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Influence of Hospital Volume on Nephrectomy Mortality and Complications: A Systematic Review and Meta-Analysis Stratified by Surgical Type

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INFLUENCE OF HOSPITAL VOLUME ON NEPHRECTOMY MORTALITY AND COMPLICATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS STRATIFIED BY SURGICAL TYPE

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ABSTRACT

Objectives

The provision of complex surgery is increasingly centralised to high volume specialist hospitals. Evidence to support nephrectomy centralisation however has been inconsistent. We conducted a systematic review and meta-analysis to determine the association between hospital case volumes and perioperative outcomes in radical nephrectomy, partial nephrectomy and nephrectomy with venous thrombectomy.

Methods

Medline, Embase and the Cochrane Library were searched for relevant studies published between 1990 and 2016. Pooled effect estimates for nephrectomy mortality and complications were calculated for each nephrectomy type using the DerSimonian and Laird random-effect model. Sensitivity analyses were performed to examine the effects of heterogeneity on the pooled effect estimates by excluding studies with the heaviest weighting, lowest methodological score, and most likely to introduce misclassification bias.

Results

Some 226,657 patients from nineteen publications were included in our review. Of these, sixteen were used in the meta-analysis. Considerable heterogeneity was noted across the included studies.

High volume hospitals were correlated with a 26% and 52% reduction in mortality for radical nephrectomy (OR 0.74, 95% CI 0.61-0.90, p<0.01) and nephrectomy with venous thrombectomy (OR 0.48, 95% CI 0.29-0.81, p<0.01) respectively. In addition, radical nephrectomy in high volume hospitals was associated with an 18% reduction in complications (OR 0.82, 95% CI 0.73-0.92, p<0.01). No significant volume-outcome relationship in mortality (OR 0.84, 95% CI 0.31-2.26, p=0.73) or complications (OR 0.85, 95% CI 0.55-1.30, p=0.44) was observed for partial nephrectomy.

Conclusions

Our findings suggest that patients undergoing radical nephrectomy and nephrectomy with venous thrombectomy have improved outcomes when treated by high volume hospitals. Evidence of this in partial nephrectomy is however not yet clear and could be secondary to the small patient number in our analyses. Further investigations are warranted to establish the full potential of centralisation particularly as existing evidence is of low quality with significant heterogeneity across studies.

STRENGTH & LIMITATIONS OF THIS STUDY

- This is a contemporary systematic review and meta-analysis of the associations between hospital case volumes and nephrectomy outcomes.
- Estimates were synthesised from seventeen studies, four folds greater than previous meta-analysis, and the study is the first to date to stratified results based on the types of nephrectomy to account for differences in technical complexity and rates of adverse outcomes.
- Multiple sensitivity and subgroup analyses were performed to assess the potential bias and confounders introduced.
- Current evidence in nephrectomy outcome-volume relationship is of low quality and considerable heterogeneity exists between studies in design, type of data used, outcomes measured and statistical methodologies.
- Our study highlights the limitations in existing evidence and suggests questions that should be addressed in future research.

INTRODUCTION

In recent years, there has been an emerging trend for the centralisation of complex operations in healthcare systems around the world [1–3]. This shift is supported by the growing research and evidence suggesting that hospitals and surgeons with high case loads have better patient outcomes [4–8]. Proponents argue that centralisation allows more effective use of clinical expertise and specialist equipment, and the increased exposure improves surgical skills and provides better training opportunities. Centralisation can also facilitate quicker adoption of care pathways, such as enhanced recovery, and may have more long-term financial sustainability for hospitals. However, differences in disease biology and surgical complexity mean that such a health service model may not be appropriate for all conditions.

Nephrectomy plays a key role in the management of many renal conditions and is often the only potentially curative treatment for renal cancer patients. Advancements in surgical techniques and technology have led to different nephrectomy types, such as partial nephrectomy, with different surgical complexities and outcomes [9,10]. With over 330,000 new annual renal cancer diagnoses worldwide and rising incidence in many countries, the number of nephrectomies being performed is also likely to increase [11,12]. It is therefore critical that health service providers understand the effects that organisational changes may have on patient outcomes. Despite the expansion on volume-outcome research, no consensus has been reached on the efficacy of centralising nephrectomy, and many uncertainties remain about its potential benefits. We present a contemporary systematic review and meta-analysis of the published literature on the association between hospital case volumes and perioperative outcomes stratified by nephrectomy types. We hypothesise that outcomes significantly improve with higher nephrectomy case volumes.

METHODS

Search criteria & data extraction

The systematic review and meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (S1 Appendix) [13]. Literature searches in Medline, Embase and the Cochrane Library were performed for relevant studies published between January 1990 and December 2016. Studies published prior to 1990 were not considered as recent medical and surgical advancements would have limited their applicability to the modern healthcare system.

Databases were searched using medical subject heading (MeSH) terms and key words for nephrectomy, case volume and relevant outcomes (S2 Appendix). We considered only studies published in English and used primary data to examine nephrectomy outcomes in adult populations across two or more hospital case volumes. Only those investigating radical or partial nephrectomy were included and articles comprised solely of nephroureterectomy were excluded.

Two investigators (R.C.J.H and J.M.) independently reviewed all studies for validity and data extraction. References were also searched manually for additional relevant studies. Any disagreement between the two reviewers was resolved by discussion and consultation with a third reviewer (J.N.A.). Where only rates of outcomes were presented, these were applied to the case number to give the number of events, within the error of the published results. Study authors were contacted for further clarification if specific rates of outcomes and case numbers were not published [14,15].

As the cut-off values for hospital volume groups differed among studies, we used the approach adopted by similar previous meta-analyses by evenly dichotomising groups into low volume (LV) and high volume (HV) when articles presented a series of volume groupings [16,17]. If a study presented an odd number of volume groups, the middle group was categorised as LV.

Methodological quality and potential risk of bias were scored using a validated system designed specifically for the evaluation of volume-outcome studies [18,19]. When studies extracted data from the same source with overlap in the studied periods, we employed the following rules to avoid duplicating populations: 1) studies with identical patient cohort but examining different outcomes were considered and analysed separately; 2) studies that derived data from older datasets were excluded in favour of the more contemporary cohort; 3) if the above rules were not applicable, studies with the lower methodological quality scores were excluded; 4) where quality scores were equal, the study covering the longest period was included.

Quantitative data synthesis

All statistical analyses were performed using Stata 14 [20]. Nephrectomy types were categorised into radical nephrectomy, partial nephrectomy and nephrectomy with venous thrombectomy and analysed separately. Studies involving multiple types of nephrectomies were analysed based on the aforementioned groups, but if this was not feasible, they were categories as radical nephrectomy. With the assumption that a distribution of effects exists amongst studies, all pooled effect size were calculated using the DerSimonian and Laird random-effect model, which provided more conservative estimates. Odds ratio (OR) and

95% confidence interval (CI) were calculated for each outcome measure using LV groups as the reference. Pooled effect size was calculated for nephrectomy mortality and complications.

When the meta-analysis demonstrated significantly better outcomes in HV hospitals, we quantified the clinical effectiveness of centralisation by calculating the numbers needed to treat, or in our case numbers needed to centralise (NNC). NNC represents the number of cases that will need to be treated by HV hospitals in order to prevent one event.

Heterogeneity

As the DerSimonian and Laird model would have only accounted for some between-study heterogeneity, we further quantified heterogeneity by calculating I^2 statistic. I^2 provides an easily understood number, which describes the proportion of total variation in estimates that is due to heterogeneity rather than chance [21]. Values of 25% or lower denote low heterogeneity and values of 75% or greater denote considerable heterogeneity [22]. Meta-regression was performed to explore the influence of potential explanatory variables on heterogeneity including each study's publication year, country, data source, number of patients and their demographics, number of hospitals, and threshold for HV hospitals.

Publication bias

Funnel plots were generated to investigate potential publication bias, and were enhanced to include contours that divide the funnel into statistically significant and non-significant areas. Funnel plot symmetry suggests low probability of publication bias and Harbord's modified test was used to test for asymmetry [23]. Harbord's test reduces false positive rates when applied to binary outcome data, especially when there is low between-study heterogeneity. Trim and fill method was also performed to account for publication bias by adjusting the meta-analysis to incorporate the theoretically missing studies [24].

Sensitivity analysis

To examine specific studies' effects on pooled effect size, sensitivity analyses were performed by excluding individual studies and repeating the meta-analyses. We examined the effects of studies with the heaviest weighting and studies with the lowest methodological quality score. As there is currently no consensus on what nephrectomy case volume is necessary to be considered as HV, we repeated our analyses by excluding studies whose standardised HV categories overlapped most significantly with the standardised LV categories in other studies to account for potential bias of misclassifying volume categories in our dichotomy.

As secondary analyses, we additionally repeated the meta-analysis three further times with different methods of dichotomising the volume groups to examine whether our initial estimates would remain consistent. The methods of dichotomising were 1) lowest volume categories and all others 2) even dichotomy and when studies present an odd number of volume categories, the middle group was considered as HV 3) highest volume categories and all others.

RESULTS

Study selection & characteristics

From the 5,680 articles initially identified, 19 were included in the systematic review containing 226,657 patients from seven countries (Figure 1). For the meta-analysis, eleven studies with 201,506 patients examining radical nephrectomy was included while four studies of 23,617 patients and two studies of 1,249 patients examining partial nephrectomy and nephrectomy with venous thrombectomy were included respectively. Publication year ranged from 2002 to 2016, while cohort periods covered from 1993 to 2013.

Tables 1 summarises the characteristics of the included studies. Variations were observed in study designs including source of data and outcomes measured. Out of a possible score of 18, the median quality score from the included studies was 8.5 (interquartile range 8 – 9) with the majority of the studies failing to adequately address potential confounders including measuring the appropriateness of patient selection, adjusting for case-mix variations and accounting for differences in clinical risks and processes of care. Variable thresholds for HV hospitals were noted across the included studies.

Table 1. Characteristics and methodological summary of studies.

	Study Characteristics								Outcomes Measured							
Reference	**Year**	**Country**	**Period**	**Data Type**	**No. of Patients**	**No. of Hospitals**	**Low[a]**	**High[a]**	**Mortality**	**Complications (breakdowns)**	**Transfusion**	**LOS**	**Conversions**	**Others**	**Case Mix**	**Quality Score (18)**
Radical Nephrectomy																
Hjelle[25]	2016	Norway	2008-2013	Admin	3,273	40	20	40	+	-	-	-	+	-	Demographics, tumour stage, nephrectomy type	8
Becker[26]/ Sun[27][b]	2014 / 2012	USA	1998-2007	Admin	48,172	N/S	5	16	+	+ (17 events inc haemorrhage, cardiac arrest, infection, wound disruption, seroma, pneumothorax, VTE etc)	+	+	-	-	Demographics, co-morbidity, nephrectomy type, laparoscopy, payer/hospital type	9
Hanchanale[28]	2010	England	1998-2005	Admin	20,672	1,181	14	35	+	-	-	+	-	-	Demographics	9
Yasunaga[29]	2010	Japan	2006-2007	Admin	7,988	646	26	65	+	+ (11 events inc surgical site infection, UTI, VTE, sepsis, ileus, stroke, cardiac events, renal, failure, peritonitis etc)	-	-	-	-	Demographics, co-morbidity, laparoscopy, hospital type, tumour location	9
Mitchell[30]	2009	USA	2003-2007	Clinical	42,988	134	99/4.5yr	500/4.5yr	+	+ (not specified)	-	+	-	ICU admission	None	9
Yasunaga[14]	2008	Japan	2006-2007	Clinical	1,704	461	9	40	+	+ (wound infection, pneumonia, ileus, renal dysfunction, others)	-	-	-	OT, EBL	Demographics, co-morbidity, laparoscopy, tumour stage & location	11
Davenport[31]	2005	England	2004	Clinical	598	48	<1/mo	>1/mo	+	+ (12 events inc bleeding, bowel injury, GI bleed, renal failure, pneumothorax, VTE, MI, splenic injury etc)	+	-	+	OT	None	4
Keoghane[32]	2004	England	2001-2002	Clinical	263	25	5	6	-	+ (16 events inc renal failure, sepsis, wound infection, bowel injury, incisional hernia, peri-hepatic collection etc)	-	-	+	-	None	3
Taub[33]	2004	USA	1993-1997	Admin	16,858	962	14	34	+	-	-	+	-	-	Demographics, co-morbidity, admission acuity	8
Goodney[34]	2003	USA	1994-1999	Admin	58,990	3,292	6	33	-	-	-	+	-	Readmission	Demographics, co-morbidity, admission acuity	8
Birkmeyer[35]	2002	USA	1994-1999	Admin	58,990	3,292	6	33	+	-	-	-	-	-	Demographics, co-morbidity, admission acuity	7
Partial Nephrectomy																

Porpiglia[36]	2016	Italy	2009-2013	Clinical	285	22	49	50	-	-	-	-	-	Trifecta[c]	Tumour growth patter, EBL	6
Couapel[37]	2014	France	2010	Clinical	570	53	4/7mo	19/7mo	+	+ (medical and surgical events, not further specified)	-	+	+	OT, EBL, Totalisation, +ve margin	N/S	8
Monn[38]	2014	USA	2009-2011	Admin	17,583	322	13	35	-	+ (organ based complications not further specified, pain, seroma, shock, haematoma, hypotension, VTE, pneumothorax)	+	+	-	Hospital cost	Demographics, co-morbidity, payer, region, hospital type	9
Abouassaly[39]	2012	Canada	1998-2008	Admin	4,292	181	146/10yr	797/10yr	+	+ (not specified)	-	-	-	-	Demographics, co-morbidity, region	12
Taub[33]	2004	USA	1993-1997	Admin	1,172	962	14	34	+	-	-	+	-	-	Demographics, co-morbidity, admission acuity	8
Nephrectomy with Venous Thrombectomy																
Toren[40]	2013	Canada	1998-2008	Admin	816	120	N/S	N/S	+	+ (40 medical and surgical events inc MI, CHF, PE, infection, organ injury, pneumothorax etc)	+	-	-	-	Demographics, co-morbidity, region	11
Yap[15]	2012	Canada	1995-2004	Admin	433	N/S	2/10yr	8/10yr	+	-	-	-	-	-	Demographics	11

[a]Low, cut-off value for lowest volume group; high, cut-off value for highest-volume group. Volume units are cases per year unless specified. [b]Becker and Sun were equal in the data source used, outcomes evaluated, periods covered and quality scores, but employed different analyses to evaluate the benefit of regionalisation and volume-outcome relationship in nephrectomy [26,27]. [c]Trifecta was defined as simultaneous absence of complications, negative surgical margins and ischemic time of <25 minutes. We therefore treated them as one single cohort, with no duplicates in our analysis. Admin: Administrative. N/S: Not specified. RN: Radical nephrectomy. PN: Partial nephrectomy. VTE: venous thromboembolism. MI: Myocardial infarction. CHF: Congestive heart failure. PE: Pulmonary embolism. UTI: Urinary tract infection. GI: Gastrointestinal. OT: Operating time. EBL: Estimated blood loss. ICU: Intensive care unit.

Mortality and Hospital Volumes

Post-operative mortality was the most frequently examined outcome, reported in fourteen studies. Ten studies reported mortality in radical nephrectomy [14,25–31,33], three in partial nephrectomy [33,37,39] and two in nephrectomy with venous thrombectomy [15,40]. The overall mortality was 1.59% (range 0.20-7.2) with mortality rates in HV and LV hospitals being 1.47% and 1.68% respectively.

Radical Nephrectomy

Meta-analysis demonstrated that patients who underwent radical nephrectomy in HV hospitals had a 26% reduction (OR 0.74, 95% CI 0.61-0.90, p<0.01) in post-operative mortality, corresponding to a NNC of 234 (Figure 2A). Significant heterogeneity was observed (I^2 75.0%, p<0.01). Meta-regression was performed to investigate the potential explanatory variables for heterogeneity, and only differences in the threshold values for HV hospitals were shown to be a significant contributor (S3 Appendix A). Subgroup analysis of the three studies examining exclusively of radical nephrectomies demonstrated a more pronounced reduction in post-operative mortality favouring HV hospitals (OR 0.62, 95% CI 0.53-0.71, p<0.01) [14,30,33]. This corresponded to a lower NNC of 166 with little residual heterogeneity (I^2 0.0 %, p=0.40). The overall funnel plot was visually asymmetrical particularly missing studies with effect estimates favouring LV hospitals (Figure 3A). However, the Harbord's modified test did not show significant asymmetry (p=0.40) and "trim and fill" method did not change the initial estimate, indicating no clear evidence of publication bias. In sensitivity analyses, exclusion of the most heavily weighted study led to a similar pooled-effect estimate (OR 0.70, 95% CI 0.55-0.88, p<0.01) [35]. Exclusion of the study with the lowest quality score also did not significantly alter our result (OR 0.74, 95% CI 0.61-0.91, p<0.01) [31]. To examine the potential bias introduced by misclassification, two cohorts were excluded [26,27,31]. This did not substantially change our pooled-effect estimate either (OR 0.73, 95% CI 0.58-0.93, p=0.01). Overall, radical nephrectomies in HV hospitals appeared to have significantly lower mortality.

Partial Nephrectomy

Meta-analysis showed that partial nephrectomy patients operated in HV hospitals had a 16% reduction in post-operative mortality but this was not statistically significant (OR 0.84, 95% CI 0.31-2.26, p=0.73) (Figure 2B). Moderate but non-significant heterogeneity was noted (I^2 36.84 %, p=0.21). Sensitivity analyses removing studies with the heaviest weighting [39] or most likely to introduce misclassification bias [37] demonstrated reduced mortality favouring HV hospitals, but these remained non-significant.

Nephrectomy with Venous Thrombectomy

Patients who underwent nephrectomy with venous thrombectomy in HV hospitals had a 52% reduction (OR 0.48, 95% CI 0.29-0.81, p<0.01) in short-term mortality compared to LV hospitals (Figure 2C). This corresponded to a NNC of 25 with low heterogeneity (I^2 0.0 %, p=0.50). Due to the small number of studies reporting this outcome, further testing of heterogeneity and publication bias was not expected to generate meaningful results and this was not attempted.

Complications and Hospital Volumes

Complication was the second most frequently investigated outcome, reported in ten studies. Six studies reported complications in radical nephrectomy [26,27,29–32] and three in partial nephrectomy [37–39]. Only one study examined volume-outcome relationship in nephrectomy with venous thrombectomy and meta-analysis was therefore not appropriate [40]. The overall complication rate was 16.26% (range 7.4-78). HV hospitals had complication rates of 15.00% compared to 17.51% in LV hospitals.

Radical Nephrectomy

Meta-analysis showed a 18% reduction (OR 0.82, 95% CI 0.73-0.92, p<0.01) in nephrectomy complications in HV centres, corresponding to a NNC of 38 (Figure 4A). Significant heterogeneity was noted (I^2 76.25%, p<0.01), but none of the factors examined in meta-regression significantly contributed to this (S3 Appendix B). Funnel plot was visually asymmetrical, but using the "trim and fill" method to account for potentially missing studies resulted in similar pooled-effect estimate (OR 0.81, 95% CI 0.72-0.91, p<0.01) (Figure 3B). Harbord's test also did not find significant funnel plot asymmetry to suggest publication bias (p=0.18). Sensitivity analyses by removing studies with the lowest quality [32] or most likely to introduce misclassification bias [31,32] did not significantly alter our initial result. Excluding study with the heaviest weighting however led to a loss of significance in the pooled-effect estimate, which however still demonstrated a 11% reduction in complications in HV hospitals (OR 0.89, 95% CI 0.74-1.08, p=0.24). Overall, radical nephrectomies performed in HV hospitals appeared to have significantly lower complications compared to LV hospitals.

Partial Nephrectomy

Partial nephrectomy patients operated in HV hospitals had a 15% reduction in complications, but this was not statistically significant (OR 0.85, 95% CI 0.55-1.30, p=0.44) (Figure 4B).

Significant heterogeneity was noted (I^2 94.80%, p<0.01). Sensitivity analysis by removing studies with the heaviest weighting [38] or most likely to introduce misclassification bias [37] did not result in significance.

Secondary analyses using different methods of dichotomising HV and LV

As there is no consensus on what constituted HV hospitals in current evidence, simple dichotomy of volume groups may introduce inherent bias to the estimates. Yet no recommendation on how best to proceed in volume-outcome analysis presently exists.
In our secondary analyses, we consistently observed significantly lower risks of mortality for both radical nephrectomy and nephrectomy with venous thrombecotmy in HV hospitals regardless how volumes were dichotomies (Table 2). The magnitudes of risk reductions were more pronounced when higher thresholds for HV hospitals were considered particularly for radical nephrectomy mortality. Partial nephrectomy mortality however continued to demonstrate no significant association to volume even when dichotomies were comparing the highest volume groups to all others.

Risks of radical nephrectomy complications remained significantly reduced in HV hospitals when the dichotomy threshold for HV hospitals was increased, but the significance was lost when the thresholds were lowered. Association between hospital volumes and partial nephrectomy complications remained insignificant regardless of how HV was defined in our dichotomy.

Table 2: Results of meta-analysis by using different methods of dichotomising volume groups.

	Lowest volume group vs. all others	Even dichotomy, middle group as HV	Even dichotomy, middle group as LV (Primary analysis)	Highest volume group vs. all others
Mortality				
Radical Nephrectomy	OR: 0.82 95%CI 0.71-0.94 p=0.01	OR: 0.83 95%CI 0.72-0.95 p<0.01	OR: 0.74 95%CI 0.61-0.90 p<0.01	OR: 0.72 95%CI 0.61-0.85 p<0.01
Partial Nephrectomy	OR: 0.48 95%CI 0.18-1.31 p=0.15	OR: 0.67 95%CI 0.17-2.75 p=0.58	OR: 0.84 95%CI 0.31-2.26 p=0.73	OR: 0.93 95%CI 0.31-2.77 p=0.90
Nephrectomy with Venous Thrombectomy	OR: 0.59 95%CI 0.35-0.99 p=0.045	OR: 0.46 95%CI 0.27-0.80 p<0.01	OR: 0.48 95%CI 0.29-0.81 p=0.01	OR: 0.48 95%CI 0.25-0.92 p=0.03
Complications				
Radical Nephrectomy	OR: 0.89 95%CI 0.78-1.01 p=0.07	OR: 0.84 95%CI 0.68-1.05 p=0.13	OR: 0.82 95%CI 0.73-0.92 p<0.01	OR: 0.82 95%CI 0.73-0.92 p<0.01
Partial Nephrectomy	OR: 0.82 95%CI 0.55-1.41 p=0.60	OR: 0.80 95%CI 0.47-1.36 p=0.40	OR: 0.85 95%CI 0.55-1.30 p=0.44	OR: 0.81 95%CI 0.53-1.24 p=0.33

DISCUSSION

Evidence on volume-outcome relationships in complex diseases and procedures has increased substantially in recent years. Many operations have been shown to have improved outcomes in HV centres, but this may not be uniform across all surgeries and no benefits have been associated to volume in percutaneous nephrolithotomy or appendicectomy [41–46]. This meta-analysis provides a contemporary review of the effects of centralisation in nephrectomy outcomes. It has revealed significant inverse associations between hospital case volumes for short-term mortality and complications for radical nephrectomies and nephrectomies with venous thrombectomies.

Considered individually, all but three studies in our review reported lack of associations between hospital volume and nephrectomy mortality [25,33,35]. However, such associations in favour of HV hospitals were apparent when considering the totality of the evidence particularly in radical nephrectomies and venous thrombectomies. This finding is consistent with the only other meta-analysis on nephrectomy volume-outcome relationship published in 2009 but includes four-fold greater number of studies [19]. Our meta-analysis demonstrates that the mortality benefit seen in radical nephrectomy may be relatively small requiring centralisation of 234 patients in order to avoid one death. However, the NNC decreased considerably to 166 in our sensitivity analyses. Coupled with the much lower NNC of 38 for radical nephrectomy complications, there is moderate evidence to support its centralisation.

Our analyses would be consistent with the “practice makes perfect” hypothesis for volume-outcome relationship [47]. Particularly, the reduction in mortality for nephrectomy with venous thrombectomy, a technically challenging operation, was observed to be more pronounced than that in radical nephrectomy with potentially one avoidable death for every 25 cases centralised to HV hospitals. However, similar trend was not seen in partial nephrectomy, also considered technically complex. Partial nephrectomy has been demonstrated to be a safe procedure with comparable short-term mortality and morbidity profile to radical nephrectomy and at such the relatively small number of partial nephrectomy patients in our meta-analysis might not have been sufficient to reveal the true presence of a volume-outcome relationship, as evident in our wide confidence interval [48]. This may also explain the lack of significant association between partial nephrectomy complications and hospital volumes. With its low mortality and morbidity rates, other outcome measures such as ischaemic time and negative surgical margins, are likely to be more appropriate quality markers in volume-outcome analysis. These have so far been poorly evaluated in current studies.

Despite the strict inclusion criteria in our studies, we observed considerable heterogeneity, especially in the meta-analyses of nephrectomy complications. One explanation for this is the lack of standardised reporting of complications by individual studies. Harder endpoints as previously discussed could have overcome this. Other more objective outcomes including transfusion rate and length of stay were reported by four [26,27,31,38] and eight studies [26–28,30,34,37,38,49] in our systematic review respectively, but they were not in adequate numbers to be stratified by nephrectomy types or in sufficiently detailed data to perform meta-analyses. In addition, variations in the threshold values for HV hospitals likely contributed to the heterogeneity, although this was not evident in the meta-regression.

Results from the multiple sensitivity analyses to adjust for these differences have remained robust and our study would therefore appear to be informative and relevant.

While there has been an expansion in the studies on nephrectomy volume-outcome relationship, many questions continue to be unanswered. The proportion of nephrectomy performed under laparoscopy or robotic assistance is growing [50,51]. There is however a paucity of evidence specifically investigating this in the volume-outcome context with only one study examining the differences in perioperative measures in robotic partial nephrectomy [38]. Three other studies have adjusted surgical techniques in multivariable regressions, but these did not directly demonstrate the effect of laparoscopic volumes on surgical outcomes [14,26,29]. Due to the small study number and data quality, it was not possible in this meta-analysis to further sub-stratify each nephrectomy type into open and minimally invasive and our results should be interpreted taking this limitation into account.

Tumour characteristics including TNM stage and grades are well established to significantly affect and predict nephrectomy mortality, but only two studies have so far adjusted for this in their analyses [14,25]. Surgeon case volume and degree of specialisation also play significant roles in determining operative outcome, and can be more important than hospital case volume alone [43,52–54]. While not the focus of this study, no significant association was found between surgeon volume and complications in radical nephrectomy [14], but 31% and 16% reduction in mortality and complications respectively was observed in partial nephrectomy in HV surgeons [39]. HV surgeons performing nephrectomy with venous thrombectomy were also reported to have reduced risk of mortality [15], but this was not observed in a subsequent study [40]. It would be of high interest to understand the interactions between surgeon volume, surgical approach and oncological factors in the volume-outcome relationship and may provide additional insights to selecting patients that will benefit the most from nephrectomy centralisation, such as those with advanced disease. Similarly, no study has examined the long-term benefits of centralising nephrectomy when high volume centres have been demonstrated to increase oncological survival in other cancer surgeries [55,56]. Results of this may further influence the recommendations for nephrectomy centralisation and this is currently being explored in our ongoing work. Other outcomes including long-term risks of chronic kidney disease and cardiovascular morbidities and patient reported outcome measures may also provide more relevant and holistic measurements of the potential efficacy of nephrectomy centralisation.

Our secondary analyses would suggest that a minimum volume threshold for nephrectomy likely exist, and beyond that, risks of adverse outcomes may continue to decrease with further increase in volume. An important limitation of this however is that this minimum threshold cannot be objectively determined from the current evidence. Volume is also likely to be a proxy marker of other specific care processes that may produce improved outcome, such as access to nurse specialists and clinical trials [57]. Increasing volume alone in itself may therefore not reduce adverse results. Future research should concentrate on identifying the qualitative differences between providers in order for the contributing good practices to be adopted by lesser performing centres.

CONCLUSIONS

Current evidence of the association between hospitals volumes and nephrectomy outcomes is of low quality with considerable heterogeneity amongst studies. Our meta-analyses have demonstrated significant reduction in mortality and complications for patients undergoing radical nephrectomy and nephrectomy with venous thrombectomy in HV hospitals. Evidence of this in partial nephrectomy is not yet clear but warrants further investigations.

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CONTRIBUTORS

RCJH, VJG and JNA contributed to the study conception and design. RCJH, JM and JNA contributed to data acquisition and risk of bias assessment. RCJH, TS, GL, VJG, JNA contributed to statistical analysis, data interpretation and critical manuscript revision. RCJH contributed to drafting the manuscript. RCJH contributed to obtaining funding. GL, VJG and JNA contributed to supervision of the study.

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COMPETING INTEREST STATEMENT

None declared.

DATA SHARING STATEMENT

No additional data are available.

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SUPPORTING INFORMATION CAPTIONS

S1 Appendix. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

S2 Appendix. Literature search algorithm used in Medline, Embase and the Cochrane Library.

S3 Appendix. Results of meta-regression investigating the potential explanatory variables for the heterogeneity in the meta-analyses for mortality in **A**. radical nephrectomy and **B**. partial nephrectomy.

S4 Appendix. List of excluded studies after full-text review and justifications.

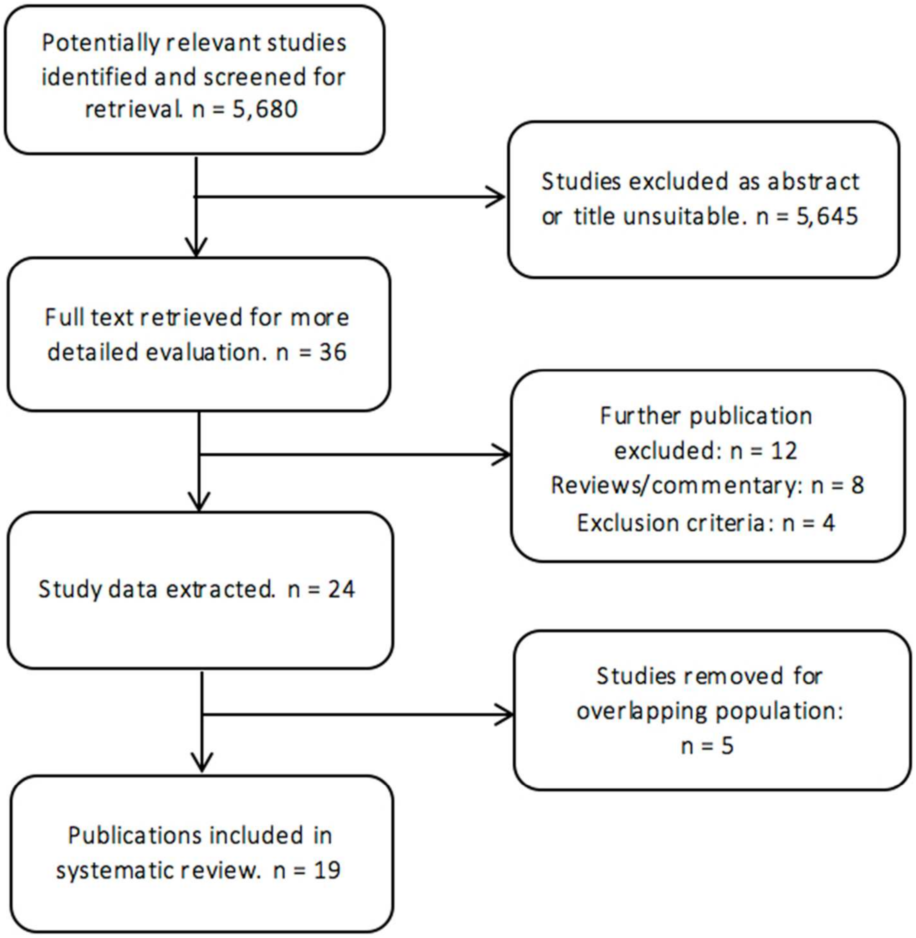

Fig 1. Flow chart of the article selection process.

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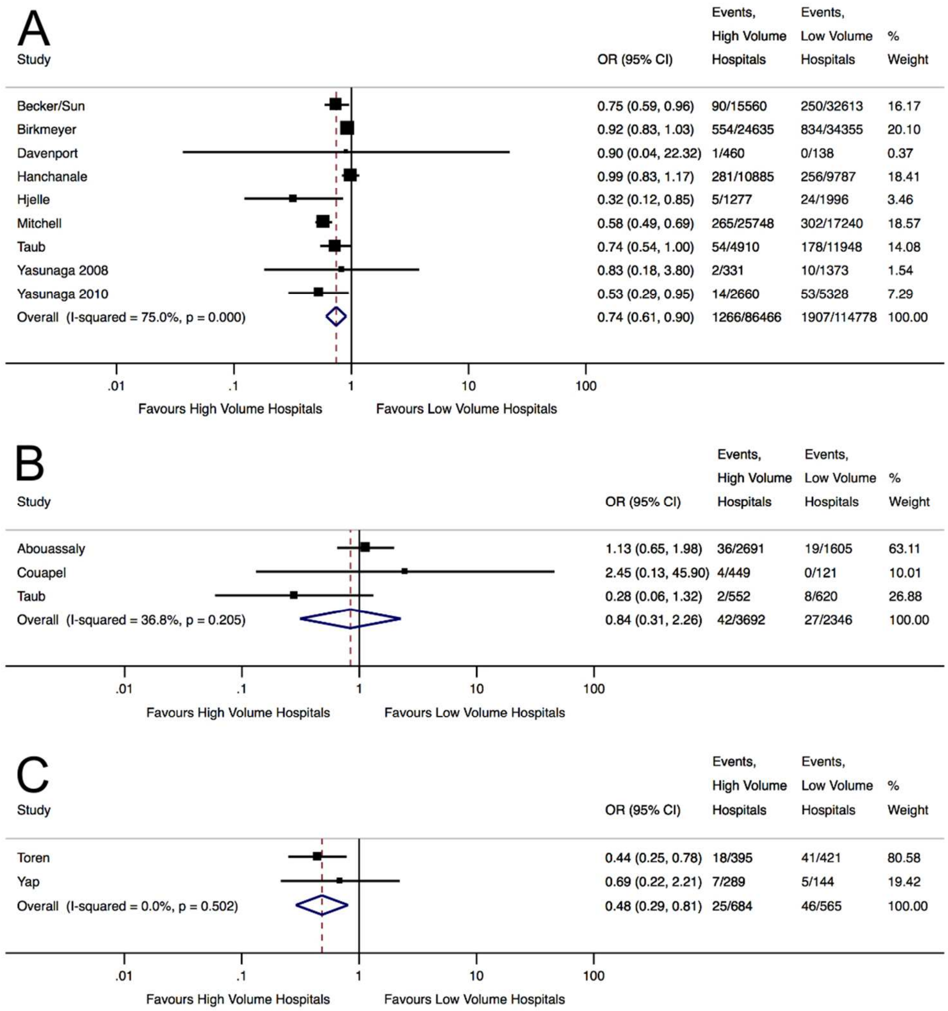

Fig 2. Forest plots displaying the pooled estimates of nephrectomy mortality in HV and LV hospitals for A. radical nephrectomy B. partial nephrectomy C. nephrectomy with venous thrombectomy.

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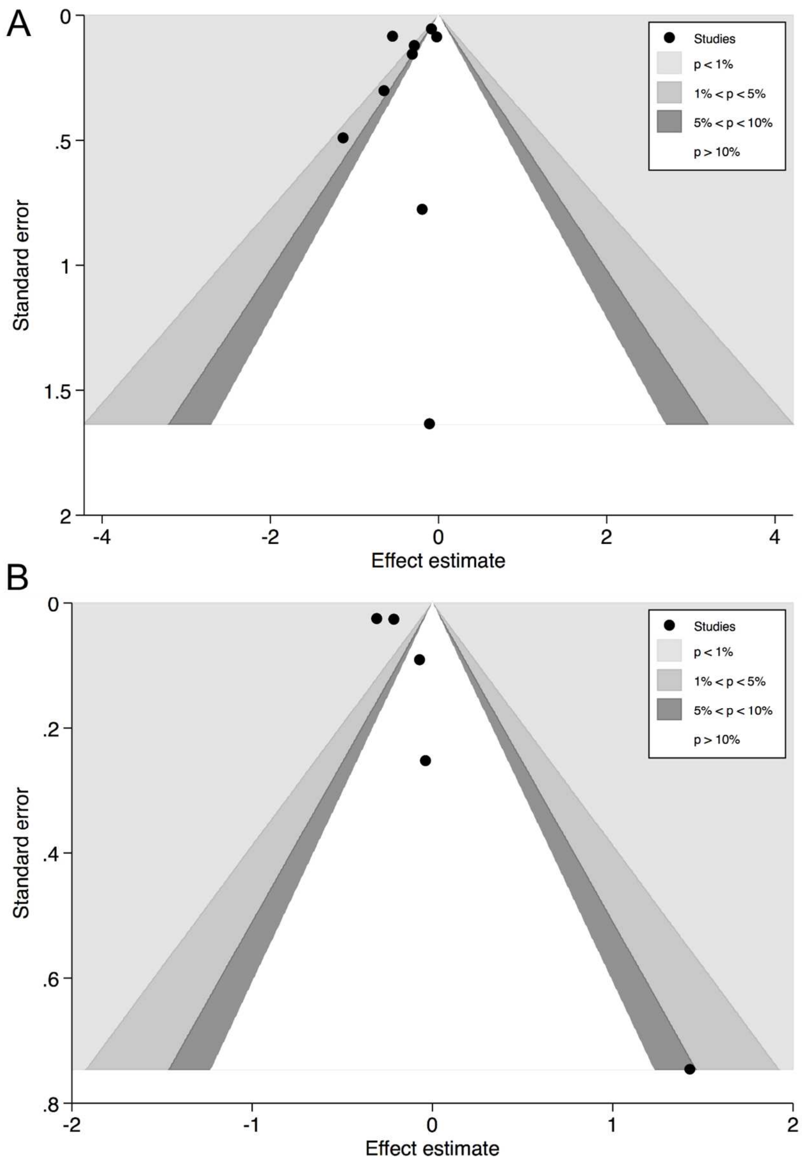

Fig 3. Contour-enhanced funnel plot of studies analysing hospital volume-outcome relationship in radical nephrectomy for A. mortality B. complications. Harbord's modified test for funnel plot asymmetry was not statistically significant for both.

111x160mm (300 x 300 DPI)

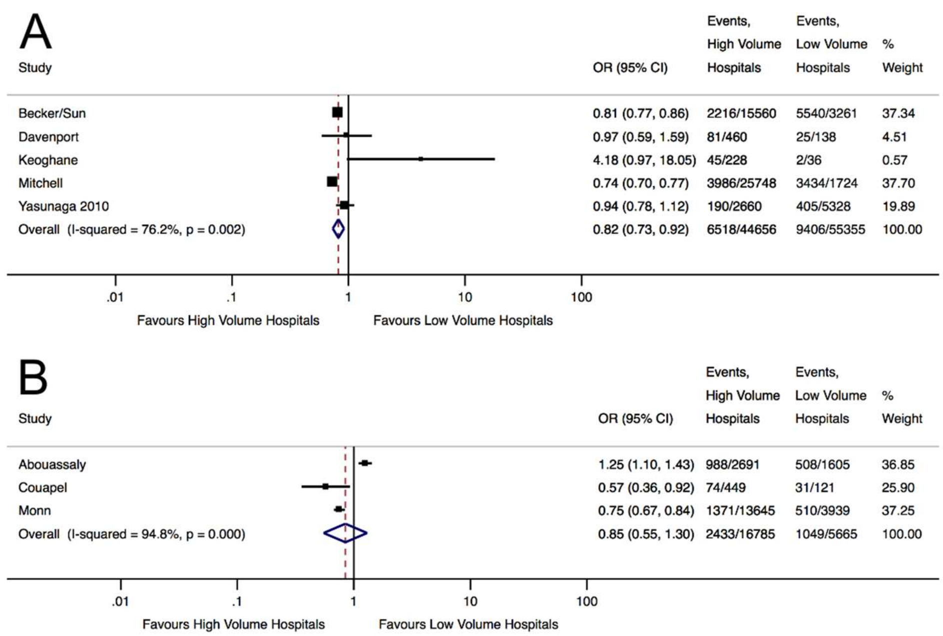

Fig 4. Forest plots displaying the pooled estimates of nephrectomy complications in HV and LV hospitals for A. radical nephrectomy B. partial nephrectomy.

101x66mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

S2 Appendix. Literature search algorithm for Medline, Embase and the Cochrane Library.

Medline

Nephrectomy Terms:

1. exp Nephrectomy/
2. nephrectom*.mp.
3. (kidney* adj5 (excision* or remov*)).mp.
4. 1 or 2 or 3

Surgeon or Hospital Volume Terms

5. ((physician* or urol* or surg* or operat* or hospital* or procedure*) adj5 (volume* or workload* or caseload* or performance* or number*)).mp.
6. exp Hospitals/
7. exp Surgeons/
8. (volume* or workload* or caseload* or performance*).mp.
9. exp Workload/
10. 6 and 8
11. 7 and 8
12. 6 and 9
13. 7 and 9
14. exp Centralized Hospital Services/
15. centrali*ation.mp.
16. 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Outcome Terms

17. exp "Outcome Assessment (Health Care)"/
18. exp Patient Outcome Assessment/
19. exp "Outcome and Process Assessment (Health Care)"/
20. outcome.mp.
21. exp Treatment Outcome/
22. exp Mortality/
23. mortalit*.mp.
24. exp Morbidity/
25. morbidit*.mp.
26. exp "Length of Stay"/
27. length of stay.mp.
28. ((duration or length or period) adj5 (stay or hospital*)).mp.
29. exp Survival/
30. survival.mp.
31. exp Patient Readmission/
32. readmission.mp.
33. exp Postoperative Complications/
34. complication*.mp.
35. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 4 and 16 and 35

Embase

Nephrectomy Terms:

1. exp Nephrectomy/
2. exp Partial nephrectomy/
3. exp "Patient history of nephrectomy"/
4. nephrectom*.mp.
5. (kidney* adj5 (excision* or remov*)).mp.
6. 1 or 2 or 3 or 4 or 5

Surgeon or Hospital Volume Terms

7. ((physician* or urol* or surg* or operat* or hospital* or procedure*) adj5 (volume* or workload* or caseload* or performance* or number*)).mp.
8. exp Hospital/

9. exp Surgeon/
10. (volume* or workload* or caseload* or performance*).mp.
11. exp Workload/
12. 8 and 10
13. 9 and 10
14. 8 and 11
15. 9 and 11
16. exp Centralization/
17. centrali*ation.mp.
18. 7 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

Outcome Terms

19. exp Outcome Assessment/
20. exp Treatment Outcome/
21. outcome.mp.
22. exp Mortality/
23. mortalit*.mp.
24. exp Morbidity/
25. morbidit*.mp.
26. exp "Length of Stay"/
27. length of stay.mp.
28. ((duration or length or period) adj5 (stay or hospital*)).mp.
29. exp Survival/
30. survival.mp.
31. exp Hospital readmission/
32. readmission.mp.
33. exp Postoperative Complications/
34. complication*.mp.
35. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 6 and 18 and 35

Cochrane Library

Nephrectomy Terms:

1. exp Nephrectomy/
2. nephrectom*
3. kidney* near (excision* or remov*)
4. 1 or 2 or 3

Surgeon or Hospital Volume Terms

5. (physician* or urol* or surg* or operat* or hospital* or procedure*) near (volume* or workload* or caseload* or performance* or number*)
6. exp Hospitals/
7. exp Surgeons/
8. volume* or workload* or caseload* or performance*
9. exp Workload/
10. 6 and 8
11. 7 and 8
12. 6 and 9
13. 7 and 9
14. exp Centralized Hospital Services/
15. centrali*ation
16. 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Outcome Terms

17. exp "Outcome Assessment (Health Care)"/
18. exp Patient Outcome Assessment/
19. exp "Outcome and Process Assessment (Health Care)"/
20. outcome
21. exp Treatment Outcome/
22. exp Mortality/

23. mortalit*
24. exp Morbidity/
25. morbidit*
26. exp "Length of Stay"/
27. length of stay
28. (duration or length or period) near (stay or hospital*)
29. exp Survival/
30. survival
31. exp Patient Readmission/
32. readmission
33. exp Postoperative Complications/
34. complication*
35. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 4 and 16 and 35

S3 Appendix. Results of meta-regression investigating the heterogeneity in the meta-analyses for mortality and its potential explanatory variables in **A**. radical nephrectomy and **B**. partial nephrectomy.

A.

Explanatory Variable	Regression Coefficient	95% Confidence Interval	p Value
Study year	0.96	0.88, 1.04	0.24
Country of Study			
England	1.46	0.70-3.02	0.24
Japan	0.76	0.28-2.04	0.50
Norway	0.42	0.10-1.76	0.18
USA	1.06	0.51, 2.21	0.85
Data type			
Administrative	1.36	0.71, 2.61	0.28
Clinical	0.74	0.38, 1.32	0.28
Number of patients	1.00	1.00, 1.00	0.45
Number of hospitals	1.00	1.00, 1.00	0.14
Patient age (mean)	0.92	0.70, 1.19	0.36
Patient gender (% of male)	0.96	0.88, 1.05	0.25
Threshold for HV hospitals	0.99	0.99, 1.00	0.01

B.

Explanatory Variable	Regression Coefficient	95% Confidence Interval	p Value
Study year	0.96	0.80, 1.14	0.51
Country of Study			
England	1.42	0.46, 4.27	0.40
Japan	1.19	0.67, 2.13	0.41
USA	0.80	0.51, 1.26	0.22
Data type			
Administrative	1.09	0.61, 1.97	0.66
Clinical	0.91	0.51, 1.65	0.66
Number of patients	1.00	1.00, 1.00	0.26
Number of hospitals	1.00	0.99, 1.00	0.80
Patient age (mean)	1.04	0.97, 1.11	0.16
Patient gender (% of male)	0.99	0.80, 1.23	0.87
Threshold for HV hospitals	1.00	0.93, 1.07	0.83

S4 Appendix. List of excluded studies after full-text review and justifications.

Reference	Justification
1. Finlayson EVA, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. *Arch Surg*. 2003;138(7):721-726.	Overlapping studied period. Eliminated as per rule 4.
2. Gilbert SM, Dunn RL, Miller DC, Daignault S, Ye Z, Hollenbeck BK. Mortality After Urologic Cancer Surgery: Impact of Non-index Case Volume. *Urology*. 2008;71(5):906-910.	Overlapping studied period. Eliminated as per rule 2.
3. Joudi FN, Allareddy V, Kane CJ, Konety BR. Analysis of complications following partial and total nephrectomy for renal cancer in a population based sample. *J Urol*. 2007;177(5):1709-1714.	Overlapping studied period. Eliminated as per rule 2.
4. Joudi FN, Konety BR. The impact of provider volume on outcomes from urological cancer therapy. *J Urol*. 2005;174(2):432-438.	Review
5. Joudi FN, Konety BR. The volume/outcome relationship in urologic cancer surgery. *Support Cancer Ther*. 2004;2(1):42-46.	Review
6. Killen SD, O'Sullivan MJ, Coffey JC, Kirwan WO RH. Provider volume and outcomes for oncological procedures. *Br J Surg*. 2005;92:389-402.	Review
7. Konety BR, Allareddy V, Modak S, Smith B. Mortality after major surgery for urologic cancers in specialized urology hospitals: are they any better? *J Clin Oncol*. 2006;24(13):2006-2012.	Overlapping studied period. Eliminated as per rule 2.
8. Mayer EK, Purkayastha S, Athanasiou T, Darzi A, Vale JA. Assessing the quality of the volume-outcome relationship in uro-oncology. *BJU Int*. 2009;103(3):341-349.	Review
9. Nuttall M, Vandermeulen J, Phillips N, et al. a Systematic Review and Critique of the Literature Relating Hospital or Surgeon Volume To Health Outcomes for 3 Urological Cancer Procedures. *J Urol*. 2004;172(6):2145-2152.	Review
10. Penson DF. Mortality after major surgery for urologic cancers in specialized urology hospitals: are they any better? *Urol Oncol*. 2006;24(5):460.	Commentary
11. Peyronnet B, Couapel J-P, Patard J-J, Bensalah K. Relationship between surgical volume and outcomes in nephron-sparing surgery. *Curr Opin Urol*. 2014;24(5):453-458.	Review
12. Pieper D, Mathes T, Neugebauer E, Eikermann M. State of evidence on the relationship between high-volume hospitals and outcomes in surgery: a systematic review of systematic reviews. *J Am Coll Surg*. 2013;216(5):1015-1025.	Review
13. Sugihara T, Yasunaga H, Horiguchi H, et al. Performance comparisons in major uro-oncological surgeries between the USA and Japan. *Int J Urol*. 2014;21(11):1145-1150.	Volume-outcome relationship not described
14. Trinh QD, Schmitges J, Sun M, et al. Does partial nephrectomy at an academic institution result in better outcomes? *World J Urol*. 2012;30(4):505-510.	Overlapping studied period. Eliminated as per rule 2.
15. Wang HH, Tejwani R, Zhang H, Wiener JS, Routh JC. Hospital Surgical Volume and Associated Postoperative Complications of Pediatric Urological Surgery in the United States. *J Urol*. 2015;194(2):506-511.	Paediatric cohort
16. Fernando A, Fowler S, O'Brien T, et al. Nephron-sparing surgery across a nation - Outcomes from the British Association of Urological Surgeons 2012 national partial nephrectomy audit. *BJU Int*. 2016;117(6):874–82.	Volume-outcome relationship not described
17. Tinay I, Gelpi-Hammerschmidt F, Leow JJ, et al. Trends in utilisation, perioperative outcomes, and costs of nephroureterectomies in the management of upper tract urothelial carcinoma: A 10-year population-based analysis. *BJU Int*. 2016;117(6):954–60.	Volume-outcome relationship in nephroureterecotmy only

BMJ Open

Influence of Hospital Volume on Nephrectomy Mortality and Complications: A Systematic Review and Meta-Analysis Stratified by Surgical Type

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016833.R1
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INFLUENCE OF HOSPITAL VOLUME ON NEPHRECTOMY MORTALITY AND COMPLICATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS STRATIFIED BY SURGICAL TYPE

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ABSTRACT

Objectives

The provision of complex surgery is increasingly centralised to high volume specialist hospitals. Evidence to support nephrectomy centralisation however has been inconsistent. We conducted a systematic review and meta-analysis to determine the association between hospital case volumes and perioperative outcomes in radical nephrectomy, partial nephrectomy and nephrectomy with venous thrombectomy.

Methods

Medline, Embase and the Cochrane Library were searched for relevant studies published between 1990 and 2016. Pooled effect estimates for nephrectomy mortality and complications were calculated for each nephrectomy type using the DerSimonian and Laird random-effects model. Sensitivity analyses were performed to examine the effects of heterogeneity on the pooled effect estimates by excluding studies with the heaviest weighting, lowest methodological score, and most likely to introduce bias from misclassification of standardised hospital volume.

Results

Some 226,372 patients from sixteen publications were included in our review and meta-analysis. Considerable between-study heterogeneity was noted and only a few reported volume-outcome relationships specifically in partial nephrectomy or nephrectomy with venous thrombectomy.

High volume hospitals were correlated with a 26% and 52% reduction in mortality for radical nephrectomy (OR 0.74, 95% CI 0.61-0.90, $p<0.01$) and nephrectomy with venous thrombectomy (OR 0.48, 95% CI 0.29-0.81, $p<0.01$) respectively. In addition, radical nephrectomy in high volume hospitals was associated with an 18% reduction in complications (OR 0.82, 95% CI 0.73-0.92, $p<0.01$). No significant volume-outcome relationship in mortality (OR 0.84, 95% CI 0.31-2.26, $p=0.73$) or complications (OR 0.85, 95% CI 0.55-1.30, $p=0.44$) was observed for partial nephrectomy.

Conclusions

Our findings suggest that patients undergoing radical nephrectomy have improved outcomes when treated by high volume hospitals. Evidence of this in partial nephrectomy and nephrectomy with venous thrombectomy is however not yet clear and could be secondary to the low number of studies included and the small patient number in our analyses. Further investigation is warranted to establish the full potential of nephrectomy centralisation particularly as existing evidence is of low quality with significant heterogeneity.

STRENGTH & LIMITATIONS OF THIS STUDY

- This is a contemporary systematic review and meta-analysis of the associations between hospital case volumes and nephrectomy outcomes.
- Sixteen primary studies, which is four folds greater in number than previous meta-analyses, were used to synthesised the pooled effect estimates for nephrectomy mortality and complications.
- To the best of our knowledge, this is the first study to date to stratify analyses based on nephrectomy type to account for differences in technical complexity and rates of adverse outcomes.
- Current evidence in nephrectomy outcome-volume relationship is of low quality and considerable heterogeneity exists between studies in design, type of data used, outcomes measured and statistical methodologies.
- Our study highlights the limitations in existing evidence and suggests questions that should be addressed in future research.

INTRODUCTION

In recent years, there has been an emerging trend for the centralisation of complex operations in healthcare systems around the world [1–3]. This shift is supported by the growing research and evidence suggesting that hospitals and surgeons with high case loads have better patient outcomes [4–8]. Proponents argue that centralisation allows more effective use of clinical expertise and specialist equipment, and the increased exposure improves surgical skills and provides better training opportunities. Centralisation can also facilitate quicker adoption of care pathways, such as enhanced recovery, and may have more long-term financial sustainability for hospitals. However, surgical centralisation requires further travel distance and limits patient choice when many would prefer to undergo surgery locally even if greater mortality risks are taken into consideration [9]. Differences in disease biology, surgical complexity and rate of adverse outcomes may also limit the perceived benefits of centralisation. Such a health service model may therefore not be appropriate for all conditions and operations.

Renal cancer accounts for over 2% of all new cancer diagnoses worldwide affecting more than 330,000 individuals annually [10]. Widespread use of cross-sectional imaging and increasing prevalence of obesity have contributed to a rising renal cancer incidence in many countries [11–13]. Despite recent developments in systemic therapies, nephrectomy is often considered the only potentially curative treatment for renal cancer, and the number of nephrectomies being performed is likely to increase as a result. It is therefore critical that health service providers understand the effects that organisational changes may have on patient outcomes. While there has been an expansion of volume-outcome research, no consensus has so far been reached on the efficacy of centralising nephrectomy, and many uncertainties remain about its potential benefits particularly as radical and partial nephrectomy carry different surgical complexities and outcomes [14,15]. We present a contemporary systematic review and meta-analysis of the published literature on the association between hospital case volumes and perioperative outcomes stratified by nephrectomy types. We hypothesise that outcomes significantly improve with higher nephrectomy case volumes.

METHODS

Search criteria & data extraction

The systematic review and meta-analysis was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1) [16]. Medical subject heading (MeSH) terms and key words for nephrectomy, case volume and outcomes were used in Medline, Embase and the Cochrane Library to search for relevant studies published between January 1990 and December 2016 (Appendix 2). Studies published prior to 1990 were not considered as recent medical and surgical advancements would have limited their applicability to the modern healthcare system. Only studies published in English were considered as the risk of potential language bias associated with this exclusion generally has little effect on summary effect estimates [17]. References were searched manually for additional relevant studies.

We included studies that presented original data in full-texts on adult nephrectomy outcomes across two or more hospital case volume categories. Abstracts, case reports, and review articles were excluded. No restriction was set on the study design and both prospective and retrospective studies were considered. Only those describing the volume-outcome relationships in radical nephrectomy with or without venous thrombectomy and/or partial nephrectomy were eligible. Paediatric cohorts were excluded as were articles comprised solely of nephroureterectomy or nephrectomy for non-oncological indications. Restriction on the reported outcomes was only applied at the end stage of the search to enable assessment of the current published evidence. Only studies reporting nephrectomy mortality and complications were included in the final analysis.

Two investigators (R.C.J.H and J.M.) independently reviewed all studies for inclusion, data extraction and methodological quality. Any disagreement between the two reviewers was resolved by discussion and consultation with a third reviewer (J.N.A.). Where only rates of outcomes were presented, these were applied to the case number to give the number of events, within the error of the published results. Study authors were contacted for further clarification if specific rates of outcomes and case numbers were not published [18,19].

As the cut-off values for hospital case volume categories differed among studies, we used the approach adopted by similar previous meta-analyses by dichotomising the volume groups presented by each study into low volume (LV) and high volume (HV) when the article presented an even number of volume groupings [20,21]. If a study presented an odd number of volume groups, the middle group was considered as LV.

Methodological quality and potential risk of bias were scored using a ten-domain system designed to measure the degree in which the study is likely to reveal generalizable conclusion about the magnitude and nature of the volume-outcome relationship [22,23]. Each domain provides a score between zero and three with a total maximum of 18, suggesting a well-designed study. The parameters included the representativeness of the sample, the number of hospitals analysed, the samples size, the number of adverse events recorded, the appropriateness of patient selection, the number of volume categories examined, the number of outcomes measured, the degree of risk adjustment performed, whether hospital and surgeon case volumes were analysed in conjunction, and whether clinical processes of care were measured.

If studies extracted data from the same source with overlaps in the study periods, we employed the following rules to avoid duplicating populations: 1) studies with identical patient cohort but examining different outcomes were considered and analysed separately; 2) studies that derived data from older datasets were excluded in favour of the more contemporary cohort; 3) if the above rules were not applicable, studies with the lower methodological quality scores were excluded; 4) where quality scores were equal, the study covering the longest period was included.

Quantitative data synthesis

All statistical analyses were performed using Stata 14 [24]. Nephrectomy types were categorised into radical nephrectomy, partial nephrectomy and nephrectomy with venous thrombectomy and analysed separately. Studies involving multiple types of nephrectomies were analysed based on the aforementioned groups, but if this was not feasible, they were categorised as radical nephrectomy. With the assumption that a distribution of effects exists amongst studies, all pooled effect size were calculated using the DerSimonian and Laird random-effects model, which provided more conservative estimates compared to fixed-effect model. Odds ratio (OR) and 95% confidence interval (CI) were calculated and presented for each outcome measure using LV groups as the reference.

When the meta-analysis demonstrated significantly better outcomes in HV hospitals, we quantified the clinical effectiveness of centralisation by calculating the numbers needed to treat, or in our case numbers needed to centralise (NNC). NNC represents the number of cases that will need to be centralised from LV hospitals and treated by HV hospitals in order to prevent one adverse event.

Heterogeneity

As the DerSimonian and Laird model would have only accounted for some between-study heterogeneity, we further quantified heterogeneity by calculating I^2 statistic. I^2 provides an easily understood number, which describes the proportion of total variation in estimates that is due to heterogeneity rather than chance [25]. Values of 25% or lower denote low heterogeneity and values of 75% or greater denote considerable heterogeneity [26]. Meta-regression was performed to explore the influence of potential explanatory variables on heterogeneity including each study's publication year, country, data source, number of patients and their demographics, number of hospitals, and threshold for HV hospitals.

Publication bias

Funnel plots were generated to investigate potential publication bias, and were enhanced to include contours that divide the funnel into statistically significant and non-significant areas. Funnel plot symmetry suggests low probability of publication bias and Harbord's modified test was used to test for asymmetry [27]. Harbord's test reduces false positive rates when applied to binary outcome data, especially when there is low between-study heterogeneity. Trim and fill method was also performed to account for publication bias by adjusting the meta-analysis to incorporate the theoretically missing studies [28].

Sensitivity analysis

To examine specific studies' effects on pooled effect size, sensitivity analyses were performed by excluding individual studies and repeating the meta-analyses. We examined the effects of studies with the heaviest weighting and studies with the lowest methodological quality score. As there is currently no consensus on what nephrectomy case volume is necessary to be considered as HV, we repeated our analyses by excluding studies whose standardised HV categories overlapped most significantly with the standardised LV categories in other studies to account for potential bias of misclassifying volume categories in our dichotomy.

As secondary analyses, we additionally repeated the meta-analysis three further times with different methods of dichotomising the volume groups to examine whether our initial estimates would remain consistent. The methods of dichotomising were 1) lowest volume categories and all others 2) even dichotomy and when studies present an odd number of volume categories, the middle group was considered as HV 3) highest volume categories and all others.

RESULTS

Study selection & characteristics

From the 5,680 articles initially identified, 16 were included in the systematic review containing 226,372 patients from six countries (Figure 1). For the meta-analysis, eleven studies with 201,506 patients examining radical nephrectomy were included while four studies of 23,617 patients and two studies of 1,249 patients examining partial nephrectomy and nephrectomy with venous thrombectomy were included respectively. Publication year ranged from 2002 to 2016, while cohort periods covered from 1993 to 2013.

Tables 1 summarises the characteristics of the included studies. Variations were observed in study designs including source of data and outcomes measured. Out of a maximum possible score of 18, the median quality score from the included studies was 9 (interquartile range 8 – 9) with the majority of the studies failing to adequately address potential confounders including measuring the appropriateness of patient selection, adjusting for case-mix variations and accounting for differences in clinical risks and processes of care (Appendix 3). Variable thresholds for HV hospitals were noted across the included studies.

Table 1. Characteristics and methodological summary of studies.

	Study Characteristics								Outcomes Measured							
Reference	Year	Country	Period	Data Type	No. of Patients	No. of Hospitals	Low[a]	High[a]	Mortality	Complications (breakdowns)	Transfusion	LOS	Conversions	Others	Case Mix	Quality Score (18)
Radical Nephrectomy																
Hjelle[29]	2016	Norway	2008-2013	Admin	3,273	40	20	40	30-day	-	-	-	+	-	Demographics, tumour stage, nephrectomy type	8
Becker[30]/ Sun[31][b]	2014 / 2012	USA	1998-2007	Admin	48,172	N/S	5	16	In-hospital	+ (17 events inc haemorrhage, cardiac arrest, infection, wound disruption, seroma, pneumothorax, VTE etc)	+	+	-	-	Demographics, co-morbidity, nephrectomy type, laparoscopy, payer/hospital type	9
Hanchanale[32]	2010	England	1998-2005	Admin	20,672	1,181	14	35	In-hospital	-	-	+	-	-	Demographics	9
Yasunaga[33]	2010	Japan	2006-2007	Admin	7,988	646	26	65	In-hospital	+ (11 events inc surgical site infection, UTI, VTE, sepsis, ileus, stroke, cardiac events, renal, failure, peritonitis etc)	-	-	-	-	Demographics, co-morbidity, laparoscopy, hospital type, tumour location	9
Mitchell[34]	2009	USA	2003-2007	Clinical	42,988	134	99/4.5yr	500/4.5yr	In-hospital	+ (not specified)	-	+	-	ICU admission	None	9
Yasunaga[18]	2008	Japan	2006-2007	Clinical	1,704	461	9	40	In-hospital	+ (wound infection, pneumonia, ileus, renal dysfunction, others)	-	-	-	OT, EBL	Demographics, co-morbidity, laparoscopy, tumour stage & location	11
Davenport[35]	2005	England	2004	Clinical	598	48	<1/mo	>1/mo	N/S	+ (12 events inc bleeding, bowel injury, GI bleed, renal failure, pneumothorax, VTE, MI, splenic injury etc)	+	-	+	OT	None	4
Keoghane[36]	2004	England	2001-2002	Clinical	263	25	5	6	-	+ (16 events inc renal failure, sepsis, wound infection, bowel injury, incisional hernia, peri-hepatic collection etc)	-	-	+	-	None	3
Taub[37]	2004	USA	1993-1997	Admin	16,858	962	14	34	In-hospital	-	-	+	-	-	Demographics, co-morbidity, admission acuity	9
Birkmeyer[38]	2002	USA	1994-1999	Admin	58,990	3,292	6	33	30-day or In-hospital	-	-	-	-	-	Demographics, co-morbidity, admission acuity	7
Partial Nephrectomy																
Couapel[39]	2014	France	2010	Clinical	570	53	4/7mo	19/7mo	N/S	+ (medical and surgical events, not further specified)	-	+	+	OT, EBL, Totalisation, +ve margin	N/S	8

Monn[40]	2014	USA	2009-2011	Admin	17,583	322	13	35	-	+ (organ based complications not further specified, pain, seroma, shock, haematoma, hypotension, VTE, pneumothorax)	+	+	-	Hospital cost	Demographics, co-morbidity, payer, region, hospital type	9
Abouassaly[41]	2012	Canada	1998-2008	Admin	4,292	181	146/10yr	797/10yr	In-hospital	+ (not specified)	-	-	-	-	Demographics, co-morbidity, region	12
Taub[37]	2004	USA	1993-1997	Admin	1,172	962	14	34	In-hospital	-	-	+	-	-	Demographics, co-morbidity, admission acuity	9
Nephrectomy with Venous Thrombectomy																
Toren[42]	2013	Canada	1998-2008	Admin	816	120	N/S	N/S	In-hospital	+ (40 medical and surgical events inc MI, CHF, PE, infection, organ injury, pneumothorax etc)	+	-	-	-	Demographics, co-morbidity, region	11
Yap[19]	2012	Canada	1995-2004	Admin	433	N/S	2/10yr	8/10yr	30-day	-	-	-	-	-	Demographics	11

[a]Low, cut-off value for lowest volume group; high, cut-off value for highest-volume group. Volume units are cases per year unless specified. [b]Becker and Sun were equal in the data source used, outcomes evaluated, periods covered and quality scores, but employed different analyses to evaluate the benefit of regionalisation and volume-outcome relationship in nephrectomy [30,31]. We therefore treated them as one single cohort, with no duplicates in our analysis. Admin: Administrative. N/S: Not specified. VTE: venous thromboembolism. MI: Myocardial infarction. CHF: Congestive heart failure. PE: Pulmonary embolism. UTI: Urinary tract infection. GI: Gastrointestinal. OT: Operating time. EBL: Estimated blood loss. ICU: Intensive care unit.

Mortality and Hospital Volumes

Post-operative mortality, defined as in-patient or 30-day, was the most frequently examined outcome, reported in fourteen studies. Ten studies reported mortality in radical nephrectomy [18,29–35,37,38], three in partial nephrectomy [37,39,41] and two in nephrectomy with venous thrombectomy [19,42]. The overall mortality was 1.59% (range 0.20-7.2) with mortality rates in HV and LV hospitals being 1.47% and 1.68% respectively.

Radical Nephrectomy

Meta-analysis demonstrated that patients who underwent radical nephrectomy in HV hospitals had a 26% reduction (OR 0.74, 95% CI 0.61-0.90, p<0.01) in post-operative mortality, corresponding to a NNC of 234 (Figure 2A). Significant heterogeneity was observed (I^2 75.0%, p<0.01). Meta-regression was performed to investigate the potential explanatory variables for heterogeneity, and only differences in the threshold values for HV hospitals were shown to be a significant contributor (Appendix 4A). Subgroup analysis of the three studies examining exclusively radical nephrectomies demonstrated a more pronounced reduction in post-operative mortality favouring HV hospitals (OR 0.62, 95% CI 0.53-0.71, p<0.01) [18,34,37]. This corresponded to a lower NNC of 166 with little residual heterogeneity (I^2 0.0 %, p=0.40). The overall funnel plot was visually asymmetrical particularly missing studies with effect estimates favouring LV hospitals (Figure 3). However, the Harbord's modified test did not show significant asymmetry (p=0.40) and "trim and fill" method did not change the initial estimate, indicating no clear evidence of publication bias. In sensitivity analyses, exclusion of the most heavily weighted study led to a similar pooled-effect estimate (OR 0.70, 95% CI 0.55-0.88, p<0.01) [38]. Exclusion of the study with the lowest quality score also did not significantly alter our result (OR 0.74, 95% CI 0.61-0.91, p<0.01) [35]. To examine the potential bias introduced by misclassification of hospital volume, two cohorts were excluded [30,31,35]. This did not substantially change our pooled-effect estimate either (OR 0.73, 95% CI 0.58-0.93, p=0.01). Overall, radical nephrectomies in HV hospitals appeared to have significantly lower mortality.

Partial Nephrectomy

Meta-analysis showed that partial nephrectomy patients operated in HV hospitals had a 16% reduction in post-operative mortality but this was not statistically significant (OR 0.84, 95% CI 0.31-2.26, p=0.73) (Figure 2B). Moderate but non-significant heterogeneity was noted (I^2 36.84 %, p=0.21). Sensitivity analyses removing studies with the heaviest weighting [41] or most likely to introduce misclassification bias of exposure [39] demonstrated reduced mortality favouring HV hospitals, but these remained non-significant.

Nephrectomy with Venous Thrombectomy

Patients who underwent nephrectomy with venous thrombectomy in HV hospitals had a 52% reduction (OR 0.48, 95% CI 0.29-0.81, p<0.01) in short-term mortality compared to LV hospitals (Figure 2C). This corresponded to a NNC of 25 with low heterogeneity (I^2 0.0 %, p=0.50). Due to the small number of studies reporting this outcome, further testing of heterogeneity and publication bias was not expected to generate meaningful results and this was not attempted.

Complications and Hospital Volumes

Complication was the second most frequently investigated outcome, reported in eleven studies. Events considered as a complication differed among studies (Table 1). Seven studies reported complications in radical nephrectomy [18,30,31,33–36] and three in partial nephrectomy [39–41]. Only one study examined volume-outcome relationship in nephrectomy with venous thrombectomy and meta-analysis was therefore not appropriate [42]. The overall complication rate was 16.26% (range 7.4-78). HV hospitals had complication rates of 15.00% compared to 17.51% in LV hospitals.

Radical Nephrectomy

Meta-analysis showed an 18% reduction (OR 0.82, 95% CI 0.73-0.92, $p<0.01$) in nephrectomy complications in HV centres, corresponding to a NNC of 38 (Figure 4A). Significant heterogeneity was noted (I^2 76.25%, $p<0.01$), but none of the factors examined in meta-regression significantly contributed to this (Appendix 4B). Sensitivity analyses by removing studies with the lowest quality [36] or most likely to introduce misclassification bias of exposure [35,36] did not significantly alter our initial result. Excluding study with the heaviest weighting however led to a loss of significance in the pooled-effect estimate, which however still demonstrated a 11% reduction in complications in HV hospitals (OR 0.89, 95% CI 0.74-1.08, p=0.24). Overall, radical nephrectomies performed in HV hospitals appeared to have significantly lower complications compared to LV hospitals.

Partial Nephrectomy

Partial nephrectomy patients operated in HV hospitals had a 15% reduction in complications, but this was not statistically significant (OR 0.85, 95% CI 0.55-1.30, p=0.44) (Figure 4B). Significant heterogeneity was noted (I^2 94.80%, $p<0.01$). Sensitivity analysis by removing studies with the heaviest weighting [40] or most likely to introduce misclassification bias of hospital volume [39] did not result in significance.

Secondary analyses using different methods for dichotomising HV and LV

As there is no consensus on what constituted HV hospitals in current evidence, simple dichotomy of volume groups may introduce inherent bias to the estimates. Yet no recommendation on how best to proceed in volume-outcome analysis presently exists. In our secondary analyses, we consistently observed significantly lower risks of mortality for both radical nephrectomy and nephrectomy with venous thrombecotmy in HV hospitals regardless how volumes were dichotomised (Table 2). The magnitudes of risk reductions were more pronounced when higher thresholds for HV hospitals were considered particularly for radical nephrectomy mortality. Partial nephrectomy mortality however continued to demonstrate no significant association to volume even when dichotomies were comparing the highest volume groups to all others.

Risks of radical nephrectomy complications remained significantly reduced in HV hospitals when the dichotomy threshold for HV hospitals was increased, but the significance was lost when the thresholds were lowered. Association between hospital volumes and partial nephrectomy complications remained insignificant regardless of how HV was defined in our dichotomy.

Table 2: Results of meta-analysis by using different methods of dichotomising volume groups.

		Lowest volume group vs. all others	Even dichotomy, middle group as HV	Even dichotomy, middle group as LV (Primary analysis)	Highest volume group vs. all others
Mortality					
Radical Nephrectomy		OR: 0.82 95%CI 0.71-0.94 p=0.01	OR: 0.83 95%CI 0.72-0.95 p<0.01	OR: 0.74 95%CI 0.61-0.90 p<0.01	OR: 0.72 95%CI 0.61-0.85 p<0.01
Partial Nephrectomy		OR: 0.48 95%CI 0.18-1.31 p=0.15	OR: 0.67 95%CI 0.17-2.75 p=0.58	OR: 0.84 95%CI 0.31-2.26 p=0.73	OR: 0.93 95%CI 0.31-2.77 p=0.90
Nephrectomy with Venous Thrombectomy		OR: 0.59 95%CI 0.35-0.99 p=0.045	OR: 0.46 95%CI 0.27-0.80 p<0.01	OR: 0.48 95%CI 0.29-0.81 p=0.01	OR: 0.48 95%CI 0.25-0.92 p=0.03
Complications					
Radical Nephrectomy		OR: 0.89 95%CI 0.78-1.01 p=0.07	OR: 0.84 95%CI 0.68-1.05 p=0.13	OR: 0.82 95%CI 0.73-0.92 p<0.01	OR: 0.82 95%CI 0.73-0.92 p<0.01
Partial Nephrectomy		OR: 0.82 95%CI 0.55-1.41 p=0.60	OR: 0.80 95%CI 0.47-1.36 p=0.40	OR: 0.85 95%CI 0.55-1.30 p=0.44	OR: 0.81 95%CI 0.53-1.24 p=0.33

DISCUSSION

Evidence on volume-outcome relationships in complex diseases and procedures has increased substantially in recent years. Many operations have been shown to have improved outcomes in HV centres, but this may not be uniform across all surgeries and benefits have not been associated with volume in percutaneous nephrolithotomy or appendicectomy [43–48]. This meta-analysis provides a contemporary review of the effects of centralisation in nephrectomy outcomes. It reveals significant inverse associations between hospital case volumes for short-term mortality and complications for radical nephrectomy, but evidence of these for partial nephrectomy and nephrectomy with venous thrombectomy remains less compelling.

Considered individually, all but three studies in our review reported lack of associations between hospital volume and nephrectomy mortality [29,37,38]. However, such associations in favour of HV hospitals were apparent when considering the totality of the evidence particularly in radical nephrectomy and venous thrombectomy. This finding is consistent with the only other meta-analysis on nephrectomy volume-outcome relationship published in 2009 but includes four-fold greater number of studies [23]. Our meta-analysis demonstrates that the mortality benefit seen in radical nephrectomy may be relatively small requiring centralisation of 234 patients in order to avoid one death. However, the NNC decreased considerably to 166 in our sensitivity analyses. Coupled with the much lower NNC of 38 for radical nephrectomy complications, there is moderate evidence to support its centralisation.

In our analyses, the mortality reduction for venous thrombectomy was observed to be more pronounced than that in radical nephrectomy. This is consistent with the "practice makes perfect" hypothesis particularly as venous thrombectomy is a technically more challenging procedure compared to radical nephrectomy, though interestingly a similar trend was not observed for partial nephrectomy [49]. These results should however be interpreted taking into consideration that only a few studies have so far reported on the volume-outcome relationships for partial nephrectomy and venous thrombectomy and the pooled effect estimates were synthesised from just two to three publications, thus the overall evidence is weak. As partial nephrectomy has only been widely adopted in the last two decades and nephrectomy centralisation also a relatively recent phenomenon, it is likely that more evidence will emerge in the coming years and repeating the meta-analysis at such point is warranted [1,50]. This will be of particular importance as partial nephrectomy has been demonstrated to be a safe procedure and the relatively small number of partial nephrectomy patients in our meta-analysis might not have been sufficiently powered to reveal the true presence of a volume-outcome relationship, as evident in our wide confidence interval [51]. This may also explain the lack of significant association between partial nephrectomy complications and hospital volumes. With its low mortality and morbidity rates, other outcome measures such as ischaemic time and negative surgical margins, are likely to be more appropriate quality markers in volume-outcome analysis, but these have so far been poorly evaluated.

Despite the strict inclusion criteria in our studies, we observed considerable heterogeneity, especially in the meta-analyses of nephrectomy complications. One explanation for this is the lack of standardised reporting of complications by individual studies. Harder endpoints as previously discussed could have overcome this. Other more objective outcomes including transfusion rate and length of stay were reported by four [30,31,35,40] and seven studies [30–32,34,39,40,52] in our systematic review respectively, but they were not in adequate numbers to be stratified by nephrectomy types or in sufficiently detailed data to perform meta-analyses. In addition, variations in the threshold values for HV hospitals likely contributed to the heterogeneity, although this was not evident in the meta-regression. Volume was also used as a proxy marker for surgical and care quality, but the precise clinical processes that may improve patient outcomes were not directly measured or identified. It is therefore conceivable for some heterogeneity to arise from these unmeasured practices. Results from the multiple sensitivity analyses to adjust for study differences have however remained robust and our study would still appear to be informative and relevant. There are other research designs that may be more appropriate in testing our hypothesis such as analysis of primary data amalgamated from multiple population cohorts. The considerable ethical concerns and logistical constraints of this may however be challenging to overcome and not practically feasible.

While there has been an expansion in the studies on nephrectomy volume-outcome relationship, many questions continue to be unanswered. The proportion of nephrectomy performed under laparoscopy or robotic assistance is growing [53,54]. There is however a paucity of evidence specifically investigating this in the volume-outcome context with only one study examining the differences in perioperative measures in robotic partial nephrectomy [40]. Three other studies have adjusted surgical techniques in multivariable regressions, but these did not directly demonstrate the effect of laparoscopic volumes on surgical outcomes [18,30,33]. Due to the small study number and data quality, it was not possible in this meta-analysis to further sub-stratify each nephrectomy type into open and minimally invasive and our results should be interpreted taking this limitation into account.

Tumour characteristics including TNM stage and grades are well established to significantly affect and predict nephrectomy mortality, but only two studies have so far adjusted for this in their analyses [18,29]. Surgeon case volume and degree of specialisation also play significant roles in determining operative outcome, and can be more important than hospital case volume alone [45,55–57]. While not the focus of this study, no significant association was found between surgeon volume and complications in radical nephrectomy [18], but 31% and 16% reduction in mortality and complications respectively was observed in partial nephrectomy in HV surgeons [41]. HV surgeons performing nephrectomy with venous thrombectomy were also reported to have reduced risk of mortality [19], but this was not observed in a subsequent study [42]. As our analyses were based on crude pooled effect estimates, future meta-analysis should ideally attempt to adjust for other possible confounders including patient demographics, socioeconomic status and comorbidities, although this may be methodologically challenging. It would be of high interest to understand the interactions between patient characteristics, surgeon volume, surgical approach, and oncological factors in the volume-outcome relationship and may provide additional insights to selecting patients that will benefit the most from nephrectomy centralisation, such as those with multiple comorbidities or advanced disease. Similarly, no study has examined the long-term benefits of centralising nephrectomy when high volume centres have been demonstrated to increase oncological survival in other cancer surgeries [58,59]. Results of this may further influence the recommendations for nephrectomy centralisation and this is currently being explored in our ongoing work. Other outcomes including long-term risks of chronic kidney disease and cardiovascular morbidities and patient reported outcome measures may also provide more relevant and holistic measurements of the potential efficacy of nephrectomy centralisation.

Our secondary analyses would suggest that a minimum volume threshold for nephrectomy likely exist, and beyond that, risks of adverse outcomes may continue to decrease with further increase in volume. An important limitation of this however is that this minimum threshold cannot be objectively determined from the current evidence. The specific care processes that may produce good outcomes, such as access to nurse specialists and clinical trials, could not be determined from our study. As volume is likely to be a proxy marker for quality, increasing volume alone in itself is unlikely to reduce adverse results [60]. Future research should concentrate on identifying the qualitative differences between providers in order for the contributing good practices to be adopted by lesser performing centres.

CONCLUSIONS

Current evidence of the association between hospitals volumes and nephrectomy outcomes is of low quality with considerable between-study heterogeneity. Our meta-analyses demonstrated significant reductions in mortality and complications for patients undergoing radical nephrectomy in HV hospitals. Evidence of this in partial nephrectomy and nephrectomy with venous thrombectomy is not yet clear but warrants further investigations.

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CONTRIBUTORS

RCJH, VJG and JNA contributed to the study conception and design. RCJH, JM and JNA contributed to data acquisition and risk of bias assessment. RCJH, TS, GL, VJG, JNA contributed to statistical analysis, data interpretation and critical manuscript revision. RCJH contributed to drafting the manuscript. RCJH contributed to obtaining funding. GL, VJG and JNA contributed to supervision of the study.

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COMPETING INTEREST STATEMENT

None declared.

DATA SHARING STATEMENT

No additional data are available.

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SUPPORTING INFORMATION CAPTIONS

Appendix 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Appendix 2. Literature search algorithm used in Medline, Embase and the Cochrane Library.

Appendix 3. Breakdown of quality assessment scores for each study included in the review.

Appendix 4. Results of meta-regression investigating the potential explanatory variables for the heterogeneity in the meta-analyses for mortality in **A**. radical nephrectomy and **B**. partial nephrectomy.

Appendix 5. List of excluded studies after full-text review and justifications.

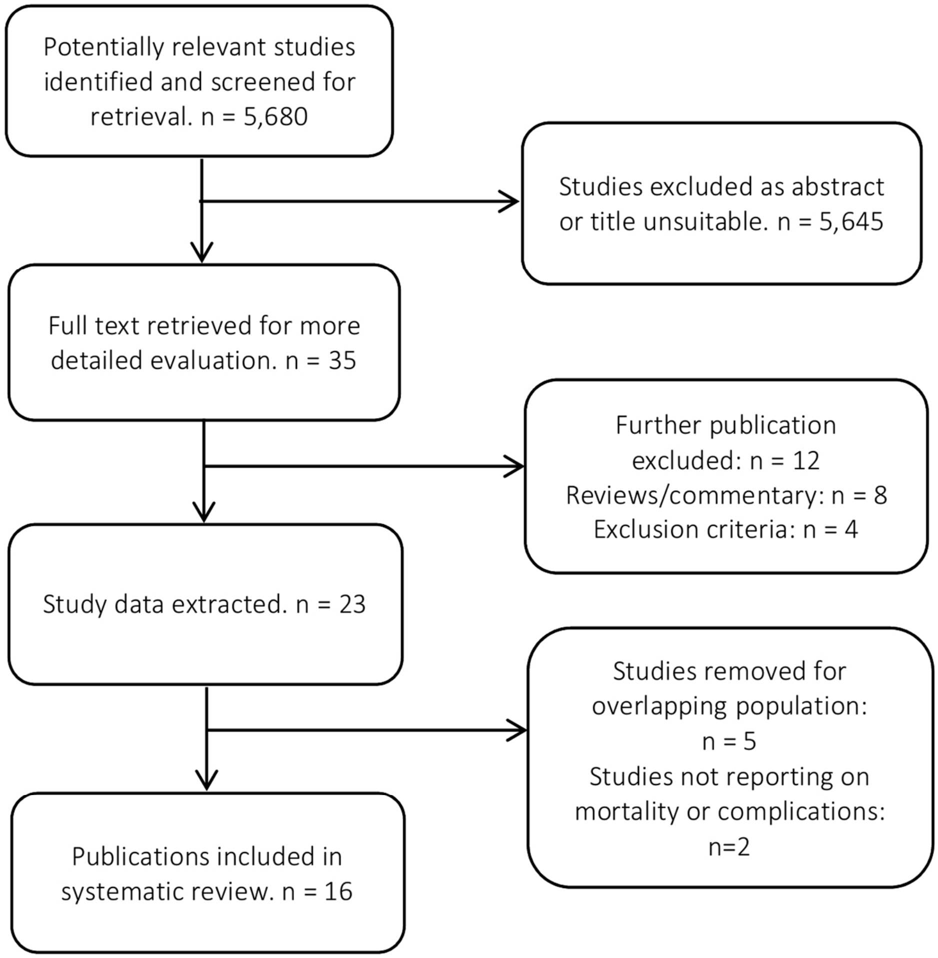

Fig 1. Flow chart of the article selection process.

122x128mm (300 x 300 DPI)

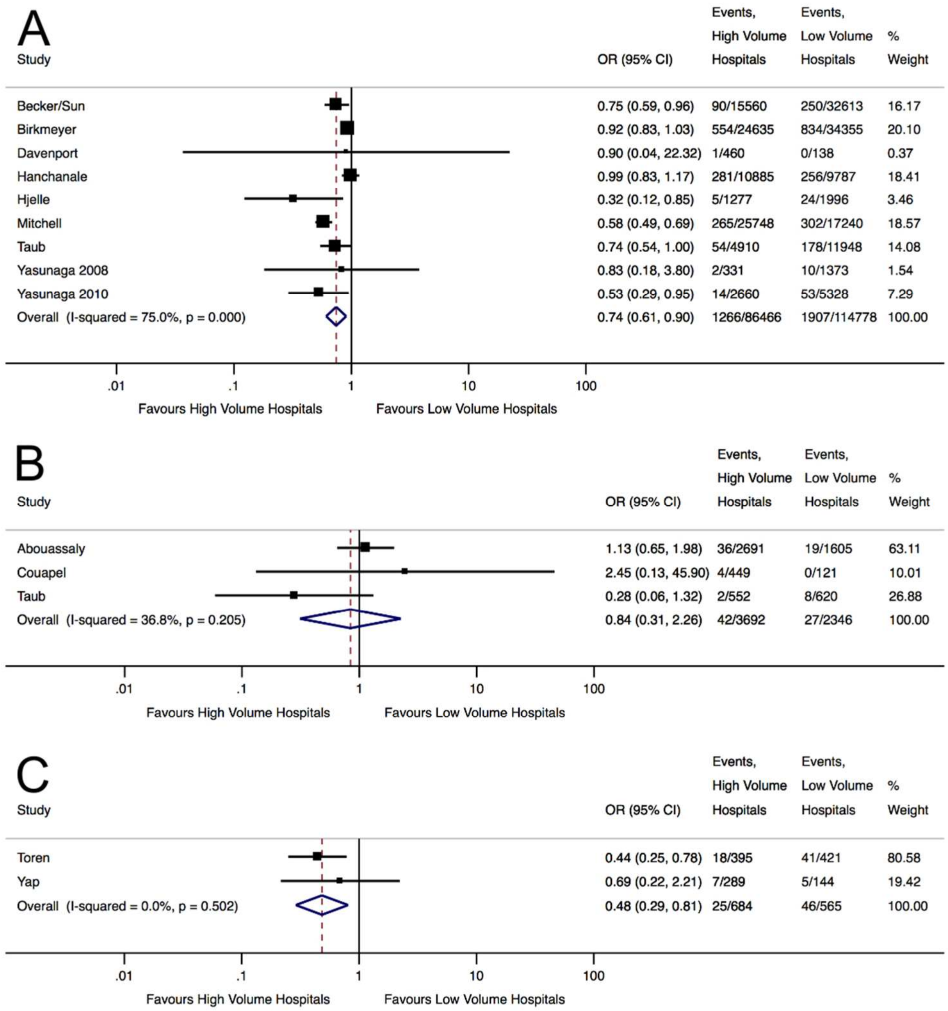

Fig 2. Forest plots displaying the pooled effect estimates of nephrectomy mortality in HV and LV hospitals for A. radical nephrectomy B. partial nephrectomy C. nephrectomy with venous thrombectomy.

100x105mm (300 x 300 DPI)

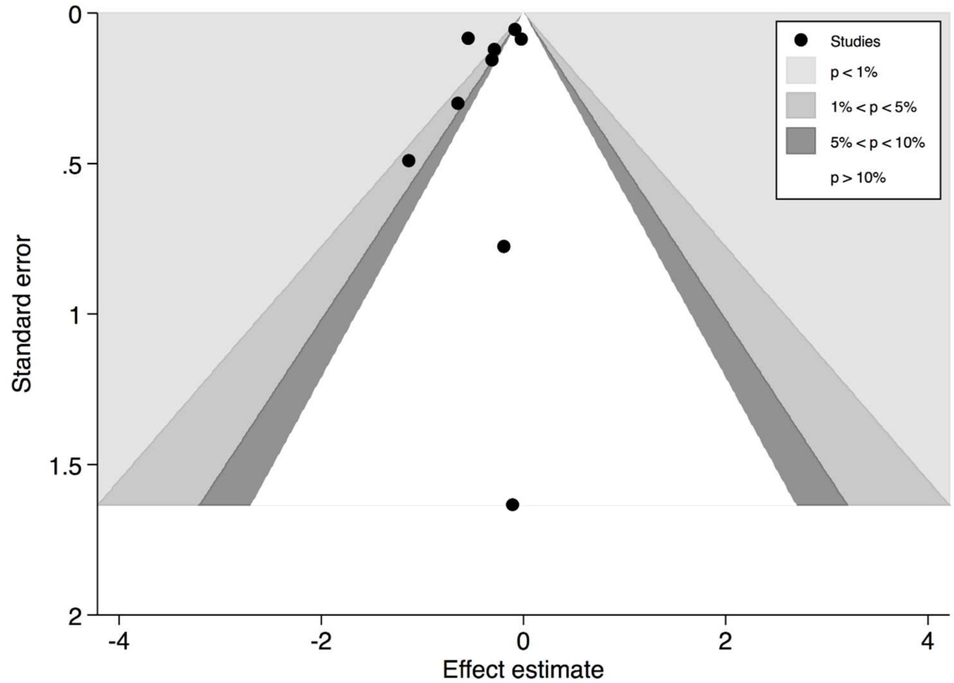

Fig 3. Contour-enhanced funnel plot of studies analysing hospital volume-outcome relationship in radical nephrectomy mortality. Harbord's modified test for funnel plot asymmetry was not statistically significant.

111x80mm (300 x 300 DPI)

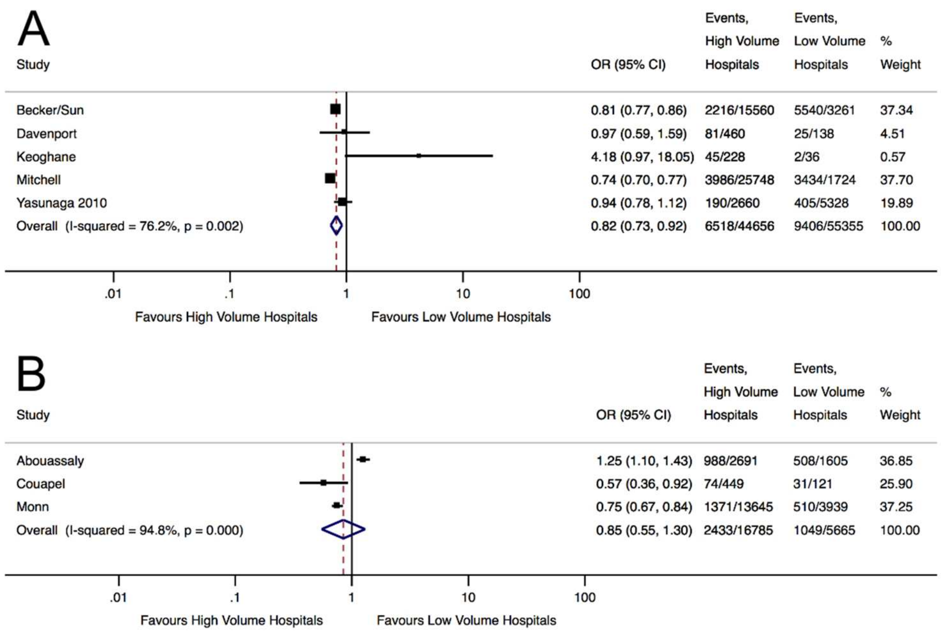

Fig 4. Forest plots displaying the pooled effect estimates of nephrectomy complications in HV and LV hospitals for A. radical nephrectomy B. partial nephrectomy.

101x66mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Report on pag
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Report on pag
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	27

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): e100(doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2. Literature search algorithm for Medline, Embase and the Cochrane Library.

<u>**Medline**</u>

Nephrectomy Terms:

1. exp Nephrectomy/
2. nephrectom*.mp.
3. (kidney* adj5 (excision* or remov*)).mp.
4. 1 or 2 or 3

Surgeon or Hospital Volume Terms

5. ((physician* or urol* or surg* or operat* or hospital* or procedure*) adj5 (volume* or workload* or caseload* or performance* or number*)).mp.
6. exp Hospitals/
7. exp Surgeons/
8. (volume* or workload* or caseload* or performance*).mp.
9. exp Workload/
10. 6 and 8
11. 7 and 8
12. 6 and 9
13. 7 and 9
14. exp Centralized Hospital Services/
15. centrali*ation.mp.
16. 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Outcome Terms

17. exp "Outcome Assessment (Health Care)"/
18. exp Patient Outcome Assessment/
19. exp "Outcome and Process Assessment (Health Care)"/
20. outcome.mp.
21. exp Treatment Outcome/
22. exp Mortality/
23. mortalit*.mp.
24. exp Morbidity/
25. morbidit*.mp.
26. exp "Length of Stay"/
27. length of stay.mp.
28. ((duration or length or period) adj5 (stay or hospital*)).mp.
29. exp Survival/
30. survival.mp.
31. exp Patient Readmission/
32. readmission.mp.
33. exp Postoperative Complications/
34. complication*.mp.
35. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 4 and 16 and 35

<u>**Embase**</u>

Nephrectomy Terms:

1. exp Nephrectomy/
2. exp Partial nephrectomy/
3. exp "Patient history of nephrectomy"/
4. nephrectom*.mp.
5. (kidney* adj5 (excision* or remov*)).mp.
6. 1 or 2 or 3 or 4 or 5

Surgeon or Hospital Volume Terms

7. ((physician* or urol* or surg* or operat* or hospital* or procedure*) adj5 (volume* or workload* or caseload* or performance* or number*)).mp.
8. exp Hospital/

9. exp Surgeon/
10. (volume* or workload* or caseload* or performance*).mp.
11. exp Workload/
12. 8 and 10
13. 9 and 10
14. 8 and 11
15. 9 and 11
16. exp Centralization/
17. centrali*ation.mp.
18. 7 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

Outcome Terms

19. exp Outcome Assessment/
20. exp Treatment Outcome/
21. outcome.mp.
22. exp Mortality/
23. mortalit*.mp.
24. exp Morbidity/
25. morbidit*.mp.
26. exp "Length of Stay"/
27. length of stay.mp.
28. ((duration or length or period) adj5 (stay or hospital*)).mp.
29. exp Survival/
30. survival.mp.
31. exp Hospital readmission/
32. readmission.mp.
33. exp Postoperative Complications/
34. complication*.mp.
35. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 6 and 18 and 35

<u>Cochrane Library</u>

Nephrectomy Terms:

1. exp Nephrectomy/
2. nephrectom*
3. kidney* near (excision* or remov*)
4. 1 or 2 or 3

Surgeon or Hospital Volume Terms

5. (physician* or urol* or surg* or operat* or hospital* or procedure*) near (volume* or workload* or caseload* or performance* or number*)
6. exp Hospitals/
7. exp Surgeons/
8. volume* or workload* or caseload* or performance*
9. exp Workload/
10. 6 and 8
11. 7 and 8
12. 6 and 9
13. 7 and 9
14. exp Centralized Hospital Services/
15. centrali*ation
16. 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

Outcome Terms

17. exp "Outcome Assessment (Health Care)"/
18. exp Patient Outcome Assessment/
19. exp "Outcome and Process Assessment (Health Care)"/
20. outcome
21. exp Treatment Outcome/
22. exp Mortality/

23. mortalit*
24. exp Morbidity/
25. morbidit*
26. exp "Length of Stay"/
27. length of stay
28. (duration or length or period) near (stay or hospital*)
29. exp Survival/
30. survival
31. exp Patient Readmission/
32. readmission
33. exp Postoperative Complications/
34. complication*
35. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 4 and 16 and 35

Appendix 3. Breakdown of quality assessment scores for each study included in the review.

uthor	Cohort representative (1)	Number of hospital/ surgeons (2)	Sample size (1)	Number of adverse events (2)	Unit of analysis (3)	Patient selection appropriate (2)	Volume categories (1)	Risk adjustment (3)	Clinical processes of care (2)	Outcomes (1)	Tota (18)
elle et al	1	1	1	1	0	1	1	2	0	0	8
cker/Sun et al	1	2	1	2	0	0	1	1	0	1	9
uapel et al	0	2	0	1	0	0	1	2	1	1	8
onn et al	1	2	1	2	0	0	1	1	0	1	9
ren et al	1	2	0	2	3	0	1	1	0	1	11
ouassaly et al	1	2	1	2	3	0	1	1	0	1	12
p et al	1	2	0	1	2	0	1	3	0	1	11
nchanale et al	1	2	1	2	0	0	1	1	0	1	9
sunaga et al 010	1	2	1	2	0	0	1	1	0	1	9
itchell et al	1	2	1	2	0	0	1	1	0	1	9
sunaga et al 008	0	2	1	2	2	0	1	2	0	1	11
venport et al	0	2	0	1	0	0	0	0	0	1	4
oghane et al	0	1	0	1	0	0	0	0	0	1	3
ub et al	1	2	1	2	0	0	1	1	0	1	9
rkmeyer et al	0	2	1	2	0	0	1	1	0	0	7

Appendix 4. Results of meta-regression investigating the heterogeneity in the meta-analyses for mortality and its potential explanatory variables in **A**. radical nephrectomy and **B**. partial nephrectomy.

A.

Explanatory Variable	Regression Coefficient	95% Confidence Interval	p Value
Study year	0.96	0.88, 1.04	0.24
Country of Study			
England	1.46	0.70-3.02	0.24
Japan	0.76	0.28-2.04	0.50
Norway	0.42	0.10-1.76	0.18
USA	1.06	0.51, 2.21	0.85
Data type			
Administrative	1.36	0.71, 2.61	0.28
Clinical	0.74	0.38, 1.32	0.28
Number of patients	1.00	1.00, 1.00	0.45
Number of hospitals	1.00	1.00, 1.00	0.14
Patient age (mean)	0.92	0.70, 1.19	0.36
Patient gender (% of male)	0.96	0.88, 1.05	0.25
Threshold for HV hospitals	0.99	0.99, 1.00	0.01

B.

Explanatory Variable	Regression Coefficient	95% Confidence Interval	p Value
Study year	0.96	0.80, 1.14	0.51
Country of Study			
England	1.42	0.46, 4.27	0.40
Japan	1.19	0.67, 2.13	0.41
USA	0.80	0.51, 1.26	0.22
Data type			
Administrative	1.09	0.61, 1.97	0.66
Clinical	0.91	0.51, 1.65	0.66
Number of patients	1.00	1.00, 1.00	0.26
Number of hospitals	1.00	0.99, 1.00	0.80
Patient age (mean)	1.04	0.97, 1.11	0.16
Patient gender (% of male)	0.99	0.80, 1.23	0.87
Threshold for HV hospitals	1.00	0.93, 1.07	0.83

Appendix 5. List of excluded studies after full-text review and justifications.

Reference	Justification
1. Joudi FN, Konety BR. The impact of provider volume on outcomes from urological cancer therapy. *J Urol*. 2005;174(2):432-438.	Review
2. Joudi FN, Konety BR. The volume/outcome relationship in urologic cancer surgery. *Support Cancer Ther*. 2004;2(1):42-46.	Review
3. Killen SD, O'Sullivan MJ, Coffey JC, Kirwan WO RH. Provider volume and outcomes for oncological procedures. *Br J Surg*. 2005;92:389-402.	Review
4. Mayer EK, Purkayastha S, Athanasiou T, Darzi A, Vale JA. Assessing the quality of the volume-outcome relationship in uro-oncology. *BJU Int*. 2009;103(3):341-349.	Review
5. Nuttall M, Vandermeulen J, Phillips N, et al. a Systematic Review and Critique of the Literature Relating Hospital or Surgeon Volume To Health Outcomes for 3 Urological Cancer Procedures. *J Urol*. 2004;172(6):2145-2152.	Review
6. Peyronnet B, Couapel J-P, Patard J-J, Bensalah K. Relationship between surgical volume and outcomes in nephron-sparing surgery. *Curr Opin Urol*. 2014;24(5):453-458.	Review
7. Pieper D, Mathes T, Neugebauer E, Eikermann M. State of evidence on the relationship between high-volume hospitals and outcomes in surgery: a systematic review of systematic reviews. *J Am Coll Surg*. 2013;216(5):1015-1025.	Review
8. Penson DF. Mortality after major surgery for urologic cancers in specialized urology hospitals: are they any better? *Urol Oncol*. 2006;24(5):460.	Commentary
9. Sugihara T, Yasunaga H, Horiguchi H, et al. Performance comparisons in major uro-oncological surgeries between the USA and Japan. *Int J Urol*. 2014;21(11):1145-1150.	Volume-outcome relationship not described
10. Fernando A, Fowler S, O'Brien T, et al. Nephron-sparing surgery across a nation - Outcomes from the British Association of Urological Surgeons 2012 national partial nephrectomy audit. *BJU Int*. 2016;117(6):874–82.	Volume-outcome relationship not described
11. Wang HH, Tejwani R, Zhang H, Wiener JS, Routh JC. Hospital Surgical Volume and Associated Postoperative Complications of Pediatric Urological Surgery in the United States. *J Urol*. 2015;194(2):506-511.	Paediatric cohort
12. Tinay I, Gelpi-Hammerschmidt F, Leow JJ, et al. Trends in utilisation, perioperative outcomes, and costs of nephroureterectomies in the management of upper tract urothelial carcinoma: A 10-year population-based analysis. *BJU Int*. 2016;117(6):954–60.	Volume-outcome relationship in nephroureterecotmy only
13. Gilbert SM, Dunn RL, Miller DC, Daignault S, Ye Z, Hollenbeck BK. Mortality After Urologic Cancer Surgery: Impact of Non-index Case Volume. *Urology*. 2008;71(5):906-910.	Overlapping studied period. Eliminated as per rule 2.
14. Joudi FN, Allareddy V, Kane CJ, Konety BR. Analysis of complications following partial and total nephrectomy for renal cancer in a population based sample. *J Urol*. 2007;177(5):1709-1714.	Overlapping studied period. Eliminated as per rule 2.
15. Konety BR, Allareddy V, Modak S, Smith B. Mortality after major surgery for urologic cancers in specialized urology hospitals: are they any better? *J Clin Oncol*. 2006;24(13):2006-2012.	Overlapping studied period. Eliminated as per rule 2.
16. Trinh QD, Schmitges J, Sun M, et al. Does partial nephrectomy at an academic institution result in better outcomes? *World J Urol*. 2012;30(4):505-510.	Overlapping studied period. Eliminated as per rule 2.
17. Finlayson EVA, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. *Arch Surg*. 2003;138(7):721-726.	Overlapping studied period. Eliminated as per rule 4.
18. Goodney PP, Stukel TA, Lucas FL, Finlayson EVA, Birkmeyer JD. Hospital volume, length of stay, and readmission rates in high-risk surgery. Ann Surg. 2003;238(2):161–7.	Did not report on mortality/complications
19. Porpiglia F, Mari A, Bertolo R, Antonelli A, Bianchi G, Fidanza F, et al. Partial Nephrectomy in Clinical T1b Renal Tumors: Multicenter Comparative Study of Open, Laparoscopic and Robot-assisted Approach (the RECORd Project). Urology.2016;89:45–51.	Did not report on mortality/complications