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REVIEW ARTICLE

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A systematic review of living kidney donor enhanced recovery after surgery

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Abstract

Enhanced recovery after surgery (ERAS) reduces complications and shortens hospital stay without increasing readmission or mortality. However, its role in living donor nephrectomy (LDN) has not yet been defined. Medline, Embase, CINAHL, PsycINFO, and Cochrane Central were searched prior to 08/01/21 for all randomized controlled and cohort studies comparing ERAS to standard of care in LDN. The study was registered on PROSPERO (CRD: CRD42019141706). One thousand, three hundred seventy-seven patients were identified from 14 studies (698 patients with ERAS and 679 patients without). There were considerable differences in the protocols used, and compliance with general ERAS recommendations was poor. Meta-analysis of laparoscopic procedures (including hand- and robot-assisted) revealed that duration of stay was significantly reduced by 0.98 days with ERAS (95% CI = 0.36–1.60, P = .002) and opiate requirement by 32.4 mg (95% CI = 1.1–63.7, P = .04). There was no significant difference n readmission rates or complications. Quality of evidence was low to moderate assessed using the GRADE tool. This review suggests there is a positive benefit of ERAS in laparoscopic LDN. However, there was considerable variation in ERAS protocols used, and the quality of evidence was low; as such, a guideline for ERAS in LDN should be developed and validated.

KEYWORDS
donor nephrectomy, enhanced recovery after surgery, fast track, renal transplantation

1 | INTRODUCTION

Living donor renal transplantation provides better patient and allograft survival compared with deceased donor transplantation and is commonly the preferred treatment choice in end-stage renal disease.[1] With the introduction of laparoscopic surgery, the number of donors amenable to living donation increased.[2,3] Laparoscopic donor nephrectomy has reduced postoperative pain, hospital stay, and return to normal function with comparable outcomes to open nephrectomy.[4] As such, it is now the favored approach for living donor nephrectomy (LDN).[1]

In the UK, just over 1000 living kidney donations take place annually and this rate has been effectively static for the last decade.[5] Expanding the pool of live kidney donors is one way to reduce the number of patients on the organ donation waiting list. Disincentives to live donation that could be improved through enhanced recovery

after surgery (ERAS) include pain following surgery, risk of complications, and duration of recuperation.[6,7]

ERAS is a rehabilitation program consisting of evidence-based, multidisciplinary, multimodal perioperative protocols which target issues that can lead to complications and delay recovery.[8] Protocols commonly involve minimally invasive surgery, improved education, nutrition, analgesia, euvolemia, and mobilization.[8] In other specialties, ERAS has been shown to reduce complications by up to 50% and shorten duration of hospital stay without an increase in readmission or mortality.[9,10] Initially developed for colorectal surgery,[11] ERAS has since expanded to general, vascular, orthopedic, urological, gynecological, and thoracic surgery.[8] Indeed, ERAS has now been trialed for renal transplant recipients and has been demonstrated to reduce duration of stay and cost.[12] However, its role in live donor nephrectomy has not yet been defined.[13]

The aims of this study were to undertake a systematic review of the literature on ERAS in live donor nephrectomy in comparison with standard of care and to describe published ERAS protocols and outcome measures.

2 | METHODS

The study protocol was registered on PROSPERO, the international prospective register of systematic reviews (CRD42019141706). A systematic search was then completed for literature that investigated ERAS in live donor nephrectomy. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed (Table S1),[14] and Medline, Embase, CINAHL, PsycINFO, and Cochrane Central were searched for all original studies prior to 08/01/21. The search terms used were as follows: 'enhanced recovery after surgery'; 'enhanced recovery'; 'ERAS'; 'fast-track'; 'fast track'; 'nephrectomy'. Search strategies for each database were adapted appropriately from these terms; the full search strategy for Embase is shown in Table S2.

2.1 | Assessment of study eligibility

Inclusion criteria were all randomized controlled trials, cohort studies, case-control studies, and conference proceedings that evaluated ERAS for LDN compared to standard of care.

Literature reviews, case reports, process evaluations, clinical trial proposals, non-English articles, and studies evaluating non-donor nephrectomy were excluded. Studies that did not describe their ERAS protocol in sufficient detail or only evaluated a single ERAS program component were excluded.

Following the removal of duplicates, titles and abstracts were screened independently by two reviewers using Rayyan, an online platform that aids reviewers in the abstract screening process.[15] Any discrepancies were resolved by consensus. The reference lists of included papers were then screened for additional articles.

2.2 | Data extraction

Eligible papers were read in full and data were extracted independently by two reviewers using a proforma. Study authors were contacted where data were incomplete, and these data were included if provided.

2.3 | Assessment of methodological quality

Results were aggregated and risk of bias was evaluated independently by two reviewers using the Cochrane Collaborators Tool for randomized controlled trials or ROBINS-I (Risk Of Bias In Non-randomised Studies—of Interventions) for non-randomized controlled trials.[16,17] Any discrepancies were resolved by consensus. Overall quality of evidence for each outcome was calculated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria.[18]

2.4 | Developing a proforma for data collection

Validated outcome measures to evaluate ERAS for donor nephrectomy have not been developed.[19] Our proforma for data collection was developed from ERAS Society guidelines, British Association of Urological Surgeon guidelines, and a systematic review by Neville et al.[8,20] ERAS Society and British Association of Urological Surgeon guidelines outline a number of items that should be included in ERAS protocols.[8,21] Neville et al.[20] conducted a systematic review of 38 studies to identify outcomes that were used to evaluate ERAS protocols in prospective studies. The proforma items can be seen in Tables 1–3.

2.5 | Statistics

Analysis was completed using Review Manager 5.3 (Cochrane). Data are presented as odds ratios (OR) with 95% confidence intervals (CI), mean difference with 95% CI or mean ± SD. A random effects model was used to adjust for heterogeneity and determine summary estimates. χ^2 and I^2 tests were used to assess heterogeneity, and *Z*-test was used to determine overall effect. I^2 values of >25%, >50%, and >75% were considered low, moderate, and high levels of heterogeneity, respectively.[22] When required, data were converted from median, interquartile range, or 95% CI to mean ± SD as described in the Cochrane Handbook so that meta-analysis could be performed.[23] Interventions that had mixed procedure types were not included in the meta-analysis. Two-sided *P* values of .050 were deemed significant.

TABLE 1 Study characteristics

Reference	Year	Country	Intervention details	Procedure type	Study type	Study design	ERAS population, *n*	Control population, *n*
Alberts et al.	2014	Netherlands	ERAS compared to standard of care	Hand-assisted laparoscopic	RCT	Non-blinded, prospective, single center	26	26
Brown et al.	2013	UK	ERAS compared to standard of care	Hand-assisted laparoscopic	Cohort	Retrospective, single center	14	22
Campsen et al.	2019	USA	ERAS with ketorolac + pregabalin compared to standard of care + placebo	Hand-assisted laparoscopic	RCT	Double blind, prospective, single center	33	29
Forbes et al.	2017	USA	ERAS with gabapentin compared to standard of care	Laparoscopic	Cohort	Retrospective, single center	62	113
Freedland et al.	2002	USA	ERAS compared to standard of care	Open	Cohort	Retrospective, single center	83	115
Hosto et al.	2018	USA	ERAS for hand-assisted laparoscopic donor nephrectomy compared to standard of care for mini-open donor nephrectomy	Mixed	Cohort	Prospective, single center	29	23
Knight et al.	2002	USA	ERAS with ketorolac alone, ERAS with ketorolac + spinal compared to standard of care	Open	Cohort	Retrospective, single center	Ketorolac alone = 31 Ketorolac + spinal = 17	12
Kuo et al.	2000	USA	ERAS compared to standard of care	Laparoscopic	Cohort	Retrospective, single center	41	21
Mansour et al.	2017	Egypt	ERAS for open donor nephrectomy versus standard of care laparoscopic donor nephrectomy	Mixed	RCT	Non-blinded, prospective, single center	109	110
Nickkholgh et al.	2018	USA	ERAS with TAP block versus LA injection at time of wound closure versus standard of care	Robotic	Cohort	Prospective, single center	TAP = 8 LA = 7	8
Quan et al.	2020	USA	ERAS with Bupivacaine TAP block versus ERAS with Liposomal Bupivacaine TAP block versus standard of care	Laparoscopic	Cohort	Retrospective, single center	Bupivacaine TAP = 96 Liposomal bupivacaine TAP = 31	50
Rege et al.	2016	USA	ERAS compared to standard of care	Laparoscopic	Cohort	Retrospective, single center	39	40
Waits et al.	2014	USA	ERAS compared to standard of care	Laparoscopic	Cohort	Retrospective, single center	60	60
Zatorski et al.	2020	USA	ERAS compared to standard of care	Laparoscopic	Cohort	Retrospective, single center	12	50

Abbreviations: ERAS, enhanced recovery after surgery; LA, local anesthetic; RCT, randomized controlled trial; TAP, transversus abdominus plane.

TABLE 2 Summary of ERAS protocols

Summary of ERAS protocol	Alberts et al.	Brown et al.	Campsen et al.	Forbes et al.	Freedland et al.	Hosto et al.	Knight et al.	Kuo et al.	Mansour et al.	Nickkholgh et al.	Quan et al.	Rege et al.	Waits et al.	Zatorski et al.
Preadmission														
Smoking and alcohol excess cessation									•				•	
Nutritional screen and support														
Medical optimization of pre-existing disease														
Discharge planning													•	
Preoperative														
Structured education						•			•			•	•	
Carbohydrate loading	•					•			•			•	•	
Thromboprophylaxis			•				•	•				•		
Antimicrobial prophylaxis			•					•	•			•		
Nausea and vomiting prophylaxis			•					•				•		
No prolonged fasting						•			•			•	•	
Bowel preparation												•		
Intraoperative														
Minimally invasive surgery	•	•	•	•		•		•		•	•	•	•	•
Anesthesia standardization	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Euvolaemia maintenance					•			•	•					•
Epidural anesthesia or regional block	•	•		•		•	•		•	•	•	•	•	•
Surgical drain avoidance														
Nasogastric tube removal—before anesthetic reversal									•					
Maintenance of body temperature									•					
Postoperative														

Summary of ERAS protocol	Alberts et al.	Brown et al.	Campsen et al.	Forbes et al.	Freedland et al.	Hosto et al.	Knight et al.	Kuo et al.	Mansour et al.	Nickkholgh et al.	Quan et al.	Rege et al.	Waits et al.	Zatorski et al.
Early mobilization—day of surgery	●				●		●	●	●			●	●	
Early oral intake—day of surgery	●	●			●		●		●			●	●	
Early catheter removal—morning of surgery		●	●									●		
Early intravenous fluid cessation—morning of surgery		●										●		
Prevention of ileus—peripheral opioid-blockage ± chewing gum														
Nutritional supplements	●													
Multimodal opioid-sparing analgesic regime	●		●	●	●	●		●	●			●	●	●
Multimodal anti-nausea and vomiting regime			●					●	●			●		

TABLE 3 Summary of measured outcomes

Outcomes	Alberts et al.	Brown et al.	Campsen et al.	Forbes et al.	Freedland et al.	Hosto et al.	Knight et al.	Kuo et al.	Mansour et al.	Nickkholgh et al.	Quan et al.	Rege et al.	Waits et al.	Zatorski et al.
Biological variables														
Postoperative complications	●	●	●		●		●	●	●	●				
Return of bowel function		●			●									
Time to oral intake					●		●							●
Pulmonary function														
Immunological measures														
Stress response														
Nutritional measures														
Body composition change														
Muscle strength														
Resting energy requirement														
Cardiovascular function														
Symptoms														
Pain	●				●				●	●		●	●	●
Fatigue	●								●					
Nausea and vomiting														
Anxiety and depression									●					
Functional status														
Duration of hospital stay	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Readmission	●	●	●	●								●	●	
Mobilization					●									●
Activities of daily living					●				●					
Return to work							●							
Cognitive function														
GP or psychological support visit														
Discharge to rehabilitation center														
General health perceptions	●								●					
Quality of life	●								●					

3 | RESULTS

A total of 312 articles were identified from the search, and fourteen studies remained after full-text articles were evaluated (Figure 1).

3.1 | Study characteristics

These studies comprised 698 patients who underwent LDN with ERAS and 679 patients without. The characteristics of the included studies are shown in Table 1. The average age of included individuals ranged from 39 to 47 years and approximately 31% of patients were male (range = 21%–69%). The procedures used for nephrectomy were as follows: laparoscopic (43%); hand-assisted laparoscopic (21%); open (14%); mixed (14%); and robotic (7%). There were three randomized controlled trials and 11 cohort studies; the majority of studies were from the USA.

3.2 | ERAS protocol

There was considerable difference in the enhanced recovery programs that patients underwent (Table 2). The mean compliance

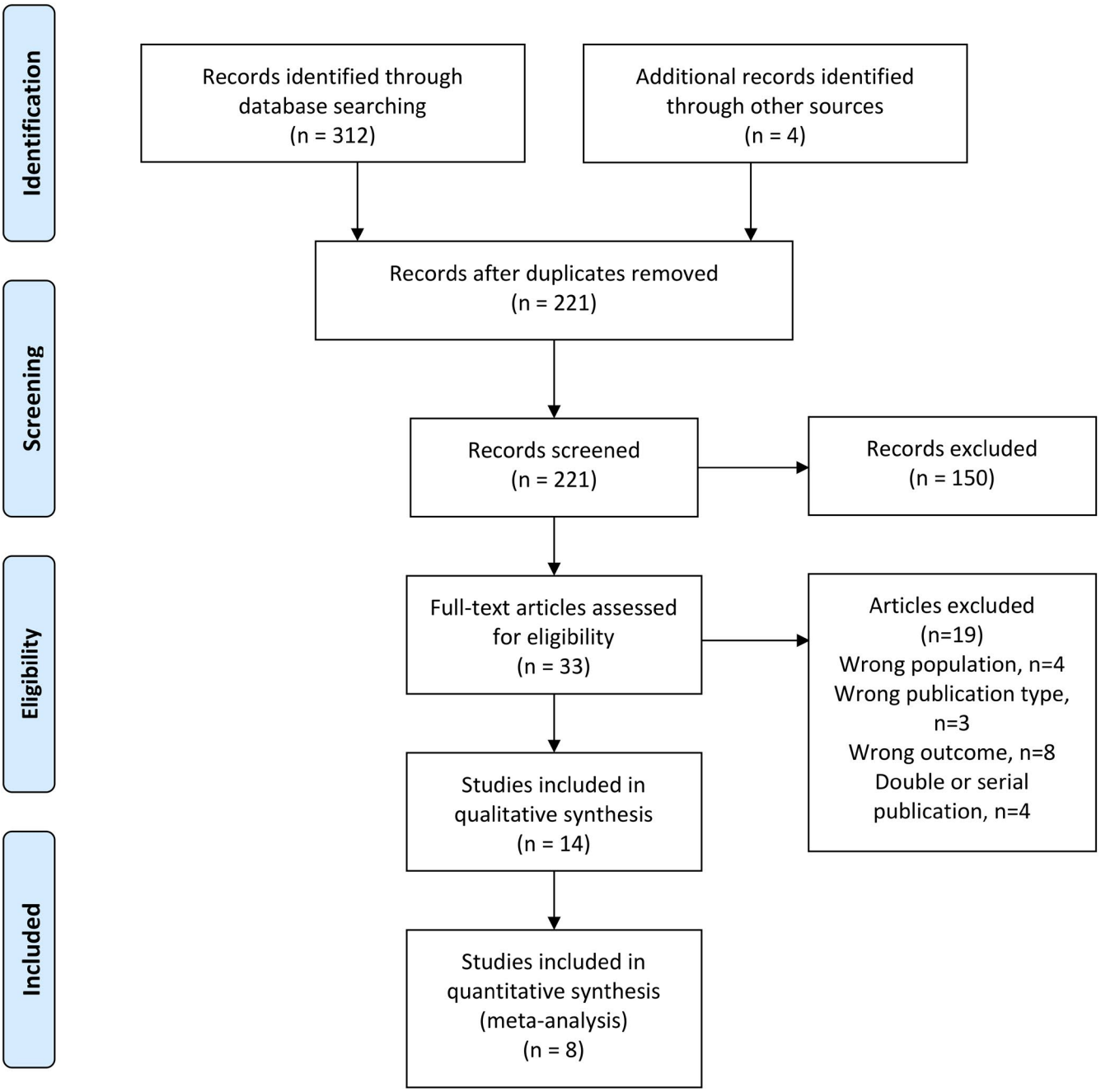

FIGURE 1 Flow diagram of search strategy following PRISMA guidelines. Studies were excluded prior to full-text review if their title and abstracts did not meet inclusion criteria

TABLE 4 Summary of main findings

		ERAS		Control		
Length of stay (Days)		**Mean**	**SD**	**Mean**	**SD**	***P* value**
Alberts et al.		3	0.7[a]	4	0.7[a]	.63
Brown et al.		3.2		4.4		.11
Campsen et al.		2.2	0.3[a]	2.4	0.5[a]	.29
Forbes et al.		2.5		2.9		<.001*
Kuo et al.		1.0	0.6[b]	2.6	0.9[b]	<.01*
Nickkholgh et al.	TAP	2.0		2.4		.04*
	LA	2.9				
Quan et al.		No difference			NS	
Rege et al.		1	0[c]	2	9.7[c]	<.001*
Waits et al.		1		2		<.001*
Zatorski et al.		3.15	0.38	4.30	0.61	<.001*
Freedland et al.[d]		3.1	0.9[b]	3.7	1.1[b]	<.001*
Hosto et al.[d]		2.3	0.5	2.9	0.9	.02*
Knight et al.[d]	Ketorolac alone	2.0	0.3	3		<.001*
	Ketorolac + spinal	2.1	0.4			
Mansour et al.[d]		3.9	1.7	2.8	1.0	.002*
Opiate usage (mg)		**Mean**	**SD**	**Mean**	**SD**	
Campsen et al.	Total	27	22[a]	45	34[a]	.006*
Forbes et al.	Intraoperative	4.38		39.21		.001*
	Postoperative	2.54		7.24		.001*
Nickkholgh et al.	Intraoperative, TAP	5.5		9.7		.01*
	Intraoperative, LA	14.2				
	Postoperative, TAP	18.7		41.5		.14
	Postoperative, LA	48.9				
Quan et al.	Day 0, Bupivicaine TAP	9.6		25.4		<.05*
	Day 0, Liposomal TAP	4.4				
	Day 1, Bupivicaine TAP	38.3		94.1		<.05*
	Day 1, Liposomal TAP	15.7				
	Total, Bupivicaine TAP	158.9		189.9		NK
	Total, Liposomal TAP	135.4				
Waits et al.	Total	21.2		45.6		<.01*
Zatorski et al.	Postoperative	16.0	33.1	66.1	58.3	.0001*
Freedland et al.[d]	Total	49.0	45.6[b]	115.4	69.7[b]	<.001*
Pain		**Mean**	**SD**	**Mean**	**SD**	
Alberts et al.	Day 1	Lower in ERAS				.0001*
	Day 2	No difference				NS
	Day 3	Higher in ERAS				.03*
Nickkholgh et al.	Highest and average	No difference				NS
Rege et al.	Day 1	3	6.4[c]	7	6.5[c]	.01*
	Peak	6	5.6[c]	8	3.2[c]	<.001*
	Minimum	0	3.2[c]	2	4.8[c]	.01*
Waits et al.	Day 1	3.87		3.97		.76
Zatorski et al.	Postoperative	3.4	2.0	4.15	1.5	.08

(Continues)

TABLE 4 (Continued)

Pain			Mean	SD	Mean	SD	
Freedland et al.[d]	Day 1, 7, and 1 month		Lower in ERAS				<.05*
Mansour et al.[d]	Day 1		7.27	1.01	4.04	1.86	.001*
	Day 2		5.53	1.28	2.42	0.87	.001*
	Day 10		1.86	0.84	1.52	0.63	.29
Readmission	**Follow-up**	***n***	**%**	***n***	**%**		
Brown et al.	NK	0	0	3	14	NS	
Forbes et al.	30 days	No difference			NS		
Kuo et al.	NK	1	3				
Rege et al.	30 days	5	13	11	28	.11	
Waits et al.	30 days	3	5	4	7	.7	
Complications	**Follow-up**	***n***	**%**	***n***	**%**		
Alberts et al.	1 month	1	4	1	4	NS	
Brown et al.	NK	2	14	11	50	.04*	
Campsen et al.	30 days	3	9	0	0	NS	
Nickkholgh et al.	4 days	0	0	0	0	NS	
Kuo et al.	NK	0	0	4	19	NS	
Freedland et al.[d]	18 months	14	17	14	12	.35	
Knight et al.[d]	10 months	No difference			NS		
Mansour et al.[d]	6 weeks	39	35.7	15	13.6	.01*	

Abbreviations: ERAS, enhanced recovery after surgery; LA, local anesthetic; TAP, transversus abdominus plane.

[a]Median (IQR) converted to mean ± SD.

[b]SEM converted to SD.

[c]Median (95% CI) converted to mean ± SD.

[d]Study evaluated patients with open nephrectomy.

*$P < .05$.

with previously published general ERAS recommendations was 29% (range = 12%–62%). Analyzing compliance across the four domains of preadmission, preoperative, intraoperative, and postoperative interventions, nearly all studies omitted preadmission interventions (mean compliance of 5% across preadmission interventions) and the majority did not include preoperative and postoperative interventions (mean compliance of 26% and 30%, respectively). Mean compliance to intraoperative interventions was 43%. All studies standardized the anesthesia used (100%). Most studies used minimally invasive surgery (79%) and epidural or regional blocks (79%), and encouraged early mobilization (50%) and oral intake (50%) with an opiate-sparing analgesic regime postoperatively (71%).

3.3 | Outcome measures

Table 3 shows a summary of the outcomes measured by each study. The studies assessed an average of only 15% (range = 4%–32%) of the outcomes previously described. There were four outcomes identified using the proforma: duration of stay (100%); complications (57%); pain (50%); and readmission (43%). Opiate usage was identified as an additional outcome; 50% of studies evaluated opiate usage. The results of these five main outcomes are summarized in Table 4. Apart from these outcomes, very few studies evaluated other biological variables, symptoms, or functional status outcomes that had been previously identified.

3.4 | Duration of stay

All studies measured duration of stay. Nine out of ten studies that evaluated laparoscopic procedures demonstrated a decrease in length of stay with ERAS compared to standard of care.[6,24–32] Meta-analysis was possible for five of these studies,[6,24,29,31,32] and there was a significant difference in the duration of stay between ERAS and standard of care of 0.98 days ($P = .002$, Figure 2). Heterogeneity was high ($I^2 = 94\%$).

Three out of four studies that evaluated open procedures demonstrated a significant decrease in length of stay with ERAS compared to standard of care. Meta-analysis was not possible for these studies due to differences in study design. The one study that did not show an improvement was a mixed procedure study that compared ERAS for open nephrectomy versus standard of care for laparoscopic nephrectomy.[33]

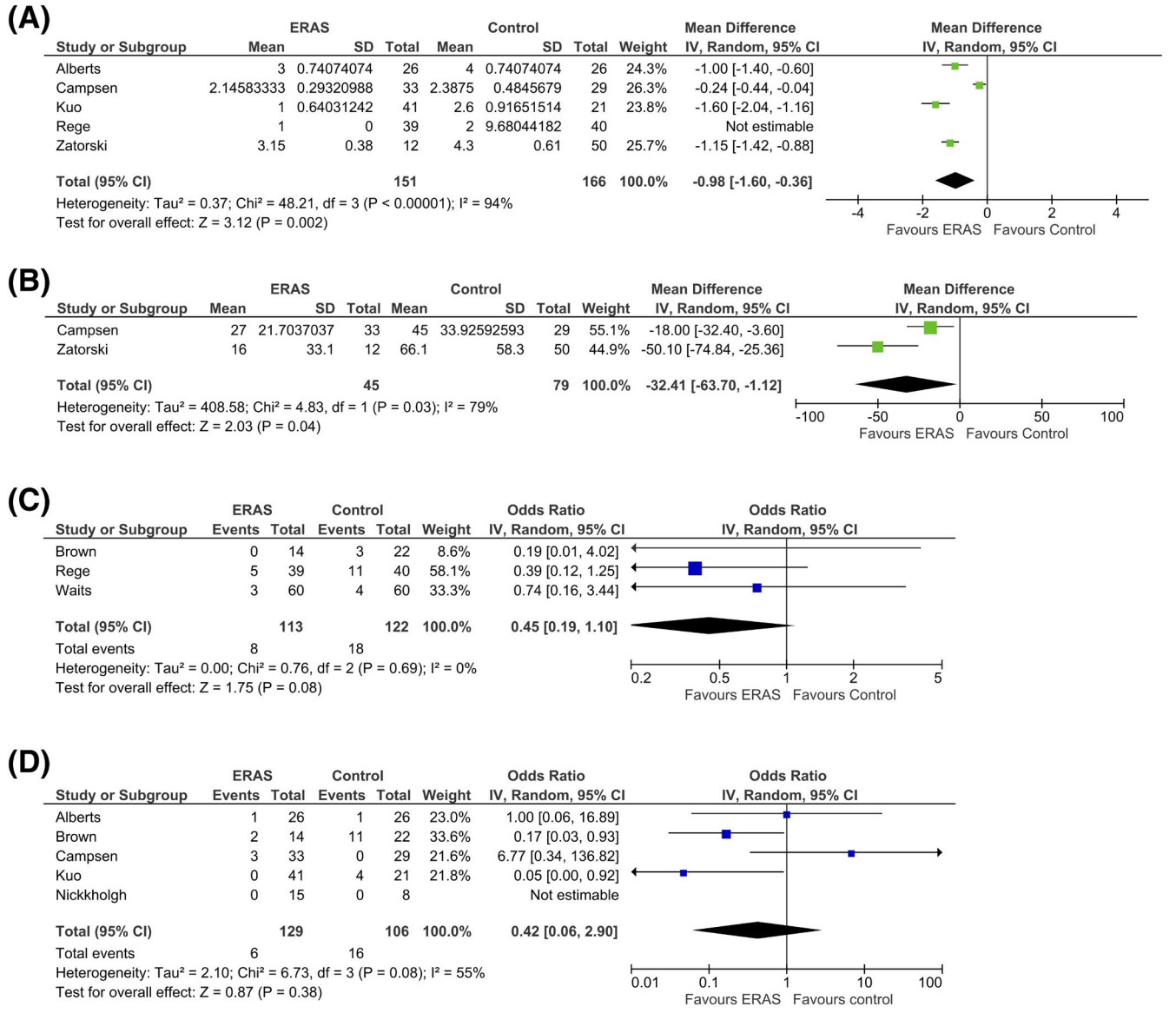

FIGURE 2 Forest plots for ERAS versus standard of care for laparoscopic live donor nephrectomy. (A) Duration of stay was significantly shorter with ERAS by 0.98 days (95% CI = 0.36–1.60, P = .002, I^2 = 94%). Meta-analysis was possible in five out of fourteen studies that evaluated duration of stay. (B) Opiate usage was significantly lower with ERAS by 32.41 mg (95% CI = 1.12–63.70, P = .03, I^2 = 79%). Meta-analysis was possible in two out of seven studies that evaluated opiate usage. (C) Readmission was numerically lower with ERAS but this was not significant (OR = 0.45, 95% CI = 0.19–1.10, P = .08, I^2 = 0%). Meta-analysis was possible in three out of five studies that evaluated readmission. (D) There was no significant difference between groups for complications (OR = 0.42, 95% CI 0.06–2.90, P = .38, I^2 = 55%). Meta-analysis was possible in five out of eight studies that evaluated complications

3.5 | Opiate usage

Seven studies measured opiate usage at different time points, including total, intraoperative, and postoperative time points. All six studies that evaluated laparoscopic procedures demonstrated a significant reduction in opiate usage with ERAS compared to standard of care, albeit at different time points.[26–28,30–32] Meta-analysis was possible for two of these studies,[31,32] and there was a significant difference in opiate use between ERAS and standard of care (P = .03, Figure 2). Heterogeneity was high (I^2 = 79%).

One study evaluated total opiate usage in open nephrectomy and demonstrated a significant reduction with ERAS compared to standard of care.[34]

3.6 | Pain

Seven studies evaluated pain using a Visual Analogue Scale at various time points (ranging from day 1 to 1 month) postoperatively and demonstrated mixed results.[24,27,29–31,33,34] The Visual Analogue

TABLE 5 GRADE scores for meta-analysis of duration of stay, opiate usage, readmissions, and complications for ERAS versus standard of care for live donor nephrectomy

Certainty assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ERAS	Control	Relative (95% CI)	Absolute (95% CI)	Certainty
Duration of stay											
5	Observational studies or RCT	Not serious	Serious[a]	Not serious	Not serious	Very strong association	151	166	–	MD **0.98 days lower** (1.60 lower to 0.36 lower)	⨁⨁⨁⊖ MODERATE
Opiate usage											
2	Observational studies or RCT	Not serious	Serious[b]	Not serious	Serious[c]	Very strong association	45	79	–	MD **32.41 mg lower** (63.70 lower to 1.12 lower)	⨁⨁⊖⊖ LOW
Readmission											
3	Observational studies or RCT	Not serious	Not serious	Not serious	Not serious	None	8/113 (7.1%)	18/122 (14.8%)	**OR 0.45** (0.19–1.10)	**75 fewer per 1000** (from 116 fewer to 12 more)	⨁⨁⊖⊖ LOW
Complications											
5	Observational studies or RCT	Not serious	Serious[a]	Not serious	Not serious	Not serious	6/129 (4.7%)	16/106 (15.1%)	**OR 0.42** (0.06–2.90)	**81 fewer per 1000** (from 140 fewer to 189 more)	⨁⊖⊖⊖ LOW

Note: GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; ERAS, enhanced recovery after surgery; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial.

[a]Downgraded one level for poor heterogeneity, however, overall effect apparent despite not being able to include all studies in meta-analysis.

[b]Downgraded one level for poor heterogeneity.

[c]Downgraded one level as there were few studies that could be included in the meta-analysis.

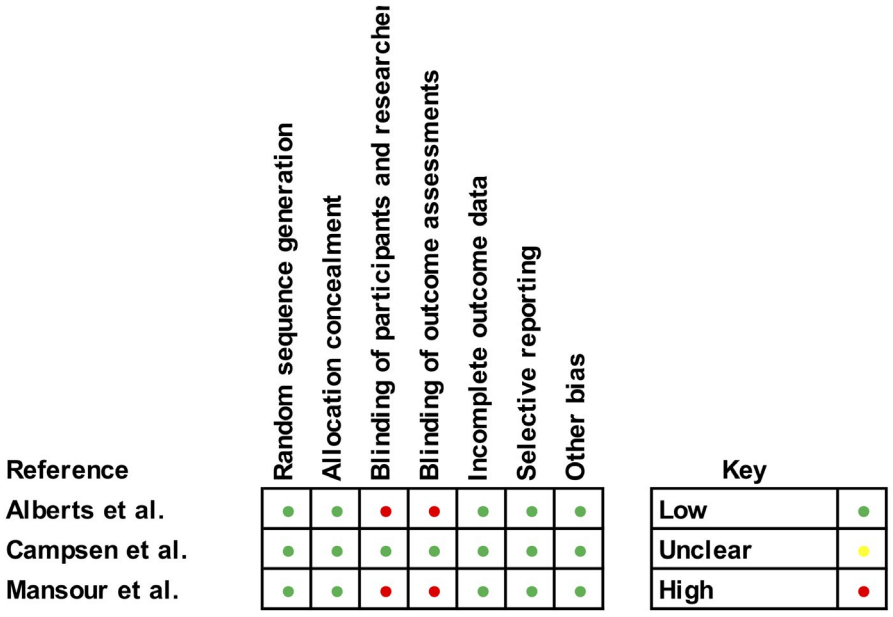

FIGURE 3 Overall risk of bias for the randomized controlled trials analyzed using the Cochrane Collaborators Tool

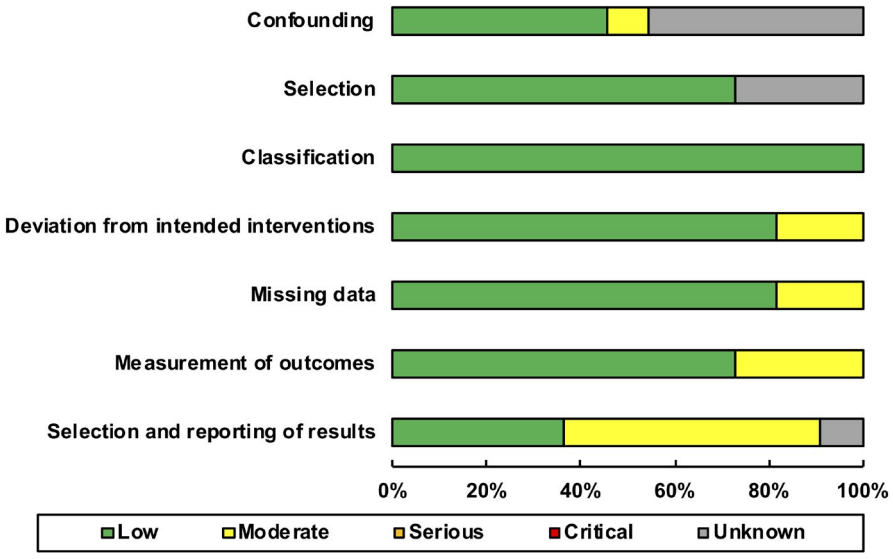

FIGURE 4 Individual risk of bias for the randomized controlled trials analyzed using the Cochrane Collaborators Tool

Scale is a validated system for measurement of a patient's current pain and consists of a scale of 'no pain at all (0)' to 'pain as bad as it could be (10)'.[35]

Evaluating studies that assessed laparoscopic procedures, Rege et al.[29] demonstrated that minimum and peak pain were significantly lower in ERAS compared with control groups. Nickkholgh et al.,[27] Waits et al.,[30] and Zatorski et al.[31] demonstrated no difference in pain. Alberts et al.[24] showed that pain was significantly lower on day 1 and then significantly higher on day 3 in the ERAS group compared with the control. Meta-analysis was not possible for this outcome due to the different time points used.

In a study of open procedures, Freedland et al.[34] demonstrated that pain was significantly lower for up to 1 month post-operation. In a study of ERAS for open nephrectomy versus standard of care for laparoscopic nephrectomy, Mansour et al.[33] demonstrated significantly higher pain in the ERAS group.

3.7 | Readmission

Five studies evaluated readmission and no studies demonstrated a significant difference in readmission rates.[6,25,26,29,30] All of these studies evaluated laparoscopic procedures. The time point used was 30 days in three studies and not reported in two studies. Meta-analysis was possible for three papers.[25,29,30] Readmission was numerically lower in ERAS compared to standard of care (OR = 0.45, 95% CI = 0.19–1.10, P = .08, Figure 2); however, this was not significant. Heterogeneity was low (I^2 = 0%), although the confidence intervals for this domain remain large.

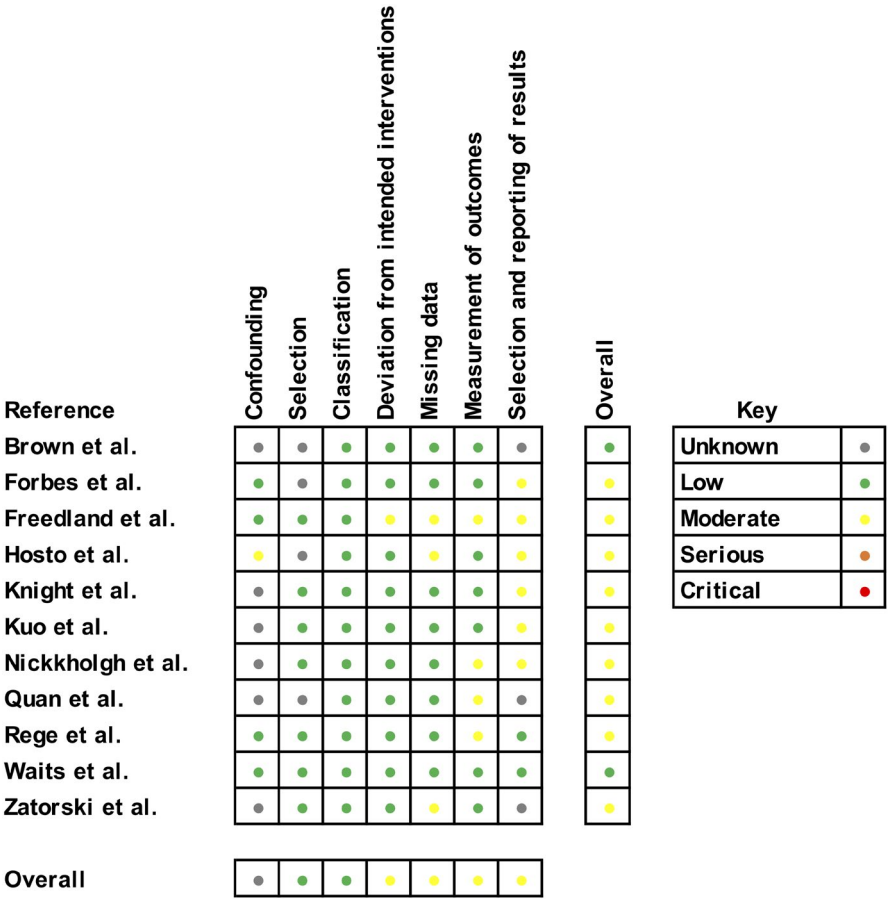

FIGURE 5 Overall risk of bias for the non-randomized controlled trials analyzed using ROBINS-1

3.8 | Complications

Eight studies evaluated complications at various time points ranging from 4 days to 18 months. Meta-analysis was possible for five laparoscopic studies, and there was no significant difference in complications (OR = 0.42, 95% CI 0.06–2.90, P = .38, Figure 2).[6,24,25,27,32] Heterogeneity was moderate (I^2 = 55%).

Three studies evaluated complications in open procedures, two studies demonstrated no significant difference between ERAS and standard of care for open nephrectomy. When open ERAS was compared to laparoscopic standard of care, Mansour et al.[33] demonstrated a significantly higher rate of complications in patients who received open nephrectomy with ERAS.

This outcome was limited by the reporting of complications. Campsen et al.[32] only measured urinary retention, Brown et al.[25] only measured gastrointestinal dysfunction. Clavien-Dindo classifications of complications were included in only one study.[33,36]

3.9 | Procedure type

It was not possible to analyze whether procedure type had an effect on any of the main outcomes. However, in a non-blinded randomized controlled trial, Mansour et al.[33] evaluated ERAS for open donor nephrectomy versus standard of care laparoscopic donor nephrectomy and demonstrated that standard of care laparoscopic donor nephrectomy was significantly superior in every outcome (rate of complications, duration of stay, general and physical fatigue, pain and perceived physical function and general health). Hosto et al.[37] evaluated ERAS for hand-assisted laparoscopic donor nephrectomy compared with standard of care for mini-open donor nephrectomy and demonstrated a significant decrease in duration of stay in the ERAS hand-assisted laparoscopic group.

3.10 | Other comparisons

Apart from the five outcomes discussed above, the studies evaluated postoperative creatinine levels, recovery of physical function, ambulation, and return of gastrointestinal function.

Six studies evaluated postoperative creatinine levels and there were no significant differences in creatinine clearance or creatinine levels postoperatively between ERAS and standard of care for laparoscopic or open procedures.[6,25,29,31,32,34] Of the six studies investigating postoperative creatinine levels, three used ketorolac as part of their postoperative analgesia.[31,32,34] Ketorolac is a first-generation non-steroidal anti-inflammatory drug (NSAID) and has the potential to be nephrotoxic. The remaining three did not employ the use of any NSAID and used local anesthetic agents, paracetamol, and opiate analgesia.[6,25,29]

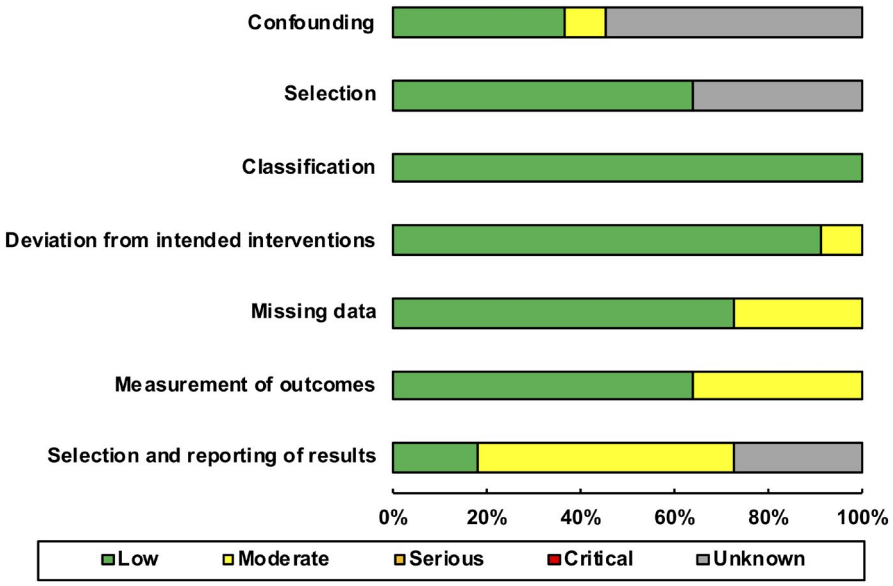

FIGURE 6 Individual risk of bias for the non-randomized controlled trials analyzed using ROBINS-1

Four studies (excluding Mansour et al.) demonstrated that there were no significant differences in postoperative function, measured by return to postoperative function, recovery of physical performance, or return to work for laparoscopic or open procedures.[6,24,34,38]

Zatorski et al.[31] found that significantly more patients ambulated on the day of the procedure (53% vs. 20%, $P = .02$) and day one postoperatively (85% vs. 54%, $P = .04$) with ERAS compared to standard of care for laparoscopic nephrectomy.

For open nephrectomy with ERAS, Knight et al.[38] demonstrated a significant decrease in delayed oral intake in the ERAS group compared with control (6% vs. 83%, $P < .001$), which was defined as oral intake after postoperative day 1. Freedland et al.[34] demonstrated similar findings in that the ERAS group had increased oral intake volume as well as a reduced time to solid foods.

3.11 | Cost of ERAS

Four studies mentioned cost savings. Kuo et al.[6] noted that ERAS resulted in a 50% decrease in hospital costs and significantly reduced the average cost from $18 600 (SD = 560) to $11 500 (SD = 550) for laparoscopic nephrectomy ($P < .01$). Knight et al.[38] also demonstrated a significant reduction in costs with ERAS for open nephrectomy from $11 600 to $9400 with Ketorolac and $9200 with Ketorolac and spinal epidural ($P = .02$). Two other studies noted cost savings; however, the measures of cost were vague. Campsen et al.[32] were unable to state exact costs due to lack of authorization but noted that the cost of ERAS for laparoscopic nephrectomy was <$10, and the cost of an extra hour in hospital was >$10. Finally, Forbes et al.[26] estimated that with their ERAS protocol for laparoscopic nephrectomy approximately 40 hospital bed days could be saved annually.

3.12 | Quality of evidence and risk of bias

GRADE was used to rate quality of evidence across the four outcomes included in the meta-analysis. The GRADE scores for each main outcome are shown in Table 5. The quality of evidence for duration of stay was moderate, opiate usage was low, readmission was low, and complications were low.

The Cochrane Collaborators tool was used to evaluate risk of bias in the three randomized controlled trials (Figure 3). Risk of bias was low apart from for 'blinding of participants and researcher' and 'blinding of outcome assessments', as only one study was double-blinded (Figure 4).

ROBINS-1 was used to evaluate risk of bias in the 11 non-randomized controlled trials (Figure 5). Risk of bias was low to moderate, and there was particular bias in the selection and reporting of results as few studies comprehensively described the planned outcomes a priori (Figure 6). Additionally, confounding bias was unknown as few studies discussed whether they had addressed confounding factors.

4 | DISCUSSION

In this systematic review and meta-analysis of ERAS in LDN, we found that introduction of ERAS in laparoscopic LDN significantly reduced duration of stay and opiate usage without an increase in rates of readmission or complications and with no difference in postoperative renal function and postoperative function. Very few studies evaluated outcomes that have previously been used in ERAS studies for other surgeries, such as nausea and vomiting, or anxiety and this is possibly due to the absence of patient-reported outcomes in LDN. ERAS may also represent a cost saving over standard of care; however, this was not well described, and the

cost of ERAS will also increase when missing ERAS components are including in protocols.

Generally, ERAS protocols are well tolerated.[39-41] For example, Zychowicz et al. surveyed 120 Polish patients' perceptions of ERAS following laparoscopic gastrointestinal surgery. One in ten patients were worried about early discharge; but, 95% did not feel a longer hospital stay was required, and 100% recommended ERAS becoming routine care.[42]

Sibbern et al. evaluated patient experiences of ERAS in a systematic review of eleven qualitative studies. They identified that perceptions were influenced by the provision of information, balance between personalized care and standardization of ERAS protocol, balancing symptoms with rapid recovery, and a feeling of security at discharge. The authors suggested experiences could be improved by providing consistent communication pre- and postoperatively.[43] Indeed, Yang et al.[44] showed that quality of discharge teaching and discharge to rehabilitation centers was associated with readiness for discharge in 130 Chinese patients who underwent colorectal surgery with ERAS.

Some patients can feel rushed by early discharge, particularly those with reduced levels of support or access to care.[45] This in turn may affect feelings of security. Kruse et al.[46] performed a randomized controlled trial of 143 Danish women and demonstrated no difference in feelings of security after early discharge cesarean section, provided appropriate follow-up was organized. In addition to this, Boniforti et al.[47] suggested using health status scoring systems to inform follow-up after ERAS to improve satisfaction.

A limitation of the studies evaluating early discharge in ERAS is that they are almost all from western countries. Looking at the non-ERAS literature from non-western studies, there appears to be similar findings. For example, a study evaluating 96 Thai patients' perceptions of discharge following surgery showed that patients felt information provided at discharge was of a low quality[48]; and the authors of a study of 1267 Tanzanian women following childbirth, recommended that to improve early discharge there needs to be improved counseling that is tailored to the patient's needs.[49]

There are several limitations to this study. We included randomized controlled trials and cohort studies, and both retrospective and prospective studies were included. The inclusion of retrospective studies was necessary as the number of randomized controlled trials was small, but as a result, there may be selection and performance bias; publication bias may also influence our findings. There were missing data described in the studies, notably SD values, and some of these had to be converted from alternative measures of spread of data such as interquartile range. Despite contacting authors, it was not possible to obtain these additional data. Furthermore, there was considerable heterogeneity in the meta-analyses undertaken. This may be due to differences in the way outcomes were measured for example the time periods used. It may also be due to differences in ERAS protocols. We found that 69% of our patients were women, which is relatively comparable to national and international statistics which shows significantly greater numbers of women donors in comparison with men.[50] There are many factors which may account for this disparity, ranging from societal factors to higher male incidence of end-stage diseases that necessitate transplant.[51] It is difficult to say whether our data are representative of the procedure types performed. This is because over the last two decades there has been a continuous decline in the number of open nephrectomies performed in comparison to laparoscopic procedures. For example, UK registry data show that in the year 2000 93% of LDN was performed laparoscopically compared to 47% in 2005.[52] More recent data show that some centers have abandoned open nephrectomy completely in favor of laparoscopic procedures, and rates of hand-assisted and robot-assisted LDN appear to be variable and dependent upon the center.[53]

The risk of bias in this study was low to moderate; however, so was the quality of the evidence as assessed by GRADE. This indicates the need for a high-quality trial to assess the role of ERAS in LDN in the domains we have discussed. However, this will not be possible until a guideline for ERAS is developed.

For early discharge following ERAS to be successful, there needs to be adequate information provision and a shared decision between the patient and the medical team that is tailored to the patients' ongoing needs and takes cultural aspects into consideration. Therefore, it is surprising that only 7% of the studies evaluating ERAS in LDN included discharge planning, and only 29% included structured education.

Avoiding open nephrectomy appears to be the most influential factor as, even when associated with an ERAS protocol, outcomes were worse than standard of care laparoscopic nephrectomy.[33] Additionally, Wilson et al.[4] previously showed that laparoscopic nephrectomy was generally associated with shorter hospital stay, less pain, reduced analgesic requirement and faster return to function compared with open nephrectomy.

Beyond this, it is difficult to comment on which aspects of LDN ERAS protocols are most effective, because each element of the protocol can incrementally improve outcomes. For example, Ricotta et al.[54] showed that a more comprehensive ERAS protocol for LDN improved return to normal function in elderly patients. Rather, the literature on each aspect should be systematically reviewed, the quality of evidence graded, and a guideline produced from this—as other ERAS guidelines have done.[55] In this way, interventions that could impact patient safety are evidence based.

Pending a guideline, the British Transplantation Society has recommended that principles from general ERAS recommendations could be incorporated into LDN and provided some suggestions of how these may be introduced.[8,13] A simple change that surgical teams could make is ensuring there is a structure for pre- and post-surgical management. This is what is currently missing from almost all current LDN ERAS protocols and is what is valued by patients. In our opinion, structured education and discharge planning preoperatively are most important as they improve patient expectations and satisfaction.

5 | CONCLUSIONS

ERAS in LDN significantly reduces duration of stay and opiate usage for laparoscopic procedures and may represent a cost saving, without increasing readmission or complications or compromising postoperative renal function. However, there was considerable variation in the ERAS protocols used and this was reflected by heterogenous data. Given the positive benefit of ERAS suggested by this review, there is a clear need for future work to develop a guideline for ERAS in LDN and a subsequent randomized controlled trial to validate it.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

MHVB, DMS, SAH, and MLN responsible for conceptualization. MHVB, AM, SAH, DMS, and MLN responsible for writing the first draft. MHVB and AM responsible for data collection. MHVB responsible for data analysis. All authors were responsible for revisions.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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