data from this meta-analysis, consistent with the body of literature, highlight the association of PBT with worse OM, even in non-metastatic RCC patients.

Predictive models for both patients with metastatic and non-metastatic RCC are widely used for clinical decision making [34,35]. However, there is a non-negligible misclassification and underestimation when using these models are common because of the suboptimal capture of the inherent biological potential of the tumor and its human host [36-39]. Further studies are, however, necessary to standardize PBT as a prognostic factor which help clinical decision making regarding adjuvant therapy, follow up and patient counseling and to investigate the possible mechanisms underlying this persistent association.

The present meta-analysis suffers from limitations. The most important limitation is that all included study designs were retrospective, resulting in reporting, selection, confirmation, and measurement bias. In addition, the variability in operative techniques and patient case mix may have led to additional bias. For example, the studies included in the analysis mostly had the risk of the selection bias of patients' comorbidity and tumor stage which influenced the PBT rates leading to worse oncologic outcomes. Additionally, surgeon's experiences also might introduce a confounder. Moreover, PBT definition was different or not reported in some studies.

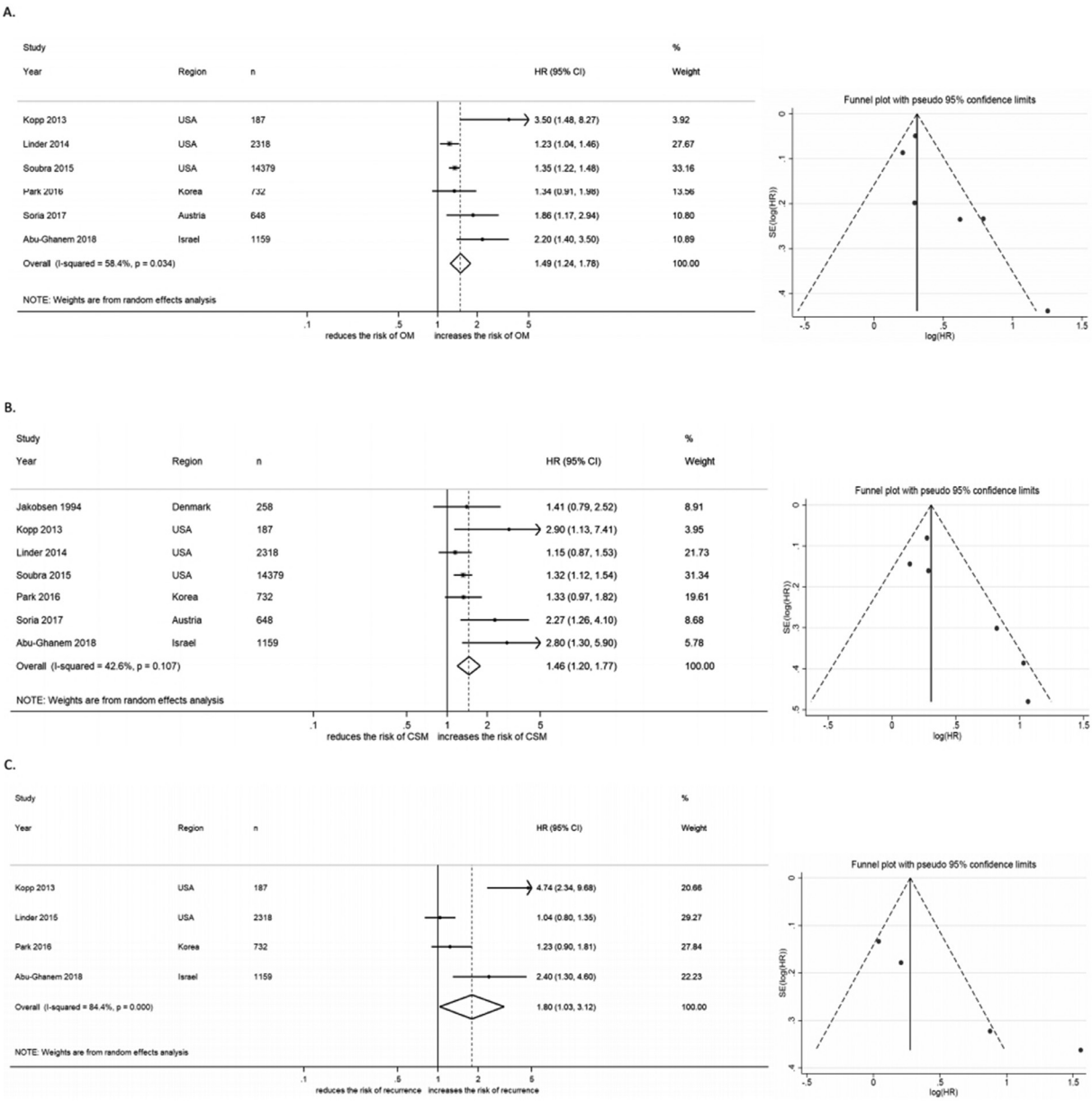


Fig. 2. Forest (left) and funnel (right) plots showing the association of PBT with oncologic outcomes: (A) Overall mortality, (B) cancer-specific mortality and (C) disease recurrence.

Additionally, the decision for PBT was often based on the discretion of the clinician (surgeon and/or anesthesiologist) without an adherence to clear and reproducible criteria for transfusion. Population-based study by Soubra et al. was weighted for a third of the OS and CSM analysis, which affected these results. In the analysis of the effect of PBT on OM, CSM and disease recurrence, a significant heterogeneity was detected. Although the random effect model takes into account the heterogeneity among studies, the conclusions should be interpreted with caution. In our meta-analysis, funnel plots showed asymmetry that might result from the reporting bias or the overestimation of PBT effects on oncologic outcomes in smaller retrospective studies. **Due to small number of included studies with a limited number of patients, we were not able to perform subgroup analysis in each operative approach**. Despite these limitations, we confirmed the impact of PBT on oncologic outcomes in patients who have undergone nephrectomy for RCC. Nevertheless, this can only be construed as hypothesis-generating and further studies are needed to uncover this association of PBT with oncologic outcomes in RCC patients treated with nephrectomy and to develop strategies to counter this detrimental effect.

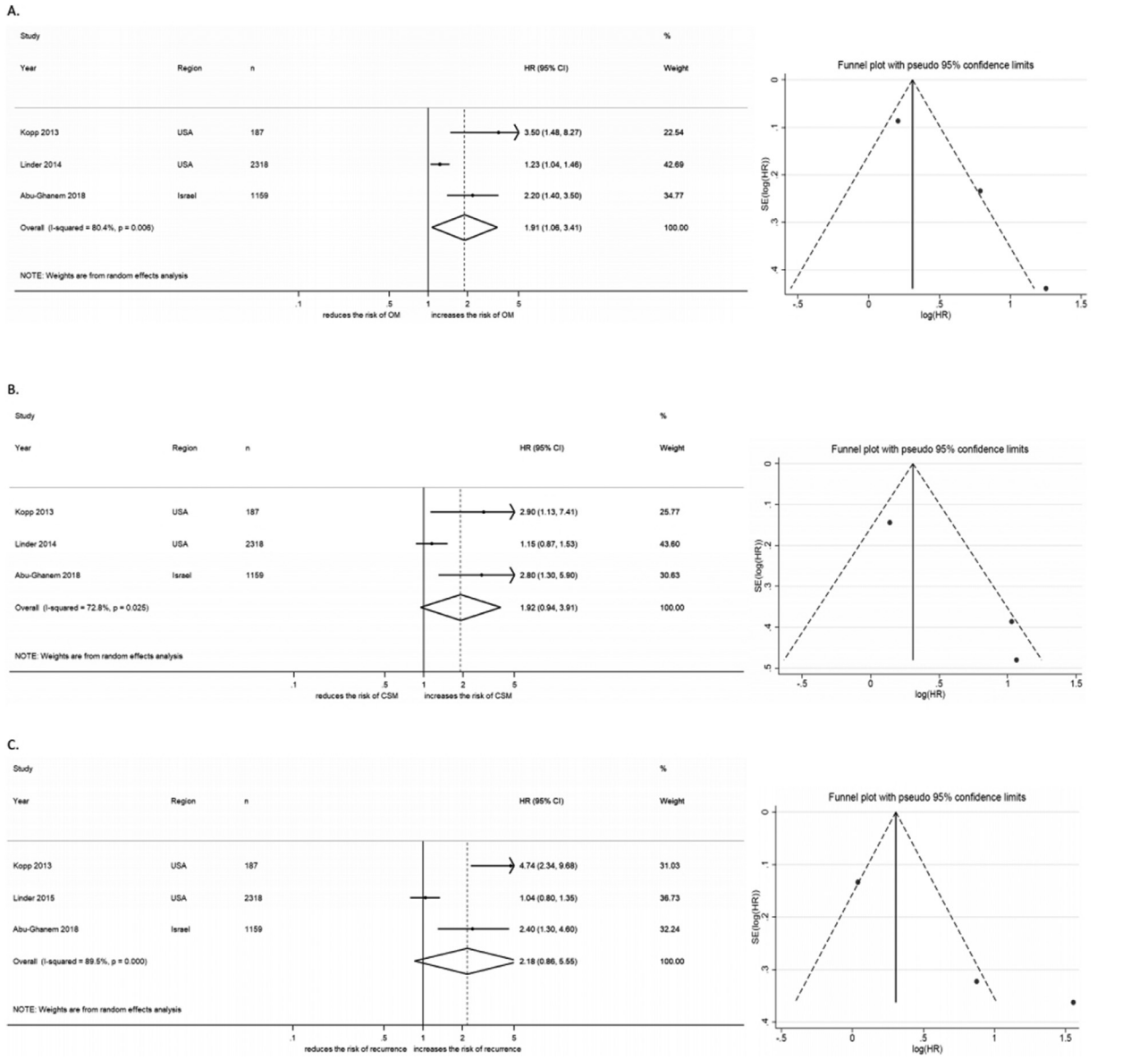


Fig. 3. Forest (left) and funnel (right) plots showing the association of PBT with oncologic outcomes (nonmetastatic group): (A) Overall mortality, (B) cancer-specific mortality and (C) disease recurrence.

## 5. Conclusions

This systematic review and meta-analysis shows that PBT is significantly associated with OM, CSM and disease recurrence in patients treated with **partial or radical** nephrectomy for RCC. In nonmetastatic RCC patients, PBT is significantly associated with OM, but not anymore with cancer specific survival outcomes. **However, current data is low quality and there is significant heterogeneity among included studies. Therefore, our findings should be validated in prospective cohorts**.

## Conflict of interest

No conflict of interest disclosures from any authors.

## Author Contributions

Project development: T Iwata, S Kimura, PI Karakiewicz, F Preisser, Y Nasu, SF Shariat

Data collection: T Iwata, S Kimura, B Foerster

Data analysis: T Iwata, S Kimura, B Foerster, M Abufaraj

Manuscript writing/editing: T Iwata, S Kimura, B Foerster, M Abufaraj, PI Karakiewicz, F Preisser, Y Nasu, SF Shariat.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.018.

## References


[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374–403. Epub 2013/03/15. https://doi.org/10.1016/j.ejca.2012.12.027. PubMed PMID: 23485231.

[2] Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67(5):913–24. Epub 2015/01/27. https://doi.org/10.1016/j.eururo.2015.01.005. PubMed PMID:25616710.

[3] Rieken M, Kluth LA, Fajkovic H, Capitanio U, Briganti A, Krabbe LM, et al. Predictors of cancer-specific survival after disease recurrence in patients with renal cell carcinoma: the effect of time to recurrence. Clin Genitourin Cancer 2018. Epub 2018/04/15. https://doi.org/10.1016/j.clgc.2018.03.003. PubMed PMID: 29653814.

[4] Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. J Clin Oncol 2006;24(19):3101–6. Epub 2006/07/01. https://doi.org/10.1200/JCO.2005.04.8280. PubMed PMID: 16809736.

[5] Richstone L, Reggio E, Ost MC, Seideman C, Fossett LK, Okeke Z, et al. First Prize (tie): hemorrhage following percutaneous renal surgery: characterization of angiographic findings. J Endourol 2008;22(6):1129–35. Epub 2008/05/24. https://doi.org/10.1089/end.2008.0061. PubMed PMID: 18498232.

[6] Wang CC, Iyer SG, Low JK, Lin CY, Wang SH, Lu SN, et al. Perioperative factors affecting long-term outcomes of 473 consecutive patients undergoing hepatectomy for hepatocellular carcinoma. Ann Surg Oncol 2009;16(7):1832–42. Epub 2009/04/15. https://doi.org/10.1245/s10434-009-0448-y. PubMed PMID: 19365625.

[7] Linder BJ, Frank I, Cheville JC, Tollefson MK, Thompson RH, Tarrell RF, et al. The impact of perioperative blood transfusion on cancer recurrence and survival following radical cystectomy. Eur Urol 2013;63(5):839–45. Epub 2013/01/22. https://doi.org/10.1016/j.eururo.2013.01.004. PubMed PMID: 23332883.

[8] Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006(1):Cd005033. Epub 2006/01/27. https://doi.org/10.1002/14651858.CD005033.pub2. PubMed PMID: 16437512.

[9] Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. Blood Rev 2007;21(6):327–48. Epub 2007/09/07. https://doi.org/10.1016/j.blre.2007.07.003. PubMed PMID: 17804128.

[10] Soubra A, Zabell JR, Adejoro O, Konety BR. Effect of perioperative blood transfusion on mortality for major urologic malignancies. Clin Genitourin Cancer 2015;13(3):e173–81. Epub 2015/01/21. https://doi.org/10.1016/j.clgc.2014.12.006. PubMed PMID: 25600760.

[11] Abu-Ghanem Y, Zilberman DE, Dotan Z, Kaver I, Ramon J. Perioperative blood transfusion adversely affects prognosis after nephrectomy for renal cell carcinoma. Urol Oncol 2018;36(1). 12.e5-.e20Epub 2017/10/11. https://doi.org/10.1016/j.urolonc.2017.09.006. PubMed PMID: 28993059.

[12] Kopp RP, Mehrazin R, Palazzi KL, Liss MA, Jabaji R, Mirheydar HS, et al. Survival outcomes after radical and partial nephrectomy for clinical T2 renal tumours categorised by RENAL nephrometry score. BJU Int 2014;114(5):708–18. https://doi.org/10.1111/bju.12580: PubMed PMID: WOS:000344254100016.

[13] Linder BJ, Thompson RH, Leibovich BC, Cheville JC, Lohse CM, Gastineau DA, et al. The impact of perioperative blood transfusion on survival after nephrectomy for non-metastatic renal cell carcinoma (RCC). BJU Int 2014;114(3):368–74. Epub 2014/01/30. https://doi.org/10.1111/bju.12535. PubMed PMID: 24471825.

[14] Park YH, Kim YJ, Kang SH, Kim HH, Byun SS, Lee JY, et al. Association between perioperative blood transfusion and oncologic outcomes after curative surgery for renal cell carcinoma. J Cancer 2016;7(8):965–72. Epub 2016/06/18. https://doi.org/10.7150/jca.15073. PubMed PMID: 27313787; PubMed Central PMCID: PMC4910589.

[15] Soria F, de Martino M, Leitner CV, Moschini M, Shariat SF, Klatte T. Perioperative allogenic blood transfusion in renal cell carcinoma: risk factors and effect on long-term outcomes. Clin Genitourin Cancer 2017;15(3):e421–e7. Epub 2017/01/17. https://doi.org/10.1016/j.clgc.2016.12.002. PubMed PMID: 28089722.

[16] Edna TH, Vada K, Hesselberg F, Mjolnerod OK. Blood transfusion and survival following surgery for renal carcinoma. Br J Urol 1992;70(2):135–8. PubMed PMID: 1393434.

[17] Manyonda IT, Shaw DE, Foulkes A, Osborn DE. Renal cell carcinoma: blood transfusion and survival. Br Med J (Clin Res Ed) 1986;293(6546):537–8. PubMed PMID: 3092905; PubMed Central PMCID: PMC1341310.

[18] Mermershtain W, Eidelberg I, Yusim I, Ariad S, Kaneti J. Perioperative homologous blood transfusion and survival in patients with surgically treated renal cell carcinoma. UroOncology 2003;3(1):23–5. https://doi.org/10.1080/1561095031000135064.

[19] Moffat LE, Sunderland GT, Lamont D. Blood transfusion and survival following nephrectomy for carcinoma of kidney. Br J Urol 1987;60(4):316–9. PubMed PMID: 3690202.

[20] Sui W, Onyeji IC, Matulay JT, Theofanides MC, James MB, DeCastro GJ, et al. Perioperative blood transfusion predicts short term morbidity after nephrectomy. Can J Urol 2016;23(4):8348–55. PubMed PMID: 27544557.

[21] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(7):e1000100. Epub 2009/07/22. https://doi.org/10.1371/journal.pmed.1000100. PubMed PMID: 19621070; PubMed Central PMCID: PMC2707010.

[22] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5. Epub 2010/07/24. https://doi.org/10.1007/s10654-010-9491-z. PubMed PMID: 20652370.

[23] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28(2):105–14. Epub 2006/06/30. https://doi.org/10.1016/j.cct.2006.04.004. PubMed PMID: 16807131.

[24] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7(3):177–88. PubMed PMID: 3802833.

[25] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clin Res ed) 2003;327(7414):557–60. Epub 2003/09/06. https://doi.org/10.1136/bmj.327.7414.557. PubMed PMID: 12958120; PubMed Central PMCID: PMC192859.

[26] Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. Br J Anaesth 2013;110(5):690–701. Epub 2013/04/20. https://doi.org/10.1093/bja/aet068. PubMed PMID: 23599512; PubMed Central PMCID: PMC3630286.

[27] Refaai MA, Blumberg N. Transfusion immunomodulation from a clinical perspective: an update. Expert Rev Hematol 2013;6(6):653–63. Epub 2013/10/31. https://doi.org/10.1586/17474086.2013.850026. PubMed PMID: 24168641.

[28] Clarke H, Pallister CJ. The impact of anaemia on outcome in cancer. Clin Lab Haematol 2005;27(1):1–13. Epub 2005/02/03. https://doi.org/10.1111/j.1365-2257.2004.00664.x. PubMed PMID: 15686502.

[29] Patel HB, Nasir FA, Nash GF, Scully MF, Kakkar AK. Enhanced angiogenesis following allogeneic blood transfusion. Clin Lab Haematol 2004;26(2):129–35. Epub 2004/04/01. https://doi.org/10.1111/j.1365-2257.2004.00589.x. PubMed PMID: 15053807.

[30] Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg 2012;256(2):235–44. Epub 2012/07/14. https://doi.org/10.1097/SLA.0b013e31825b35d5. PubMed PMID: 22791100.

[31] Wang YL, Jiang B, Yin FF, Shi HQ, Xu XD, Zheng SS, et al. Perioperative blood transfusion promotes worse outcomes of bladder cancer after radical cystectomy: a systematic review and meta-analysis. PLoS One 2015;10(6):e0130122. Epub 2015/06/17. https://doi.org/10.1371/journal.pone.0130122. PubMed PMID: 26080092; PubMed Central PMCID: PMC4469696.

[32] Vricella GJ, Finelli A, Alibhai SMH, Ponsky LE, Abouassaly R. The true risk of blood transfusion after nephrectomy for renal masses: a population-based study. BJU Int 2013;111(8):1294–300. https://doi.org/10.1111/j.1464-410X.2012.11721.x:PubMed PMID: WOS:000319520800031.

[33] Xia L, Hu G, Guzzo TJ. Prognostic significance of preoperative anemia in patients undergoing surgery for renal cell carcinoma: a meta-analysis. Anticancer Res 2017;37(6):3175–81. Epub 2017/05/30. https://doi.org/10.21873/anticanres.11677. PubMed PMID: 28551661.

[34] Zisman A, Pantuck AJ, Dorey F, Said JW, Shvarts O, Quintana D, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001;19(6):1649–57. Epub 2001/03/17. https://doi.org/10.1200/jco.2001.19.6.1649. PubMed PMID: 11250993.

[35] Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17(8):2530–40. Epub 1999/11/24. https://doi.org/10.1200/jco.1999.17.8.2530. PubMed PMID: 10561319.

[36] Antonelli A, Cozzoli A, Zani D, Zanotelli T, Nicolai M, Cunico SC, et al. The follow-up management of non-metastatic renal cell carcinoma: definition of a surveillance protocol. BJU Int 2007;99(2):296–300. https://doi.org/10.1111/j.1464-410X.2006.06616.x.

[37] Sun M, Shariat SF, Cheng C, Ficarra V, Murai M, Oudard S, et al. Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol 2011;60(4):644–61. Epub 2011/07/12. https://doi.org/10.1016/j.eururo.2011.06.041. PubMed PMID: 21741163.

[38] Cindolo L, Patard JJ, Chiodini P, Schips L, Ficarra V, Tostain J, et al. Comparison of predictive accuracy of four prognostic models for nonmetastatic renal cell carcinoma after nephrectomy: a multicenter European study. Cancer 2005;104(7):1362–71. Epub 2005/08/24. https://doi.org/10.1002/cncr.21331. PubMed PMID: 16116599.

[39] Heng DYC, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14(2):141–8. https://doi.org/10.1016/s1470-2045(12)70559-4.