

REVIEW

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# Robotic versus open partial nephrectomy in the context of mild severity complications: a meta-analysis of comparative studies supplemented by meta-regression

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## Abstract

**Background** The incidence of mild postoperative complications has been shown to be strongly associated with the beneficial effects provided through minimally invasive surgery. The main objective of the present study was to compare robotic and conventional open partial nephrectomy in terms of the incidence of mild postoperative complications.

**Main body** The literature search process included all the comparative studies identified up to April 2022. Inclusion criteria concerned studies published in English, involving exclusively adult patients with solitary or multiple renal masses, who underwent robotic/robot-assisted or open partial nephrectomy. As mild postoperative complications, were defined those of Clavien–Dindo grade  $\leq$  II. The meta-analysis included a total of 16 studies (3238 patients) and was also supplemented by appropriate subgroup analysis and meta-regression analysis to investigate for any additional sources of heterogeneity. Pooled data analysis revealed a statistically significant advantage with the adoption of the robotic approach ( $_{\text{peto}}\text{OR} = 0.52$ ,  $\text{CI}_{95\%} [0.43; 0.64]$ ), while similar results were obtained from the analysis of the subgroups of studies with or without patient matching, those conducted in a single or multiple centers, as well as those published after 2015. From meta-regression, a time-independent superiority of robotic over open partial nephrectomy emerged, characterized by a tendency to broaden over the years. This finding was attributed to inherent features of robotic technology, the utilization of which is optimized in the context of its wider adoption in current kidney surgery practice.

**Short conclusion** The main conclusion that can be drawn implies the clear superiority on the part of robotic partial nephrectomy over open surgery, in reducing the incidence of mild postoperative complications.

**Keywords** Robotic partial nephrectomy, Open partial nephrectomy, Mild complications, Complication rates, Meta-analysis.

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## Background

The modern trend for the adoption of minimally invasive techniques has been widely accepted with particularly favorable results in several cases of patients in current kidney surgery practice (Lin et al. 2021; Li et al. 2020; Muaddi et al. 2021). With technology developments and the commercial availability spread of robotic systems, a significant number of comparative studies show that robotic or robot-assisted partial nephrectomy (RPN/RAPN) offers comparable postoperative outcomes with those of laparoscopic (LPN). The high-resolution and 3D visualization systems, as well as the multi-joint arms of modern surgical robotic platforms, have been described to allow the treating surgeon to perform precise tissue handling, both during the neoplastic tumor excision and during the renal parenchyma reconstruction. These features theoretically offer clear advantages over the laparoscopic approach. Furthermore, as the experience with the robotic approaches expands, there has been a growing preference for the excision of even larger and anatomically more complex tumors by adopting RPN/RAPN over the conventional open partial nephrectomy (OPN). In the general case, tumor's size and its anatomical characteristics should be meticulously examined preoperatively, in order to clarify the degree of complexity of the upcoming intervention (Garisto et al. 2018).

The complexity of the operation along with the surgical approach may be related to the incidence of mild postoperative complications, i.e., those referring to grades I and II in the Clavien–Dindo classification scale (Dindo et al. 2004; Clavien et al. 2009). Considering the incidence of mild complications as an indicator of the level of surgical precision achieved intraoperatively, we could argue that as a parameter it should be analyzed thoroughly and individually before any connection between the two is made. In the present study, we intend to compare RPN/RAPN and OPN concerning the incidence of minor complications in the immediate postoperative period, in the context of a systematic review and meta-analysis, supplemented by meta-regression analysis. For the purpose of this review, all the available literature was searched for comparative studies in adult populations of patients with small renal masses who underwent robotic or conventional open partial nephrectomy.

## Materials and methods

### Methodology

Briefly describing the outline of the present study, we could divide it into three distinct sections. The first concerns the literature search process and the isolation of a sample of relevant comparative studies, containing data that can be used to obtain an estimate of the comparative effect, between RPN/RAPN and OPN as for the

frequency with which low severity complications occur during the immediate postoperative period. The second involves the qualitative classification of the incorporated studies according to the protocol proposed by the Newcastle—Ottawa scale (NOS) (Cook and Reed 2015), as well as the extraction of the relevant quantitative data required to formulate the outcome of interest, in the context of which the two aforementioned surgical approaches are compared. Finally, the third and last part concerns the meta-analysis of the comparative quantitative data between RPN/RAPN and OPN. At this point, it is worth mentioning that this review was not registered in advance; however, the methodology followed is described clearly and in a step-by-step fashion, while the presentation of the statistical background utilized is performed in an explanatory manner in every section.

### Evidence acquisition

The exploration process of the available international literature in terms of relevant reports took place until April 2022, and appropriate electronic databases were accessed in a systematic manner, in search of comparative studies by utilizing the terms: "open," "robotic," "robot-assisted," "partial nephrectomy." The criteria on the basis of which each evaluated study was incorporated into the final sample of assembled studies include: studies only in the English language, comparative studies examining robotic or robot-assisted partial nephrectomy versus the conventional open approach, comparative studies with useful data in both parts of the comparison for further statistical analysis, and also comparative studies which include cost analysis. On the other hand, the exclusion criteria refer to studies that are not in English, studies that were retrieved only in the form of a summary or reports without the accompanying data or the necessary text, non-comparative studies, comparative studies with insufficient data for further statistical analysis, and studies which include data for only one part of the comparison. Finally, those comparative studies that included pediatric patients or patients with a solitary kidney were also excluded. "PubMed," "CENTRAL" and "Google Scholar" databases were the main source of the required frequentist data. The full search strategy is clearly presented in Additional file 1: Table S1. The "EndNote X7®" software (Eapen 2006; Gotschall 2021) was used as an automatic bibliography search engine and also as a references manager, while the reporting of the present study was carried out according to the PRISMA statement checklist (Moher et al. 2009; Amir-Behghadami and Janati 2021), as specified in the relevant recommendations of the EQUATOR network (Simera et al. 2010; Catalá-López et al. 2019; Banno et al. 2019). After the successful formation of the initial sample of studies, two reviewers on an independent basis

(SA, DA) undertook the implementation of the eligibility criteria, which was carried out in the online graphical environment of the "Sysrev" (Bozada et al. 2021) platform (<https://sysrev.com/u/8078/p/119881>). Subsequently, data curation along with the extraction of numerical data followed, only from those studies that meet the eligibility criteria. The exported data were kept in two different records in the same database. An appropriately formatted Excel file (.xlsx) was utilized as a database, available in csv format at: <https://github.com/sotbike/TB5> and named as: "mildcomp.csv". After both evaluators had completed the process, cross-evaluation was used as the finalizing step, to assess for the existence of any deviations. In such a case any differences were resolved with the intervention of a third evaluator (IS). Uniformly, the outcome sought was that of mild postoperative complications defined as those of grade less than or equal to II in the Clavien–Dindo classification. Data recording was carried out in the form of frequencies in terms of the entire patient population analyzed by each study. In the event that frequentist data were available separately for Clavien–Dindo grades I and II, then we proceeded to calculate the cumulative frequencies for the outcome of interest. Additional variables that were captured, concern statistically significant differences in baseline characteristics between patient populations under comparison, as well as specific parameters corresponding to mild complications, in those cases in which these were clearly described. After obtaining the final sample of studies to be analyzed, the quality evaluation process through the NOS followed, which was conducted by two evaluators (SA, IS) on an independent basis, with the definitive rating of each study emerging as the average of the two. Within this framework, the included studies were categorized according to their baseline characteristics and design.

### Statistical analysis

The main part of our computational investigation corresponds to the process of meta-analysis for the final set of studies retrieved from the international literature. As stated previously, the incidence of mild complications after robotic or robot-assisted partial nephrectomy versus conventional open surgery was thoroughly analyzed. These complications refer to grades I–II according to the Clavien–Dindo classification scale (Dindo et al. 2004; Clavien et al. 2009). As it becomes apparent, the parameter of interest practically represents a discrete variable and therefore for the estimation of the overall effect from each approach, the odds ratio (OR) was utilized as the effect size of the meta-analysis. The selection of OR as the effect size was made based on some of its further advantages over the relative risk (RR) (Bakbergenuly et al. 2019), as well as its ability to respond adequately, under

the  $\text{peto}$  OR form, in the event of zero frequencies for specific events (Efthimiou 2018; Bohning et al. 2021). More specifically, the  $\text{peto}$  method was preferred for the determination of OR over the corresponding Mantel–Haenszel (MH) approach, due to the, in general, more compact estimates it provides (Kaya et al. 2021; Smolinsky 2019; Webb et al. 2020). Since the present investigation constitutes an in-deep single-variable analysis, a compact table of the studies that were considered eligible for inclusion was formed, in which both their individual characteristics and significant differences are presented. In addition, no missing data were observed, while no conversions of measurement units were required, since the extracted data essentially describe frequencies. The last column of the above table also includes the results when comparing robotic and open partial nephrectomy from each individual study, while after data synthesis is completed, the extracted results are tabularized separately.

The open-source "R" programming language (Berry et al. 2021) along with the "OriginPro<sup>®</sup>" modeling software (Seifert 2014) were used to complete the required computational procedures. Heterogeneity assessment (Du et al. 2022), was performed via the statistical parameters of Cochran's Q (Hoaglin 2016; Migliavaca et al. 2022) and Higgins  $I^2$  (Migliavaca et al. 2022; Ruppap 2020; Spineli and Pandis 2020). In particular, Q is defined as the weighted sum of squares of the standard deviations of the estimates provided by each study, for the comparative effect of each approach on the respective outcome, while  $I^2$  expresses the percentage of between-study variation (inter-study variation), due to heterogeneity and not to gross randomness. When accessing the heterogeneity level in each forest plot, the result of the statistical inference regarding the presence or not of significant heterogeneity is expressed, which is reflected by the p value in the lower and left part of the respective diagram. Specifically for  $p \leq 0.05$ , the presence of statistically significant heterogeneity was assumed, concerning the particular subset of studies that describes the comparative effect between the robotic and open approach for partial nephrectomy as for the outcome of interest. On the contrary, for  $p > 0.05$  we considered that there is no significant heterogeneity, and consequently we preferred to adopt a fixed effects model (FE) in the process of determining the overall effect. In this model, it is assumed that there is a variation of the comparative effect only at the study level (intra-study variation), which stems from the sampling process in the population under investigation. In this case, any variation between the results of different studies is attributed to simple chance and is not modeled. On the other hand, in case of substantial heterogeneity, then a random

effects model (RE) was to be adopted. In this model, the inter-study variation is added to the aforementioned variance and is denoted by:  $\tau^2$ . The main difference in the latter model compared to the former is that it provides a wider confidence interval which makes it more conservative in terms of statistical inference. The DerSimonian and Laird method of moments (Jackson et al. 2010; George and Aban 2015) was predetermined to be used for the estimation of  $\tau^2$  in case of substantial heterogeneity. Only in case of excessively high heterogeneity (above 60%), was it decided in advance to apply sensitivity analyses. This particular methodology involves removing from the original set of studies those that appear to be responsible for the high rate of heterogeneity, and then permits re-analyzing the data and comparing the modified results with the basal level of pooled outcomes.

Upon further investigation for heterogeneity, meta-regression analysis was also implemented, by utilizing the year of publication from every assembled study as a sole moderator. This process contributed to the formation of appropriate time series, in which the annual evolution of the overall comparative effect from both RPN/RAPN and OPN, concerning the comparative incidence of mild complications following PN, was graphically represented. In this section, the overall effect was analyzed at the level of subgroups as well, to investigate for any additional qualitative sources of heterogeneity. The graphs that were generated by the procedure described above represent the selected effect size on the logarithmic scale, denoted as:  $\log(\text{petoOR})$ . Their main concern involved an optimal understanding of the presence of either an emerging trend of dominance, or an already established advantage of one approach over the other, regarding the outcome of interest in each case.

Publication bias was assessed through appropriate funnel plots and radial plots, but also through the Egger's test (Lin and Chu 2018; Spineli and Pandis 2021; Mathur and VanderWeele 2021), which was graphically embedded into the above diagrams in the form of a regression line.

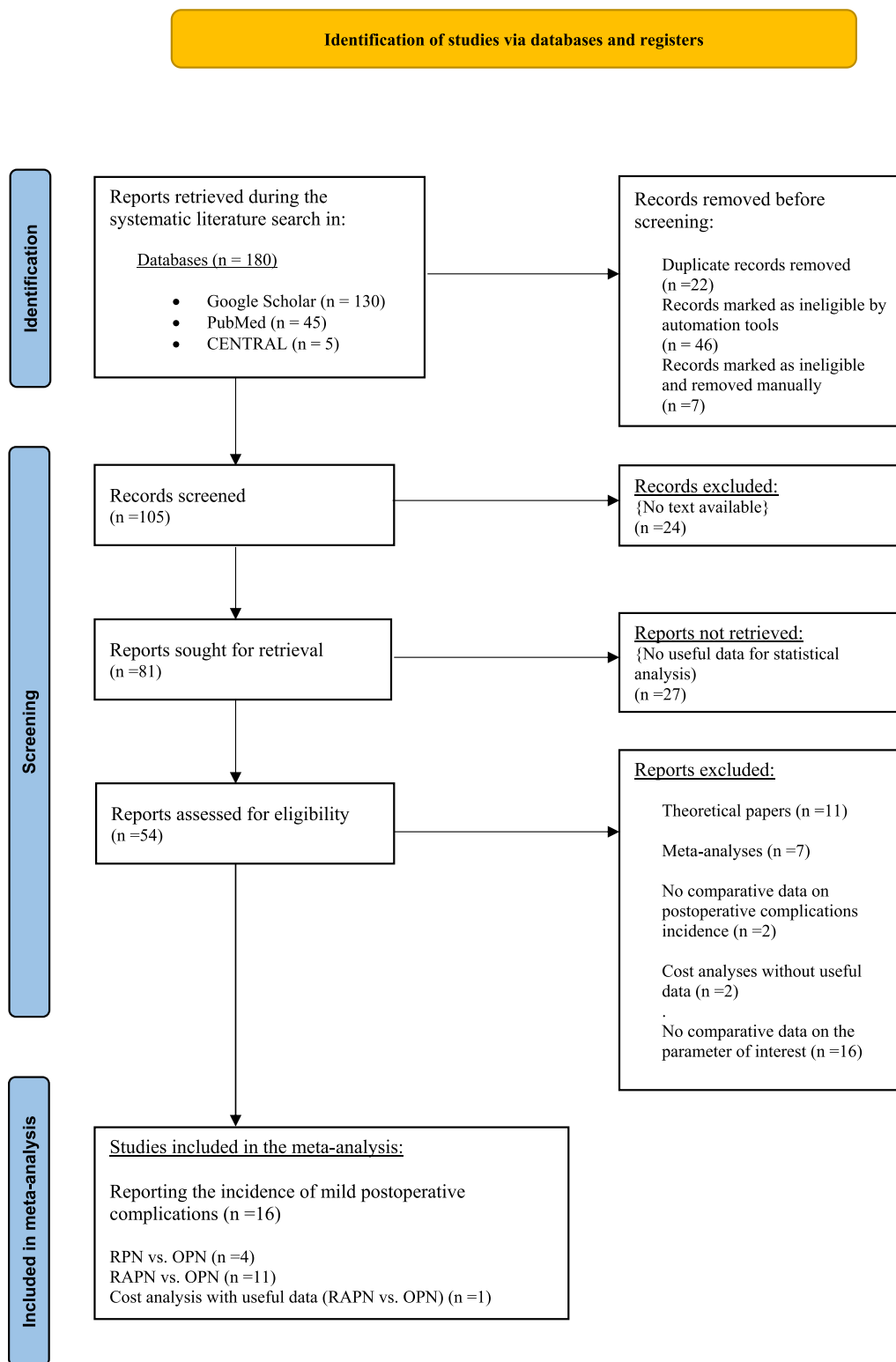
Finally, it is worth noting that our analysis was performed both at the level of aggregate data and at the level of subgroups. The above process was initiated only after the division of the pooled sample of included studies based upon whether any kind of patient characteristics matching was implemented, whether they were conducted by a single or multiple referral centers, and lastly whether they were published before or after 2015. Notably, all results from the analyses above are presented with a confidence level of 0.05, as the effects size ( $\text{petoOR}$ ) and its 95% confidence interval ( $CI_{95\%}$ ).

## Results

### Study retrieval and quality assessment

The literature search included all available comparative studies until April 2022. This process resulted in a total of 180 reports, of which 130 were retrieved from the "Google Scholar," 45 from the "PubMed," and 5 from the "CENTRAL" databases, respectively. Of this initial set of reports, 22 were excluded as duplicates, 46 were excluded due to incompatibility of their title with automated means, and 7 were excluded due to incompatibility of their title after a relevant evaluation by the authors. The above procedure resulted in 105 relevant reports toward the evaluation of their content. Of these, 24 were excluded due to unavailable text, resulting in a total of 81 reports with available text for further evaluation. The text from 27 of them was not retrieved, since it did not contain usable statistical data and therefore these reports were excluded, resulting in 54 relevant reports with available text and usable statistical data. Of this set, 11 studies were excluded since they were not comparative, 7 were excluded as meta-analyses, 2 were excluded as they did not contain comparative data on postoperative complications incidence, and lastly 2 were excluded as they reported comparative data only on the effect of each approach on patients' hospitalization costs. Finally, 16 more studies were excluded as they did not report frequentist data on our parameter of interest. The resulting set of 16 studies included 3238 patients and it was further analyzed in the 3rd step of the procedure we followed, which concerns the meta-analysis of the observed frequentist data. These data refer to the occurrence or non-occurrence frequencies of non-severe postoperative complications, both in the experimental arm (RPN/RAPN) and in the control arm (OPN) of each study. Comparability between cases and controls in the final sample of studies isolated was considered sufficient, without missing individual studies with more targeted patient populations.

The step-by-step recovery of the final sample of studies that forms the backbone of the analysis we performed is summarized in the flowchart of Fig. 1 based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Page et al. 2020a, 2020b). Table 1 includes the 16 studies that were integrated into the meta-analysis and at the same time highlights their individual characteristics, such as data on the author, year of publication, duration in days, patient populations, number of quality stars obtained during the evaluation through the Newcastle–Ottawa Scale (NOS) (Cook and Reed 2015), and data on the methodology that each one of them followed. Figure 2a shows the contribution rates from each country in the total of studies that were finally incorporated into the analysis, both at the



**Fig. 1** Flowchart of studies according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)



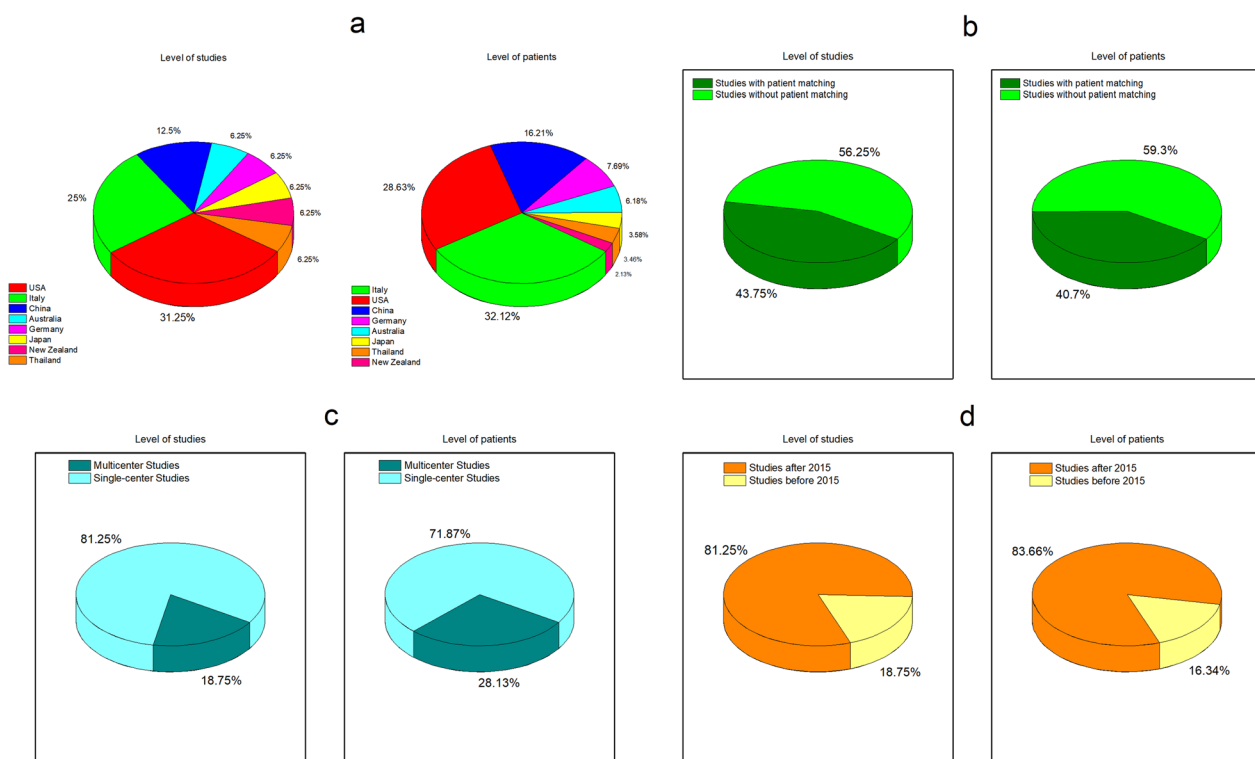












**Fig. 2** Pie charts describing at the level of both studies and patients the percentage distribution according to: **a.** country of origin, **b.** patient characteristics matching, **c.** number of contributing referral centers, **d.** bilevel publication period prior and post-2015

study and at the patient levels. From the above diagram, it becomes apparent that the main body of data had as country of origin the USA, Italy and China, with a cumulative percentage of 70% at the level of studies, and about 77% at the level of patients. Additional file 2: Figure S1 presents the above contribution rates in the form of a map chart, where the representativeness of the final sample of assembled studies becomes apparent at an international level. Figure 2b shows the percentages of studies based upon whether any kind of matching among patient characteristics was applied prior to the statistical analysis procedure. From this diagram, it appears that the final sample was relatively balanced in terms of patient matching. Figure 2c presents the corresponding percentages of those studies that were performed either by a single or by multiple referral centers. This diagram shows that more than 75% of the available data at both study and patient levels were related to single-center studies. Figure 2d reveals the percentages of those studies that were published before or after 2015. From this graph, it appears that at both levels, more than 80% of the available data came from studies published after 2015. The selection of this year, as a cutoff value for the formation of the above graph, was made on the basis that the beginnings of the adoption of the robotic approach for partial nephrectomy

operations are placed around 2009, which results in 2015 to divide the period from 2009 until today into two equal time frames (Morrell et al. 2021). Finally, as already mentioned, the structure of the present study was formed based on the PRISMA checklist, provided as Additional file 3: Table S2.

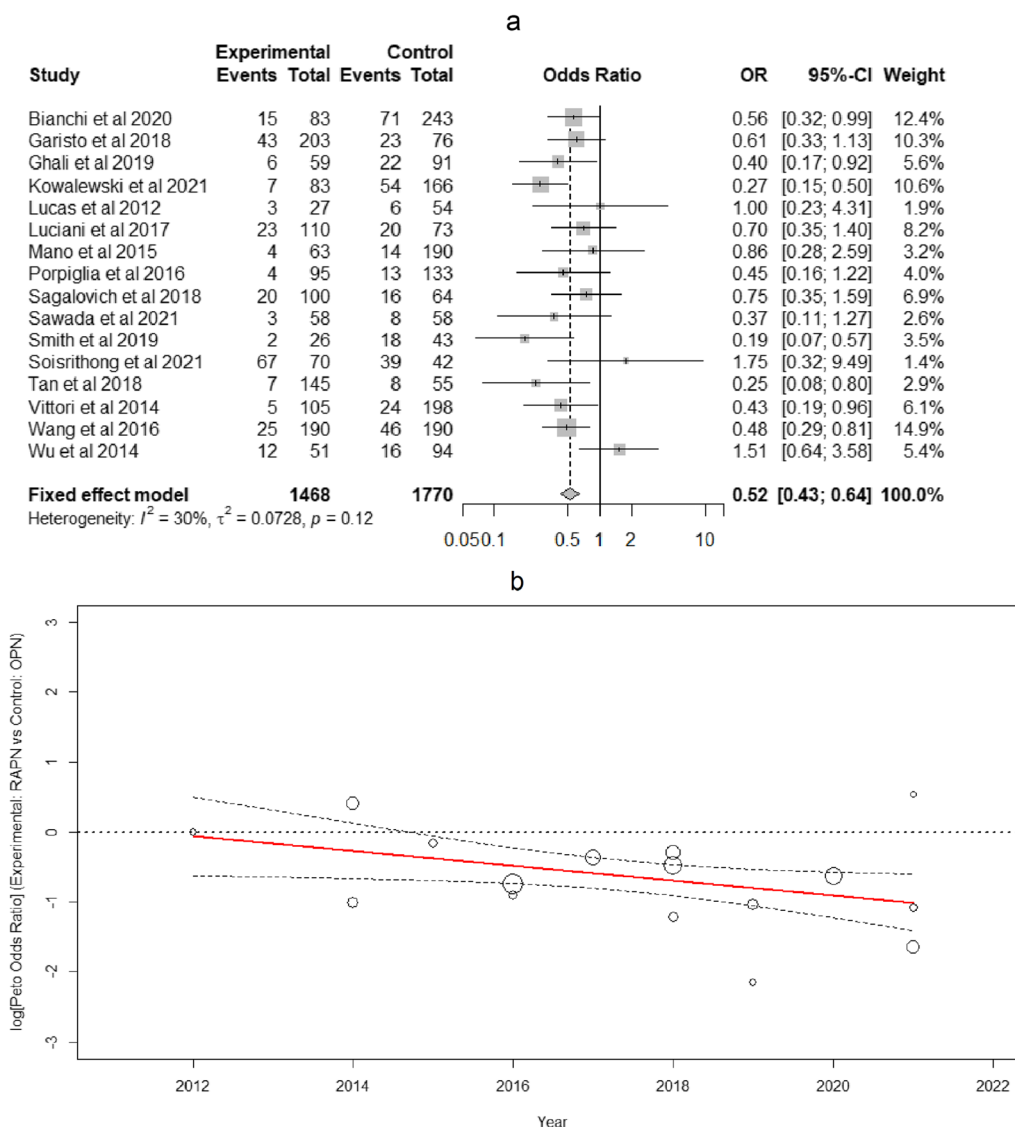
**Meta-analysis and subgroup analysis**

In this section, the results from the meta-analysis procedure are presented, which included all the available data retrieved from the set of 16 comparative studies that emerged from the international literature research. Regarding the parameter of interest, represented by the incidence of mild postoperative complications, the heterogeneity assessment begins at the level of aggregated studies. After determining the amount of heterogeneity, as estimated through Cochran’s Q and Higgins I<sup>2</sup>, then the appropriate model (i.e., fixed or random effects model) is selected to perform the meta-analysis. Subsequently, the estimation of the comparative effect from all available studies follows, in the form of a forest plot, through the effect size of  $_{\text{peto}}\text{OR}$  along with its 95% confidence interval (CI<sub>95%</sub>). In the next step subgroup analysis is performed, to determine any possible contribution of qualitative differences among the assembled studies,

regarding the presence of additional heterogeneity. Also in this case, the comparative effect emerging from each subgroup is described in the form of a forest plot. Each diagram of this type includes the results from each individual study as well as those after the data synthesis, and both procedures described above are supplemented by meta-regression analysis. Finally, the relevant investigation as for the significance of publication bias is presented with the aid of a funnel plot, while the resulting

Egger’s test is depicted in the form of a regression line incorporated into the corresponding radial plot.

From the aggregate data reported by the 16 studies included, during the heterogeneity exploration it emerged:  $I^2=30\%$ ,  $p=0.12$  and for this reason, a fixed effects model was utilized. Figure 3a shows the forest plot for the overall effect, which turned out to be:  $_{\text{peto}}\text{OR}=0.52$ , with 95% confidence interval:  $\text{CI}_{95\%}: [0.43; 0.64]$ . Based on this result, it becomes apparent that



**Fig. 3 a:** Pooled analysis forest plot under the fixed effects model, showing a statistically significant reduction in the odds for mild complications in robotic compared to the open approach ( $_{\text{peto}}\text{OR}=0.52$ ,  $\text{CI}_{95\%} [0.43; 0.64]$ ). **b:** Corresponding meta-regression analysis bubble plot and regression line, along with its 95% confidence interval, depicting the annual change in the overall estimate of the effect in log scale. This graph demonstrates a statistically significant difference between the two approaches that is progressively expanding beyond 2014. According to this finding, patients undergoing robotic partial nephrectomy are less prone to the development of mild postoperative complications (CD: I and II) compared to those undergoing conventional open surgery, with the relative benefit becoming larger and larger over the years. Abbreviations: CD: Clavien–Dindo classification of postoperative complications

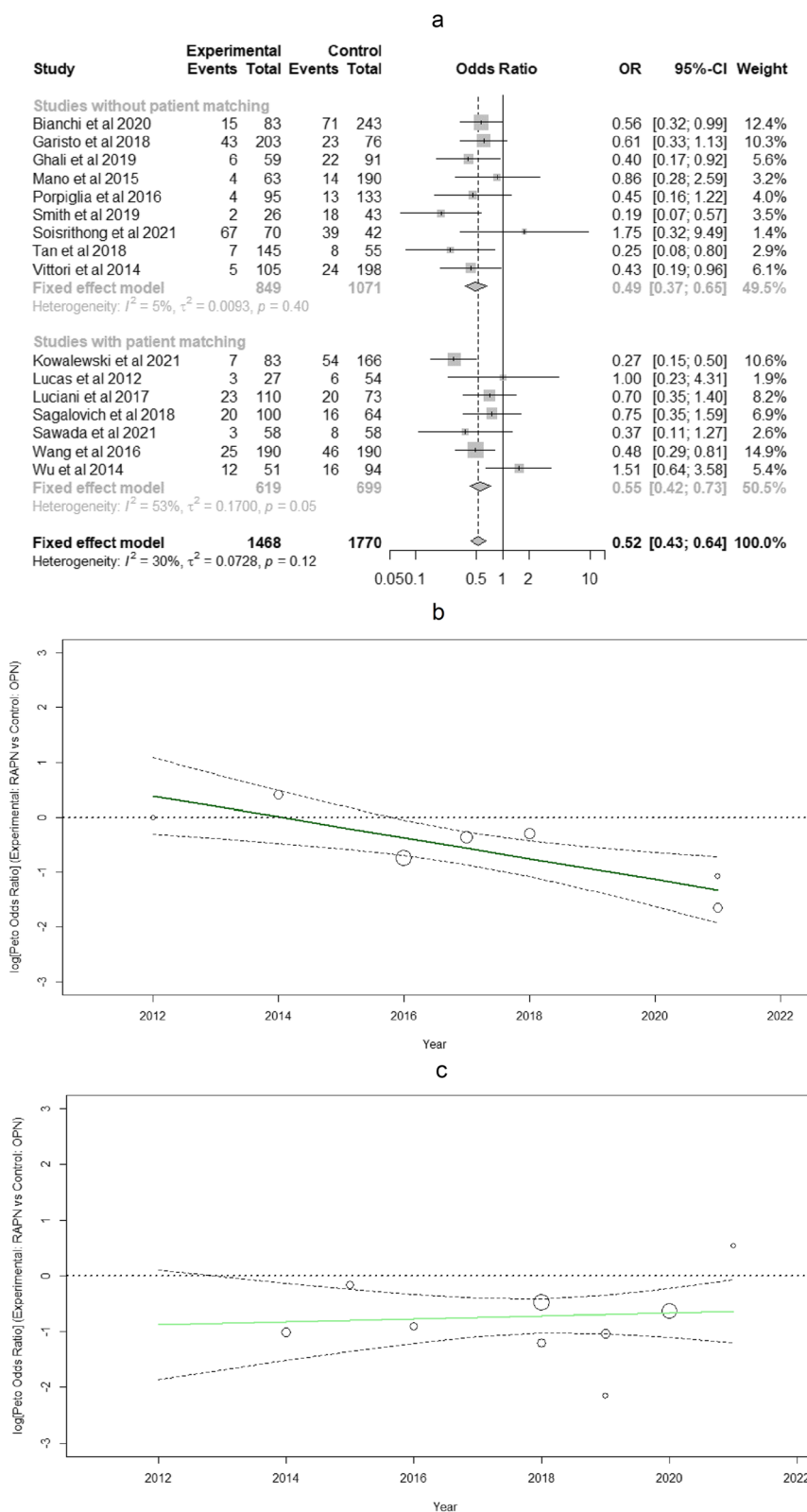
RPN/RAPN has a clear advantage over OPN as for the incidence of mild postoperative complications. From the pooled data meta-regression analysis, the relevant diagram presented in Fig. 3b was produced, depicting the regression line that corresponds to the change in the comparative effect between the two approaches, in terms of the incidence of mild postoperative complications over the years, from 2012 to 2021. In this diagram, each included study corresponds to a circle with radius proportional to the weight of its participation in shaping the final comparative effect. In particular, it becomes apparent that  $\log_{\text{peto}}(\text{OR})$  varies linearly from the value corresponding to its point of intersection with the horizontal axis of equivalence ( $\log_{\text{peto}}(\text{OR}) = 0 \Rightarrow \text{petoOR} = 1$ ) in 2012, to a value around: -1 in 2021. This graph reveals the formation of a temporally expanding advantage of RPN/RAPN over OPN in terms of the incidence of mild postoperative complications, which becomes statistically significant from 2015 and onwards. Regarding the quality level of the pooled studies analyzed in this section, Table 1 reveals an overall quality (average NOS rating) of 7.125/9 (79.17%), which can be considered quite satisfactory given that they were not randomized. Additionally, a number of observations relating to specific qualitative differences can be also drawn from the above table. Initially, it becomes apparent that there were no differences as for patients' baseline characteristics, in 6 out of the total of 16 studies (37.5%). Small differences in nephrometry scores between the compared populations were found in 3 of the 16 studies (18.75%). Significant differences concerning the type or duration of ischemia applied intraoperatively, were observed in 5 of the 16 studies (31.25%). Potentially deviating differences in baseline characteristics of the population groups under comparison emerged in 4 of the 16 studies (25%). Finally, statistically significant differences in the incidence of mild postoperative complications when comparing RPN/RAPN vs. OPN were observed in 4 of 16 studies (25%). The first conclusion that can be drawn from the above findings has to do with the satisfactory level of quality of the set of studies analyzed, a fact that is aligned with the low rate of heterogeneity ( $I^2 = 30\%$ ). This is also the reason why no further sensitivity analyses were subsequently performed. The second conclusion underlines

the usefulness of the meta-analysis methodology, as only 25% of the studies are compiled with the final result of the pooled analysis, which supports the significant benefit provided by the robotic approach in terms of the incidence of mild postoperative complications. In this very case, the meta-analysis proved to be capable of providing a robust result.

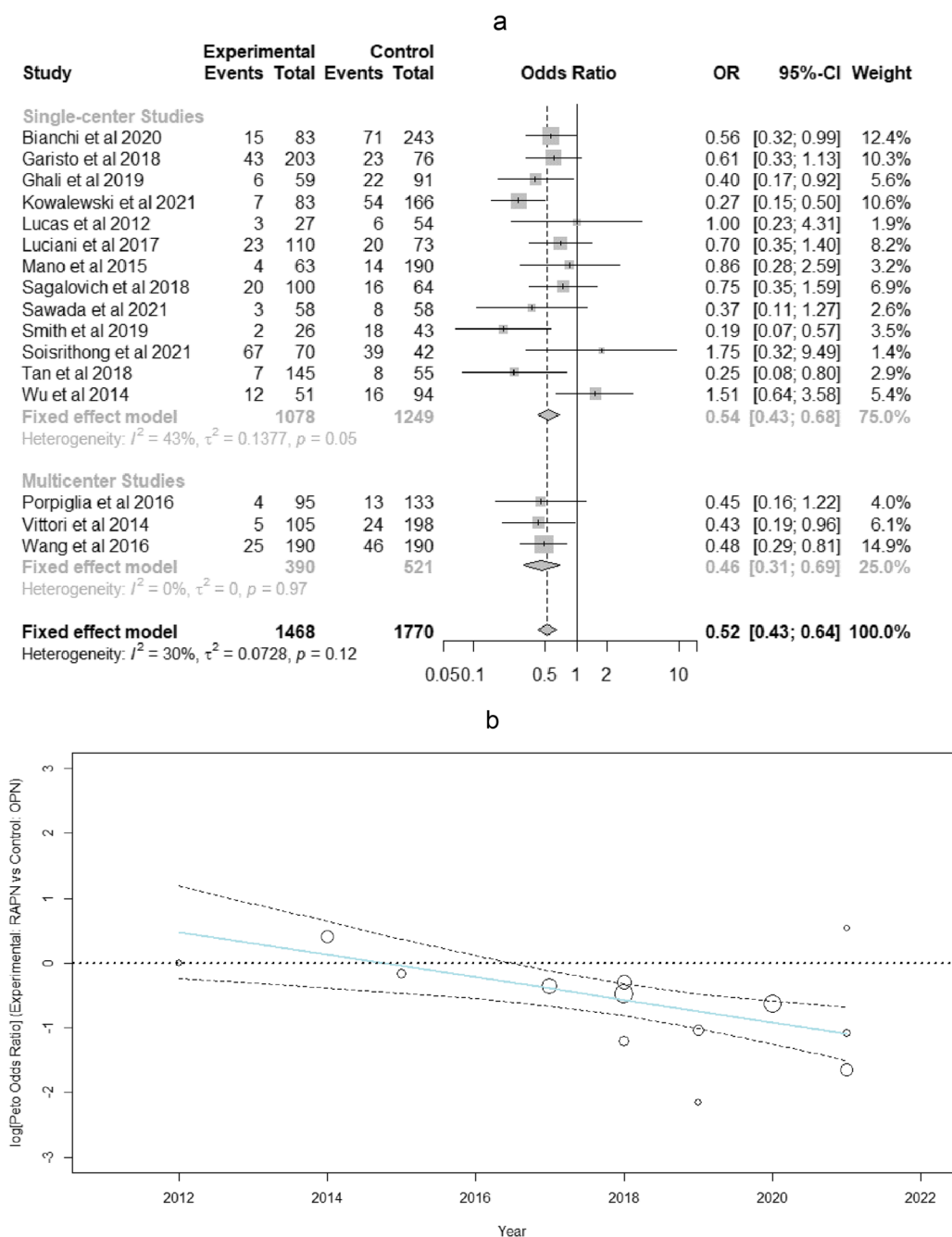
With the aim of investigating any additional source of heterogeneity, the results from the subgroup analysis are presented below. Specifically, in Fig. 4a follows the forest plot of subgroup analysis based on whether any type of patient characteristics matching was applied. From the analysis of the relevant studies with patient matching ( $n = 7$ , average NOS rating: 80.95%), it emerged:  $I^2 = 53\%$ ,  $p = 0.05$ ,  $\text{petoOR} = 0.55$ , with  $CI_{95\%}: [0.42; 0.73]$ , while for those studies in which no kind of patient matching was implemented ( $n = 9$ , average NOS rating: 77.78%), it resulted:  $I^2 = 5\%$ ,  $p = 0.40$ ,  $\text{petoOR} = 0.49$ , with  $CI_{95\%}: [0.37; 0.65]$ , without a statistically significant difference between them. When reviewing the results, it becomes apparent that in both subgroups, RPN/RAPN is associated with the statistically significant advantage of lower incidence of mild postoperative complications compared to OPN. Figure 4b shows the straight line of meta-regression analysis, for those studies that did apply some sort of patient characteristics matching protocol. Specifically in this graph, the change of  $\log_{\text{peto}}(\text{OR})$  occurs linearly from the value +0.2 in 2012 to the value -1.1 in 2021. In this case as well, there is a temporally expanding advantage of RPN/RAPN over OPN regarding the incidence of mild postoperative complications, which becomes statistically significant from 2016 and onwards. On the other hand, Fig. 4c shows the straight line of meta-regression analysis, for those studies that did not apply any kind of patient characteristics matching. In this case, the  $\log_{\text{peto}}(\text{OR})$  regression line transits from the value -0.9 in 2014 to the value -0.5 in 2021. This graph supports that the statistically significant advantage offered by RPN/RAPN over OPN, remains almost constant over the years, while its significance is achieved from 2014 and onwards. Subsequently, in Fig. 5a follows the forest plot of subgroup analysis based on whether the studies were conducted and completed by a single or multiple referral centers. From the analysis of the relevant studies carried out in an

(See figure on next page.)

**Fig. 4 a:** Forest plot under the fixed effects model stratified by whether any method for patient characteristics matching was utilized in each study. The subgroup analysis demonstrates a statistically significant reduction in the odds for mild complications in robotic compared to the open approach in both subgroups (for the studies without patient matching:  $\text{petoOR} = 0.49$ ,  $CI_{95\%}: [0.37; 0.65]$ , and for the studies with patient matching:  $\text{petoOR} = 0.55$ ,  $CI_{95\%}: [0.42; 0.73]$ ). **b:** Meta-regression analysis bubble plot and regression line, along with its 95% confidence interval, for the overall estimate of the effect in log scale, by year, and for the subgroup of studies with patient matching. This graph demonstrates a statistically significant difference between the two approaches that is progressively expanding after 2015, in favor of the robotic approach. **c:** Corresponding meta-regression analysis bubble plot for the subgroup of studies without patient matching. According to this graph, patients undergoing robotic partial nephrectomy are less prone to the development of mild postoperative complications, while the relative benefit seems to remain almost time constant. Abbreviations: CD: Clavien–Dindo classification of postoperative complications



**Fig. 4** (See legend on previous page.)



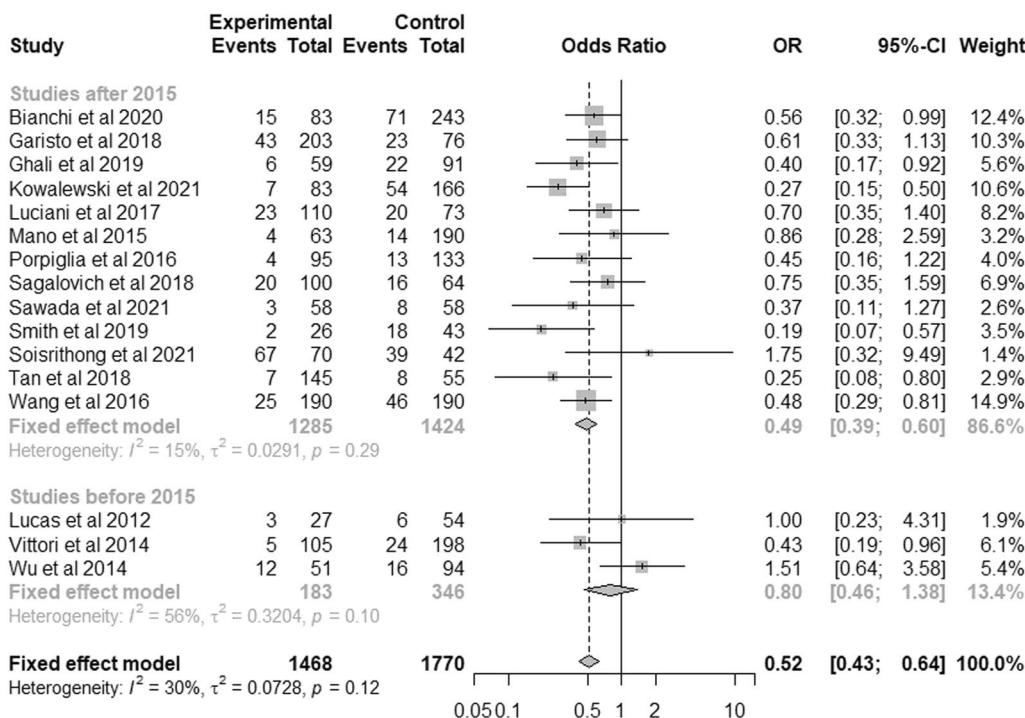
**Fig. 5 a:** Forest plot under the fixed effects model for the subgroup analysis based on whether each study was performed by a single or multiple centers. A statistically significant reduction in the odds for mild complications in robotic compared to the open approach is demonstrated in both subgroups (for the single-center studies:  $_{\text{peto}}OR = 0.54$ ,  $CI_{95\%}: [0.43; 0.68]$ , and for the multicenter studies:  $_{\text{peto}}OR = 0.46$ ,  $CI_{95\%}: [0.31; 0.69]$ ). **b:** Meta-regression analysis bubble plot and regression line, along with its 95% confidence interval, for the annual change in the overall estimate of the effect in log scale, referring to the single-center studies. This graph demonstrates a statistically significant difference between the two approaches that is progressively expanding after 2016. According to this finding, patients undergoing robotic partial nephrectomy are less prone to the development of mild postoperative complications (CD: I and II) compared to those receiving open surgery, with a relative benefit that is broadening over the years. Abbreviations: CD: Clavien–Dindo classification of postoperative complications



individual center (n = 13, average NOS rating: 75.21%), it emerged:  $I^2 = 43\%$ ,  $p = 0.05$ ,  $_{\text{peto}}\text{OR} = 0.54$ , with  $\text{CI}_{95\%}$ : [0.43; 0.68], while for the multicenter studies (n = 3, average NOS rating: 96.29%), it emerged:  $I^2 = 0\%$ ,  $p = 0.97$ ,  $_{\text{peto}}\text{OR} = 0.46$ , with  $\text{CI}_{95\%}$ : [0.31; 0.69], without a statistically significant difference between them. The analysis of the results showed that in both subgroups, RPN/RAPN is associated with the statistically significant advantage of lower incidence of mild postoperative complications compared to OPN. Figure 5b reveals the straight line of meta-regression analysis, for those studies performed by a single referral center. More specifically,  $\log(\text{petoOR})$  changes linearly in this case between the values: +0.2 in 2012 and -0.9 in 2021. In this diagram, the statistically significant advantage of RPN/RAPN over OPN in reducing the incidence of mild postoperative complications appears to be expanding over the years, with statistical significance being achieved from 2017 and onwards. At this point, it is worth noting that since the main body of available data refers to studies conducted by a single center (13/16), the diagram described above does not differ significantly from the one depicting the temporal change in the overall effect (Fig. 3b). This is also the reason why no meta-regression analysis was performed for the subgroup of multicenter studies, as it included only

3 data points (i.e., studies) (Harrer et al. 2021). Finally, in Fig. 6 follows the forest plot of subgroup analysis based on whether the publication year concerned the period before or after 2015. The analysis of the relevant studies published after 2015 (n = 13, average NOS rating: 76.92%) showed:  $I^2 = 15\%$ ,  $p = 0.29$ ,  $_{\text{peto}}\text{OR} = 0.49$ , with  $\text{CI}_{95\%}$ : [0.39; 0.60], while for the studies published before 2015 (n = 3, average NOS rating: 88.89%), it emerged:  $I^2 = 56\%$ ,  $p = 0.10$ ,  $_{\text{peto}}\text{OR} = 0.80$ , with  $\text{CI}_{95\%}$ : [0.46; 1.38], without a statistically significant difference between them. Of the aforementioned subgroups of studies, only those published after 2015 describe a statistically significant benefit from RPN/RAPN over OPN, in terms of the incidence of mild postoperative complications.

Based on the above findings, we can divide the individual subgroups into two main clusters depending on the level of heterogeneity. The “low heterogeneity” cluster consists of the subgroups of the multicenter studies (n = 3,  $I^2 = 0\%$ ), those without patient matching (n = 9,  $I^2 = 5\%$ ), and those conducted after 2015 (n = 13,  $I^2 = 15\%$ ). By carefully examining the results from each subgroup, their agreement on the statistically significant superiority of RPN/RAPN over OPN becomes apparent, as well as the direct connection between the magnitude of provided benefit and the progression of time.

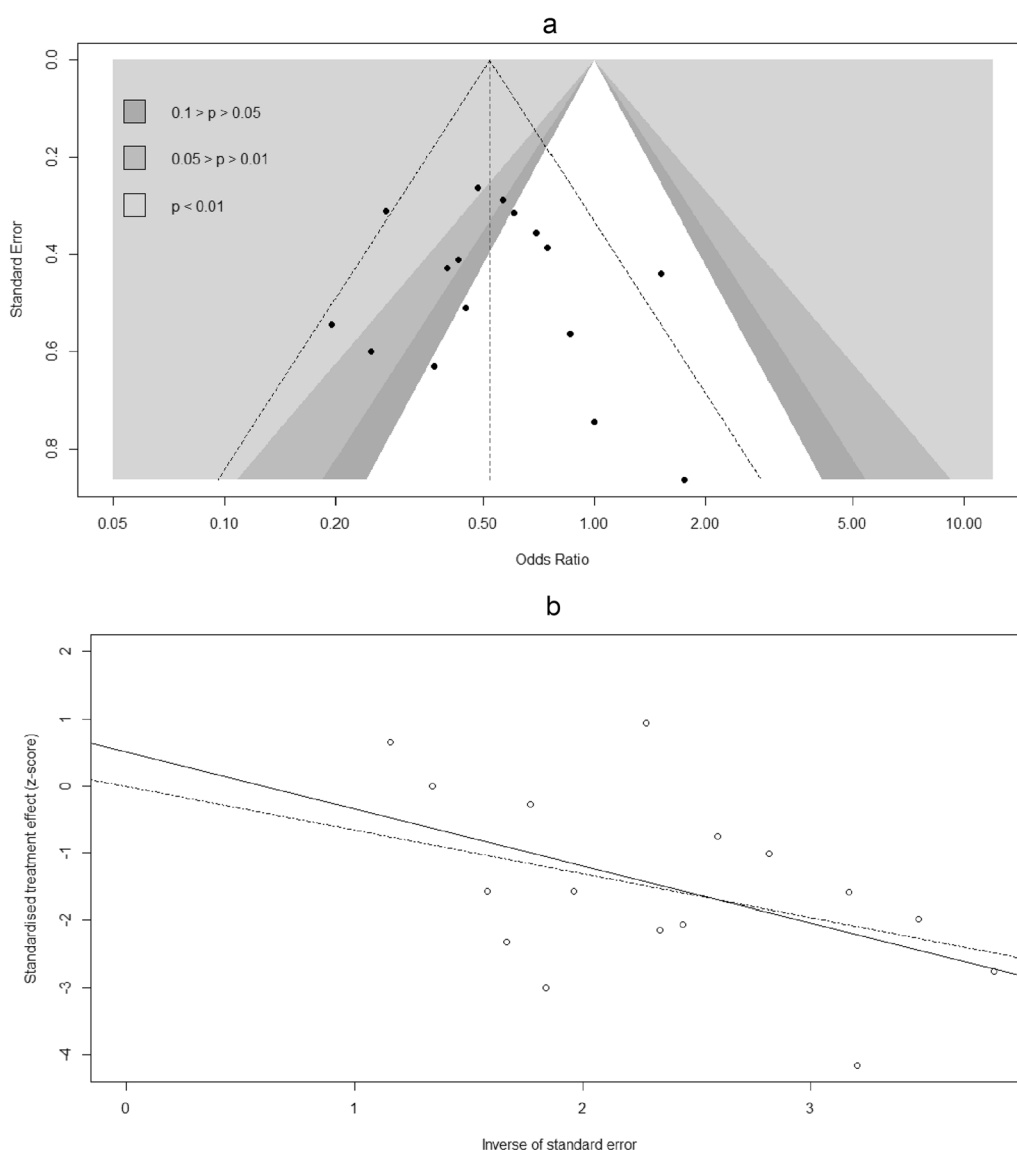


**Fig. 6** Forest plot under the fixed effects model for the subgroup analysis based on whether each study was published before or after 2015. The subgroup analysis demonstrates a statistically significant reduction in the odds for mild postoperative complications (CD: I and II) in robotic compared to the open approach only for those studies published after 2015 ( $_{\text{peto}}\text{OR} = 0.49$ ,  $\text{CI}_{95\%}$ : [0.39; 0.60]). Abbreviations: CD: Clavien–Dindo classification of postoperative complications

In the “high heterogeneity” cluster belong the subgroups of the single-center studies ( $n=13$ ,  $I^2=43\%$ ), those with patient matching ( $n=7$ ,  $I^2=53\%$ ), as well as those conducted before 2015 ( $n=3$ ,  $I^2=56\%$ ). This body of studies is observed to be in discordance with each other, concerning the temporal evolution of the benefit provided by robotic partial nephrectomy, but also on the very basis of its statistical significance.

When accessing publication bias, the funnel plot shown in Fig. 7a emerged, including appropriately placed zones of statistical significance, to easily

distinguish those studies that report the presence of a significant difference when comparing RPN/RAPN with OPN, in terms of the incidence of mild postoperative complications. By reviewing the symmetry of this diagram, but also as shown in Fig. 7b, which indirectly represents the result of Egger’s test in the form of a radial plot, it becomes apparent that the presence of publication bias does not seem to be substantial. Based on the above, it becomes evident that the possibility of risk of bias due to missing results in the pooled set of studies is particularly low.



**Fig. 7 a:** Funnel plot under the fixed effects model, with contours for the different levels of statistical significance, for the included sample of studies, demonstrating the absence of substantial publication bias due to adequate symmetry around the overall estimate of the  $_{\text{peto}}\text{OR}$ . **b:** Radial plot under the fixed effects model, demonstrating the absence of significant deviation of our studies’ regression line (dashed line through the origin) from the included regression line for the Egger’s test (solid line)

**Table 2** Summary of results from the meta-analysis of the 16 studies included

Parameter/model	Method	Pooled studies	Studies with patient matching	Studies without patient matching	Single-center studies	Multicenter studies	Studies published after 2015	Studies published before 2015
CD ≤ II (n = 16) FE	MA	0.52 [0.43; 0.64] There is a resulting formation and expansion of an advantage provided by the robotic over the open approach, which becomes statistically significant from 2015 and onwards	0.55 [0.42; 0.73] There is a resulting formation and expansion of an advantage provided by the robotic over the open approach, which becomes statistically significant from 2016 and onwards	0.49 [0.37; 0.65] There is an almost constant advantage provided by the robotic over the open approach, which becomes statistically significant from 2014 and onwards	0.54 [0.43; 0.68] There is a resulting formation and expansion of an advantage provided by the robotic over the open approach, which becomes statistically significant from 2017 and onwards	0.46 [0.31; 0.69] x	0.49 [0.39; 0.60] x	0.80 [0.46; 1.38] x
	MR							

Note that the bold black font corresponds to statistically significant results, whereas gray to non-statistically significant. Abbreviations: CD ≤ II: incidence of mild postoperative complications (Clavien–Dindo grades I and II), MA: meta-analysis (outside the brackets lies the expected value of the  $\text{Peto-OR}$ , while inside the brackets its 95% confidence interval is presented), MR: meta-regression analysis, FE: fixed effects model, n: number of studies

In conclusion, we can observe that the adoption of the robotic approach over conventional open surgery in partial nephrectomy may be associated with a significant reduction in the incidence of mild postoperative complications. Since by definition, as we have argued above, this type of complications may be related to the surgical approach, the results obtained could be attributed to inherent features of RPN/RAPN that endow it with several advantages over OPN, such as its minimal invasiveness, optimized ergonomics, precision in tissue handling due to the elimination of tremor, and better visualization of the surgical field. It was therefore found that the odds on the part of RPN/RAPN are reduced by about 50% compared to open surgery, with this finding resulting from both the analysis of the aggregate data and also the majority of the subgroups investigated. An exception to the above were those studies published prior to 2015, from the relevant analysis of which only a trend of a restriction emerged as for the incidence of mild complications post-surgery, with this finding being not statistically significant though. From the time series analysis procedure performed above, meta-regression analysis revealed the formation and subsequent extension of an advantage on the part of RPN/RAPN over OPN, in terms of reducing the incidence of mild complications in the early postoperative period, which became statistically significant, roughly in 2015 and onwards.

The relevant results produced in this section are briefly summarized in Table 2. Data and statistical code are freely available at: <https://github.com/sotbike/TB5.git>.

## Discussion

The gold standard for the surgical treatment of renal neoplasms is consistently represented by radical nephrectomy. This intervention is traditionally performed with the open approach, while during the last decades special emphasis is being given on minimally invasive techniques, such as laparoscopic and robotic approaches. The adoption of minimally invasive surgery (MIS) for the resection of malignant renal tumors is considered to be associated with a shorter hospital stay, reduced intraoperative blood loss, and potentially lower rates of postoperative complications. Additionally, current surgical literature shows that MIS techniques are at least equal in terms of oncological outcomes and postoperative renal function with conventional open surgery (Banapour et al. 2018). In light of recent developments in research into the effect of radical nephrectomy on renal function as well as the survival of patients with malignant tumors of the kidney, the relevant indications as for the adoption of partial nephrectomy and other nephron-sparing surgery (NSS) techniques have been expanded. Open partial nephrectomy for small kidney lesions has been shown to

provide comparable oncological control to that of radical nephrectomy (Lucas et al. 2012).

The laparoscopic approach began to gain popularity over the conventional open, for the management of localized kidney tumors, as it seemed to be able to provide oncological outcomes equal to the latter. However, the technical and ergonomic challenges associated with laparoscopic partial nephrectomy (LPN) have become substantial inhibitory factors in its widespread use over the years, with the open approach being used quite frequently even in modern kidney surgery practice (Wang et al. 2016). The evidence behind LPN implementation has expanded over time to include tumors of higher anatomical complexity, such as those adjacent to the vascular hilum of the kidney. Specifically, renal masses adjacent to the renal hilum are considered as a separate pathological entity, while their spatial relationship with renal vessels led to the delayed application of minimally invasive surgical techniques for this particular class of tumors. Gill et al. first in 2005 described laparoscopic partial nephrectomy for localized kidney tumors adjacent to the renal hilum (Gurram and Kavoussi 2020). Despite the relevant advances that have been made in MIS techniques, the laparoscopic approach remains highly technically demanding to this day. According to the most current view, when performed by a specialized surgeon, LPN is considered to be associated with similar oncological outcomes to open partial nephrectomy, with the added benefit of reduced need for analgesia and shortening of patients' hospital stay. Moreover, RPN/RAPN and LPN have been extensively studied and compared during the last decade, showing almost similar outcomes with perhaps a small lead characterizing the first (Klaassen et al. 2014). The utilization of modern surgical robotic platforms has been shown to facilitate the excision of even tumors of high anatomical complexity, as well as the reconstruction of the remaining normal parenchyma, providing a clear advantage over laparoscopic (Sagalovich et al. 2018; Hanzly et al. 2015).

Robotic and robot-assisted techniques are considered to be one of the most important technological innovations in the modern era of surgery, albeit there is limited literature supporting a clear advantage over conventional open surgical approaches. In terms of radical prostatectomy, robotic surgery has been promoted to such an extent that it is nowadays considered as the most important technique in the USA, while at the same time its application seems to be increasing in several European countries. A different pattern of adoption is observed regarding the application of robotic and robot-assisted approaches for partial nephrectomy procedures, with the percentage of patients undergoing RPN/RAPN reaching nearly 60% in the USA.

According to the Clavien–Dindo classification (Dindo et al. 2004; Clavien et al. 2009), minor postoperative complications are defined as those of grades I and II. The first category includes all those adverse events that cause deviation from the patient's normal postoperative course. Usually, these complications are resolved with the administration of antiemetics, antipyretics, conventional analgesics, diuretics as well as with adequate electrolyte replenishment and the provision of appropriate physiotherapy. On the other hand, grade II involves all those complications that usually require transfusion with blood products, administration of advanced antibiotics, and caloric support with total parenteral nutrition (TPN). Therefore, mild postoperative complications may be associated with inadequate surgical preparation of patients, in cases mandating the need for preoperative transfusion with red blood cell concentrates (RBCC) to improve the hemoglobin level, preoperative nutritional support with appropriate dietary supplements, and optimization of renal function prior to surgery. Subsequently, these types of complications may also be related to the surgical approach, apart from the severity of the operation. In fact, the benefits of minimally invasive surgery regarding the absence of large surgical incisions are well known. Minimal invasiveness of robotic access has been associated with faster patient mobilization, which aids in the prevention of atelectasis development, which affects patients' postoperative respiratory function, and predisposes to the development of early postoperative fever. Furthermore, additionally to the reduced need for analgesics due to smaller surgical incisions, the removal of catheters occurs at an earlier stage, a fact that acts protectively against the development of urinary tract infections (UTI). Finally, minimization of the metabolic response to trauma reduces the need for intensive patient support and facilitates maintenance of an optimal acid–base balance, as well as adequate electrolyte and caloric replenishment. Based on the above, at a theoretical level the surgical approach seems to play a leading role in shaping the frequency under which mild postoperative complications occur. Thus, their incidence could be utilized as an indicative comparison parameter between RPN/RAPN and OPN, in order to determine whether the differences concerning their “invasiveness,” affect the postoperative clinical course of patients to the expected.

In this study, our main goal was to highlight any differences between RPN/RAPN and OPN in terms of the incidence of mild complications during the early postoperative period. The relevant investigation was carried out using the methodology of meta-analyses, supplemented with appropriate subgroup analysis and meta-regression analysis in order to investigate for any qualitative sources of additional heterogeneity. Two recent meta-analyses

investigated the comparative effect between robotic and open partial nephrectomy in patients with small renal masses (disease stage  $\leq$  cT2a). In particular, Tsai et al. in 2019 integrating a set of 26 studies, concluded that robotic partial nephrectomy is associated with a statistically significant reduction in overall complication compared to open surgery (OR = 0.578, CI<sub>95%</sub>: [0.514; 0.649], I<sup>2</sup> = 14.538%) (Tsai et al. 2019). In the subgroup analysis performed specifically for minor postoperative complications, it emerged: OR = 0.600, CI<sub>95%</sub>: [0.498; 0.725]. This study was also supplemented by meta-regression analysis, while sensitivity analysis was omitted due to the low rate of heterogeneity observed. Subsequently, Ni et al. in 2022 concluded in a final set of 6 studies to investigate the comparative effect after RPN/RAPN vs. OPN on the incidence of overall postoperative complications (Ni and Yang 2022). In this study as well, the authors concluded that the robotic approach provides an advantage over open surgery by determining the relative benefit at: OR = 0.51, CI<sub>95%</sub>: [0.38; 0.68], I<sup>2</sup> = 0%. In this case, a targeted investigation on the incidence of mild postoperative complications was not performed, while no subgroup or meta-regression analyses were implemented due to the absence of significant heterogeneity. The above two robust studies demonstrate results similar to those of the present analysis at both the pooled and subgroup levels. Key elements of the latter come to include the in-depth analysis of heterogeneity based on the design of each study that was incorporated, but also the utilization of meta-regression analysis to elucidate the temporal change of the comparative effect, a parameter that proved to have a strong impact. Particularly, it can be argued that the continuous penetration of robotic technology in the modern practice of kidney surgery leads to the derivation of an increasingly greater benefit in terms of minimizing mild postoperative complications after partial nephrectomy.

The main limitation of this study stems from the fact that it incorporates a set of non-randomized comparative studies. The inclusion of such studies in analytical procedures intending to reach an estimate of the overall effect is generally known to lead to increased levels of heterogeneity, while it is also related to the need for careful elaboration in order to draw the safest conclusions possible. In the case of our analysis, the percentage of heterogeneity that cannot be explained, as expressed through the I<sup>2</sup> statistic, did not appear to be substantially high, resulting in the implementation of a fixed effects model. On the other hand, the relevant recommendations from the PRISMA statement (Moher et al. 2009; Liberati et al. 2009) regarding the usefulness of subgroup analyses in such cases of initial studies were extensively adopted. A second limitation has to do with the heterogeneity observed within the



definition given to the parameter of interest. Specifically, minor postoperative complications seem to be determined not only by the type of surgical approach, but also other parameters related to the preoperative preparation of patients, the severity of the operation, the treating surgeon's level of experience, the patient's comorbidity, the familiarity of other medical staff with the implementation of patient recovery protocols and more. However, the association of the incidence of mild postoperative complications with surgical approach seems to be stronger than in the case of major complications, enhancing the reliability of this outcome concerning its utilization as a comparison parameter between RPN/RAPN and OPN.

## Conclusions

The present study provides a comprehensive documentation of the superiority of RPN/RAPN over OPN concerning the incidence of minor postoperative complications. Specifically, from the meta-analysis of the aggregate data and regardless of whether any patient matching protocol was applied, or whether the studies were completed by a single or multiple referral centers, it emerged that the odds in the case of the robotic approach in partial nephrectomy account for almost 50% of those related to open surgery. Subsequently, meta-regression analysis of both pooled studies and subgroups revealed a progressive expansion of the comparative advantage from 2015 and beyond, likely demonstrating the successful integration of robotic technology into modern kidney surgery practice. This finding is compatible with the expected cumulative augmentation of the effect from a potentially superior surgical precision level provided through robotic technology. Further studies will be required in the near future to further evaluate the above findings.

## Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CD	Clavien–Dindo classification
CI <sub>95%</sub>	95% Confidence interval
FE	Fixed effects model
LPN	Laparoscopic partial nephrectomy
MH	Mantel–Haenszel method
MIS	Minimally invasive surgery
NOS	Newcastle–Ottawa scale
NSS	Nephron-sparing surgery
OPN	Open partial nephrectomy
OR	Odds ratio
PN	Partial nephrectomy
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RAPN	Robot-assisted partial nephrectomy
RBCC	Red blood cell concentrates (packed red blood cells)
RE	Random effects model
RPN	Robotic partial nephrectomy
RR	Relative risk
TPN	Total parenteral nutrition
UTI	Urinary tract infection

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s42269-023-01008-x>.

**Additional file 1. Supplementary Table 1:** Table showing the search strategy followed in each database that was utilized.

**Additional file 2. Supplementary Figure 1:** Map charts with color scale describing the percentage distribution of the included studies according to their country of origin. Notice that data visualization is stratified at both study and patient population levels.

**Additional file 3. Supplementary Table 2:** PRISMA statement checklist as a guideline for the reporting of the present meta-analysis. The location of every object is denoted by the manuscript page where it is reported, and the respective subsection. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7):e1000097. <https://doi.org/10.1371/journal.pmed1000097>.

## Acknowledgements

Not applicable.

## Author contributions

Conceptualization: [SA, IK]; Data curation: [SA, DA, IS]; Formal Analysis: [SA, DA, IS]; Funding acquisition: []; Investigation: [SA, DA]; Methodology: [SA, IK]; Project administration: [SA, DA]; Resources: [SA, DA, IS]; Software: [SA, IK]; Supervision: [KT, GZ]; Validation: [SA, DA, IS, IK]; Visualization: [SA]; Writing—original draft: [SA, IS]; Writing—review and editing: [SA, IK, KT]. All authors have read and approved the final manuscript.

## Funding

All authors confirm that no funds, grants, or other support were received.

## Availability of data and materials

All the data utilized and statistical code developed are available at the following link: <https://github.com/sotbike/TBS.git>

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

## Competing interests

Sotirios Artsitas (SA)<sup>1</sup>, Dimitrios Artsitas (DA)<sup>2</sup>, Ioanna Segkou (IS)<sup>3</sup>, Irene Koronaki (IK)<sup>4</sup>, Konstantinos G. Toutouzas (KT)<sup>5</sup>, George C. Zografos (GZ)<sup>6</sup> declare that they have no conflict of interest.

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Received: 19 October 2022 Accepted: 22 February 2023

Published online: 06 March 2023



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