# Robotic *Versus* Laparoscopic Approaches to Distal Pancreatectomy: Quality Assessment of the Current Evidence

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# **ABSTRACT**

Pancreatic surgery, associated with technical difficulties and high complication rates, remains a challenge for surgeons. The laparoscopic approach has been shown to have benefits over the open approach; however laparoscopic distal pancreatectomy (LDP) still has its challenges. Robotic distal pancreatectomy (RDP) offers a technical edge over the laparoscopic approach in terms of superior imaging and ergonomics. Whether the technical advantages translate into improved outcomes is to be established. The aim of this study was to produce an overview of systematic reviews, summarising the evidence to date comparing RDP and LDP in terms of intraoperative, post-operative, and oncological outcomes and assessing the quality of the included reviews. Three electronic databases, PubMed, Embase, and Scopus, were searched to identify systematic reviews with meta-analyses comparing RDP with LDP. The AMSTAR-2 format was used to assess the quality of the studies. Fourteen systematic reviews were identified for inclusion. RDP had a significantly higher rate of spleen preservation, significantly shorter hospital stay, and a significantly lower rate of conversion to open surgery, whilst having higher total costs compared to LDP. The overall quality of the reviews was variable. The evidence suggests that RDP has potential advantages over LDP in terms of higher spleen preservation rate, shorter hospital stays, and lower conversion rate to open surgery, whilst maintaining comparability with most other outcomes. Based on the variable quality evidence, RDP is a safe alternative to LDP.

Key Words: Pancreatectomy, Laparoscopic distal pancreatectomy, Robotic surgery, Outcome.

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# **INTRODUCTION**

Anatomical complexities coupled with high postoperative complications and morbidity rates make pancreatic surgery, particularly distal pancreatectomies, one of the most challenging disciplines in surgery. A distal pancreatectomy (DP) involves the surgical removal of the body and tail of the pancreas. The most common indication for this procedure is resection of tumours such as pancreatic adenocarcinomas and neuroendocrine tumours. In 1994, Cuschieri performed the first-ever laparoscopic distal pancreatectomy (LDP). Since then, LDP has been on the rise and studies have shown LDP to be a safe and effective alternative to open distal pancreatectomy (ODP) and has even proven to be superior in certain outcomes, such as length of hospital stay, blood loss, complication rates, and wound infection. Not long after, Melvin performed the first-ever robotic distal pancreatectomy (RDP) in 2003.

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Robotics have been a source of great excitement amongst the surgical community in recent years. Despite a lack of tactile feedback compared to laparoscopic/open approaches, robotics offers numerous advantages over the laparoscopic approach, such as 3D visuals, image magnification, better ergonomics for the surgeon, tremor filtering, and an increased range of wrist manoeuvrability afforded by EndoWrist instruments.<sup>7</sup> An overview of 154 systematic reviews conducted in 2021 outlined many benefits of the robotic approach in surgery; for example, it found that robotic prostatectomies had better outcomes in urinary and sexual functions as well as better quality of recovery and pain outcomes when compared to the laparoscopic approach. It found that robotic surgery for endometrial cancer had a smaller conversion rate when compared to laparoscopic approaches. In addition, it found a lower conversion rate in robotic rectal surgery compared to laparoscopic. <sup>8</sup> Can such successes of robotic surgery be translated into the high morbidity, high complication world of pancreatic surgery?

To date, several systematic reviews have been published comparing RDP with LDP. <sup>2,9-23</sup> The consensus amongst some of these reviews seems to be that RDP may have advantages over LDP in outcomes such as length of hospital stay, spleen preservation, and blood loss. <sup>11,13,21</sup> However, they also report

longer operative times (likely attributed to the lengthier setup time for RDP) and associate RDP with higher costs. 13-15

Most of the reviews seem to focus only on a particular set of outcomes, such as perioperative or oncological with only a small number of them reporting on all three categories of intraoperative, postoperative, and oncological/long-term outcomes all at the same time. Given that numerous systematic reviews have already been published examining the evidence, the aim of this study was to synthesise an overview of current systematic reviews, summarising the findings of intra-operative, postoperative, and oncological outcomes. In addition, no methodological quality assessment of the reviews has been conducted to date, the authors aim to conduct a methodological quality assessment of the existing reviews using the AMSTAR-2 format.<sup>24</sup> To the authors' knowledge, this is the first overview of systematic reviews of its kind to date.

# **METHODOLOGY**

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Inclusion criteria for this study consisted of full-text systematic reviews comparing outcomes of RDP with LDP regardless of surgical indication and subgroups. Studies without a meta-analysis were excluded. Two independent researchers (AUK and AK) conducted a systematic search of PubMed, Scopus, and EMBASE on the 17<sup>th</sup> of June 2023. The search terms employed included distal pancreatectomy, laparoscopic surgery, robotic surgery, and robot. The search was limited to systematic review studies in the last 10 years. No restrictions on language were made in the search (Figure 1).

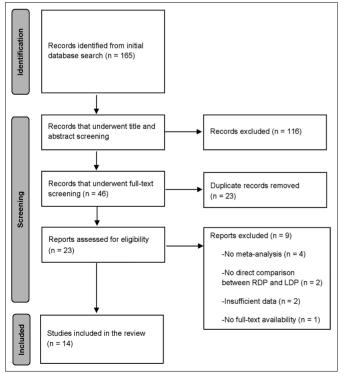


Figure 1: Study selection process.

The same two researchers independently screened titles and abstracts of the resulting studies based on the inclusion/exclusion criteria. Duplicate studies were removed using EndNote 20 citation software. Following title and abstract screening, a full-text assessment was conducted of the remaining potentially eligible studies. Any disagreements were resolved through discussion.

The outcomes measured included were as follows: Intraoperative outcomes including blood loss, conversion rate to open surgery, operative time and spleen preservation, postoperative outcomes including length of hospital stay, major complications (defined as Grade III or greater according to Clavien-Dindo classification system for surgical complications), mortality, pancreatic fistula formation, oncological outcomes including a number of harvested lymph nodes, R0 resection rate and tumour size, and the total cost.

Two independent researchers (AUK and AD) extracted data from the included papers using a Microsoft Excel spreadsheet. Disagreements were resolved via discussion. In studies that had multiple arms, only data directly comparing RDP with LDP were included. The extracted data included study characteristics (study name, author name, year of publication, disease, number of patients undergoing RDP and LDP, total number of patients in study, number of databases searched, number of RCT and non-RCT trials, risk of bias assessment tool used, quality rating of study according to AMSTAR-2 format, and the critically flawed domains according to AMSTAT-2), intraoperative data, postoperative data, oncological data, and total cost. The sam two independent researchers assessed the quality of the included studies using the AMSTAR-2 format. AMSTAR-2 is a quality assessment tool for systematic reviews that categorises the quality of studies into high quality, moderate quality, low quality, and critically low quality. This categorisation is based on 16 domains, 7 of which are considered critical domains and the other 9 as non-critical domains. A study is considered to be of high quality if it contains no critical weaknesses and no more than one non-critical weakness. If a study contains no critical weakness but more than one non-critical weakness, it is considered to be of moderate quality. If a study contains one critical weakness only, it is considered to be of low quality. If a study has more than one critical weakness, it is deemed to be of critically low quality.

The critical domains involve following a protocol and protocol registration, use of an appropriate literature search strategy, providing a list of excluded studies and reasoning their exclusions, assessing risk of bias of included studies, appropriate methods used for meta-analysis if one was conducted, accounting for the risk of bias in results/discussion and investigation any potential publication bias.

The non-critical domains involve research questions containing PICO elements, review authors explaining the choice of study designs included for the review, performing study selection in duplicate, performing data extraction in duplicate, description of the included studies in a good level of detail,

reporting on sources of funding for studies included in the review, accounting for the impact of risk of bias on meta-analysis, discussion of any heterogeneity observed, and reporting potential conflicts of interests/sources of funding.

For each one of the outcome measures, a descriptive analysis was conducted. Continuous variables were described using mean difference (MD), weighted mean difference (WMD) or standard mean difference (SMD) with a 95% confidence interval. Dichotomous variables were described as odds ratio (OR) or rate difference (RD) with a 95% confidence interval. The Cochrane Handbook for Systematic Reviews of Interventions offers guidance on interpreting I² values for haeterogeneity. It regards 0-40% as low heterogeneity, 30-60% as moderate heterogeneity, 50-90% as substantial heterogeneity, and 75-100% as considerable heterogeneity. These were used to judge the level of heterogeneity in the descriptive analysis of each outcome.

# **RESULTS**

The initial literature search yielded 165 results. Following title and abstract screening, 49 studies remained, of which 26 were removed due to duplication. Therefore, 23 studies were left for a full-text review. Upon full-text screening, nine studies were excluded; four had no meta-analysis, two of the studies had no direct comparison between RDP and LDP, two contained insufficient data, and one study had no full-text availability. A total of 14 systematic reviews were left for inclusion<sup>2,9-16,18-21,23</sup> as illustrated in Figure 1. Two of these studies compared LDP with RDP instead of the other way round. <sup>15,18</sup> As a result, the meta-analysis results of these two studies were reversed in order to allow a uniform direction of comparison across all studies.

The study characteristics of the included studies are summarised in Table I. Publication years of the included reviews ranged from 2016-2023. No study employed less than three databases for their initial literature search. No RCTs were included in any of these reviews, all studies were non-randomised. Finally, all reviews used the Newcastle-Ottawa scale as a risk-of-bias assessmenttool.

Three reviews contained no critical flaw with no more than one non-critical flaw and therefore deemed as being of high quality. Five studies contained no critical flaw but more than one non-critical flaws and therefore deemed as being moderate quality. Five studies had one critical flaw only and therefore deemed as being of low quality. Only one study had more than one critical flaw and was therefore of critically low quality (Table I).

Eleven studies reported on intraoperative blood loss and reported it as the mean difference (MD) with a 95% confidence interval. Four of these studies found there to be significantly less blood loss in RDP compared to LDP. The other seven studies found no significant difference. The majority of these studies had high  $\rm l^2$  values suggesting considerable heterogeneity for this outcome. The overall quality of evidence for this outcome was variable with five studies being of low/critically low quality and six studies being moderate/high quality.

Twelve studies reported on the rate of conversion to open surgery. Ten of these studies reported it as an odds ratio (OR) with a 95% confidence interval. The other two studies reported it as the rate difference (RD) with a 95% confidence interval. Eight studies found RDP to have a significantly lower conversion to open rate than LDP, two studies found LDP to have a significantly lower conversion rate, and two studies found no significant difference. The majority of these studies had low I² values suggesting minimal heterogeneity. The overall quality of evidence for this outcome was variable with five studies being of low/critically low quality and seven studies being moderate/ high quality.

All fourteen studies reported on mean operating time. All studies reported it as the mean difference (MD) or weighted mean difference (WMD) with a 95% confidence interval. Five of these studies found RDP to have a significantly longer operating time as compared with LDP. The remaining nine studies found no significant difference. The majority of these studies had high  $l^2$  values suggesting considerable heterogeneity. The overall quality of evidence for this outcome was variable with six studies being of low/critically low quality and eight being moderate/high quality.

Twelve studies reported on the rate of spleen preservation (Table II). Eleven of these studies reported it as the odds ratio (OR) with a 95% confidence interval. One study reported it as the rate difference (RD) with a 95% confidence interval. Eight studies found RDP to have a significantly higher rate of spleen preservation than LDP. The remaining four studies found no significant difference. The majority of these studies had I² values between 50% and 90% suggesting substantial heterogeneity. The overall quality of evidence for this outcome was moderate-high.

Twelve studies reported on the length of hospital stay. All studies reported it as the mean difference (MD) or weighted mean difference (WMD) with a 95% confidence interval. Seven studies found RDP to have significantly lower length of hospital stay. The remaining five studies found no significant difference. The majority of these studies had I² values between 50% and 90% suggesting substantial heterogeneity. The overall quality of evidence for this outcome was variable with five studies being of low/critically low quality and seven being moderate/high quality.

Ten studies reported the rate of major complications (Table III). Nine of these studies reported it as the odds ratio (OR) with a 95% confidence interval and one study reported it as the rate difference (RD) with a 95% confidence interval. All ten studies found no significant difference in the rate of complications between RDP and LDP. The majority of these studies had I² values ranging between 0 and 40% suggesting low heterogeneity. The overall quality of evidence for this outcome was variable with five studies being of low/critically low quality and five being moderate/high quality.

Table I: Study characteristics.

Authors	Year	Disease	No. of RDP/LDP	Total number of patients in the study	No. of databases searched	No. of RCT trials	No. of non-RCT trials	Risk of bias assessment tool	Quality	Critically flawed domain(s)
Chen et al.2	2022	N/A	1413/3189	4062	4	0	15	NOS	Moderate	None
Feng et al. <sup>10</sup>	2021	Pancreatic ductal adenocarcinoma	152/420	572	5	0	6	NOS	Low	7
Gavriilidis et al. <sup>12</sup>	2019	N/A	795/1279	3432	4	0	21	NOS	Critically low	7 and 15
Guerrini et al.14	2017	N/A	267/546	813	3	0	10	NOS	High	None
Hu et al.9	2020	N/A	779/2519	3298	4	0	22	NOS	Low	15
Huang et al. <sup>16</sup>	2016	Benign and malignant disease	238/929	1167	3	0	9	NOS	Moderate	None
Kamarajah et al.11	2019	N/A	860/2456	3316	3	0	20	NOS	Moderate	None
Di Martino et al.15	2021	N/A	561/625	1187	3	0	11	NOS	Low	15
Mavrovounis et al.18	2020	N/A	910/2724	3634	3	0	22	NOS	Low	13
Niu et al.19	2019	N/A	409/970	1379	5	0	17	NOS	High	None
Rompianesi et al.20	2021	N/A	323/362	685	3	0	11	NOS	Low	15
van Ramshorst et al.21	2023	N/A	2514/4243	6757	3	0	43	NOS	High	None
Xu et al.23	2019	N/A	343/1053	1396	3	0	13	NOS	Moderate	None
Zhou et al.13	2016	N/A	211/357	568	3	0	7	NOS	Moderate	None

N/A = Not available, NOS = Newcastle-Ottowa score.

Table II: Spleen preservation.

Authors	Year	Studies (n)	RDP (n)	LDP (n)	Estimation measure	Estimation	95% CI range	p-value	In favour of (RDP or LDP)	l <sup>2</sup>
Chen et al. <sup>2</sup>	2022	11	1087	1832	OR	2.19	1.36 to 3.54	0.001	RDP	78%
Gavriilidis et al.12	2019	13	496	682	OR	1.68	0.95 to 2.96	0.08	NS	66%
Guerrini <i>et al.</i> <sup>14</sup>	2017	7	198	281	OR	2.89	1.78 to 4.71	< 0.0001	RDP	13%
Hu <i>et al.</i> 9	2020	16	NR	NR	OR	2.02	1.085 to 3.758	0	RDP	73.40%
Huang et al.16	2016	5	79	177	OR	2.37	0.5 to 11.3	0.68	NS	77%
Kamarajah <i>et al.</i> <sup>11</sup>	2019	16	596	1292	OR	1.38	0.82 to 2.32	0.22	NS	58%
Mavrovounis et al.18	2020	18	1489	693	OR	2.04	1.26 to 3.22	0.003	RDP	61%
Niu <i>et al</i> .19	2019	11	NR	NR	OR	2.16	1.12 to 4.17	0.017	RDP	53.60%
Rompianesi et al.20	2021	11	323	362	RD	0.24	0.15 to 0.33	< 0.00001	RDP	63%
van Ramshorst et al.21	2023	20	NR	NR	OR	2.23	1.37 to 3.64	0.02	RDP	53%
Xu et al. <sup>23</sup>	2018	8	191	376	OR	1.97	0.58 to 6.65	0.28	NS	78%
Zhou et al.13	2016	6	181	263	OR	3.01	1.92 to 4.73	< 0.00001	RADP	2%

NS = Not significant, MD = Mean difference, OR = Odds ratio, NR = Not reported.

Table III: Major complications.

Authors	Year	Studies (n)	RDP (n)	LDP (n)	Estimation measure	Estimation	95% CI Range	p-value	In favour of (RDP or LDP)	l <sup>2</sup>
Chen et al.2	2022	8	754	962	OR	0.96	0.71 to 1.30	0.8	NS	35%
Gavriilidis et al.12	2019	17	530	729	OR	1.04	0.73 to 1.47	0.85	NS	20%
Guerrini et al.14	2017	9	246	931	OR	1.19	0.73 to 1.91	0.52	NS	NR
Hu et al.9	2020	9	NR	NR	OR	1.337	0.858 to 2.084	0.199	NS	41.10%
Kamarajah <i>et al.</i> <sup>11</sup>	2019	10	351	525	OR	1.09	0.6 to 1.95	0.78	NS	34%
Di Martino et al.15	2021	6	276	341	OR	0.99	0.57 to 1.7	0.96	NS	0
Mavrovounis et al. 18	2020	12	400	563	OR	1.08	0.72 to 1.61	0.7	NS	27%
Rompianesi et al.20	2021	6	197	209	RD	-0.04	-0.11 to 0.03	0.27	NS	0
van Ramshorst et al. <sup>21</sup>	2023	31	NR	NR	OR	0.93	0.76 to 1.14	0.31	NS	9.70%
Zhou et al.13	2016	5	211	357	OR	0.83	0.57 to 1.22	0.35	NS	0%

 $OR = Odds \ ratio, \ RD = Rate \ difference, \ NS = Not \ significant.$ 

Six studies reported on mortality rates. This was reported as the rate difference (RD) or odds ratio (OR) with a 95% confidence interval. All studies found no significant difference in mortality rates between RDP and LDP. The majority of these studies had very low I² values suggesting minimal heterogeneity. The overall quality of evidence for this outcome was variable with three studies being of low quality and three being moderate/high quality.

Twelve studies reported on the rate of pancreatic fistula formation. Eleven studies reported it as an odds ratio (OR) with a 95% confidence interval, and one study reported it as the rate difference (RD) with a 95% confidence interval. All studies found no significant difference in the rate of pancreatic fistula formation between RDP and LDP. All studies reported I² values of 0%, suggesting minimal heterogeneity. The overall quality of evidence for this outcome was vari-

able, with five studies being of low/critically low quality and seven being moderate/high quality.

Nine studies reported on the number of harvested lymph nodes. Seven studies reported it as the mean difference (MD) with a 95% confidence interval, one study as the WMD with a 95% confidence interval and one study as an odds ratio (OR) with a 95% confidence interval.

Two studies found RDP to have a significantly higher number of harvested lymph nodes. The remaining seven studies found no significant difference between RDP and LDP. The majority of studies reported high I<sup>2</sup> values suggesting considerable heterogeneity. The overall quality of evidence for this outcome was variable with four studies being of low/critically low quality and five being moderate/high quality.

Eight studies reported on R0 resection rate. Five studies reported it as an odds ratio (OR) with a 95% confidence interval. Three studies reported it as a rate difference (RD) with a 95% confidence interval. One study found RDP to have a significantly higher R0 resection rate than LPD. The remaining seven studies found no significant difference between RDP and LDP. The majority of studies reported low I² values, suggesting low heterogeneity. The overall quality of evidence for this outcome was variable, with three studies being of low quality and five being moderate/high quality.

Five studies reported on mean tumour size, and all of them reported it as the mean difference (MD) with a 95% confidence interval. Two studies found RDP patients to have a significantly smaller mean tumour size than LDP patients. The remaining three studies found no difference between RDP and LDP. The majority of these studies had low l² values, suggesting low heterogeneity. The overall quality of evidence for this outcome was variable, with two studies being of low/critically low quality and three being moderate/high quality.

Seven studies reported on total costs. Four reported it as the MD and 3 reported it as the standardised mean difference (SMD) with a 95% confidence interval. Six studies reported RDP to have significantly higher total costs than LDP. One study found no significant difference between RDP and LDP. The majority of these studies had high I² values suggesting considerable heterogeneity. The overall quality of evidence for this outcome was variable with three studies being of low quality and four being moderate/high quality.

# **DISCUSSION**

This study is an overview of systematic reviews using 12 independent outcomes to compare RDP with LDP. The 14 reviews included in this study had a combined total of 9'584 RDP patients and 21'020 LDP patients. The majority of studies within this review found no significant difference in intraoperative blood loss. Several factors, such as the quantity of blood loss and inadequate visualisation of important

anatomical structures, can influence a conversion from minimally invasive to open surgery.<sup>27</sup> Most studies in this review found RDP to have a lower conversion rate than LDP. The spleen has an important autoimmune function, and its preservation is beneficial with regard to the prevention of post-splenectomy complications such as recurrent infections, thromboembolisms, haematological malignancies, and coronary artery disease.28 Although preservation is preferred, it is not always possible and depends on a range of other factors, including method of preservation (Kimura vs. Warsaw) and extent/severity of disease. 29 Most of the studies within this review found RDP to have a higher spleen preservation rate than LDP. The apparent advantages of RDP over LDP with regard to conversion rate and spleen preservation rate may be attributed to the technical advantages of robotics mentioned in the introduction section. When it comes to operative time, the majority of reviews found no significant difference. However, 5 reviews found robotics to have a longer operative time, which may be explained by the setup/docking process of robotic surgery taking up to 30 minutes to complete. 30 In addition, a consideration for the various stages of the learning curve that individual surgeons may be at can also explain the longer operating times found in these reviews.31 Most of the studies were in favour of RDP when it came to the length of hospital stays. Nearly every study that reported on total cost found RDP to have a higher cost. A retrospective analysis by Waters in 2010 concluded that when taking into account cost of hospital stay, RDP was found to be more cost-effective than LDP. 32 It is possible that further development of robotic systems and their introduction into a more competitive marketplace can have the effect of driving future prices of RDP down. 11 Major complications were defined as being Grade III or greater on the Clavien-Dindo scale of surgical complications. 33 Grade III refers to any surgical complication requiring surgical, radiological, or endoscopic intervention. There was no significant difference between RDP and LDP in the incidence of major complications. Pancreatic fistula formation is regarded as the most common abdominal complication following a distal pancreatectomy.<sup>34</sup> It has an incidence averaging 20-25% following distal pancreatectomy and prolongs hospital stay.<sup>35</sup> The risk factors for the development of postoperative pancreatic fistula (POPF) include high BMI, high intraoperative blood loss and prolonged operative time.<sup>36</sup> POPF can develop into further complications such as life-threatening sepsis, abscess formation, and death. There was no significant difference in the incidence of POPF between RDP and LDP. The number of harvested lymph nodes and the rate of R0 resection are important prognostic indicators for oncological disease.37,38 RO resection refers to resection that results in total remission according to the R classification system, a system used to categorise the presence/absence of residual tumour post-resection.39 A study by Konstantinidis found that five-year survival and median survival were nearly twice for R0 as they were for R1.40 Nearly every single review that reported on these two outcomes found no significant difference between the robotic and laparoscopic approach which supports the use of RDP as a safe alternative to LDP. Only five studies reported on tumour size. Three of them found no significant difference and two of them found RDP to have a significantly smaller tumour size. This suggests that the RDP population contained a greater proportion of benign or early-stage disease cases and may be explained by the surgeons tending to reserve the more complex malignant cases for the more familiar laparoscopic approach.<sup>2</sup> No significant difference was found between the two approaches when it comes to mortality rates.

This review has important strengths to note such as including 14 systematic reviews, and to our knowledge) being the first overview of systematic reviews comparing RDP and LDP. Most reviews included within this study were based on studies that were of high methodological quality. It had a detailed data extraction and most reviews (8/14) included within this overview were either of moderate/high quality according to AMSTAR-2. However, every study should be interpreted in the context of its limitations as well. Firstly, all reviews included in this study were made up of studies that were observational in design. The lack of randomised trials produces an inherent vulnerability to selection biases. Secondly, some of the outcomes of this study had only a few reviews reporting on them. For example, only 6 reviews reported on mortality. This may be attributed to the short follow-up periods of studies within the included reviews. Thirdly, there exists a degree of overlap in terms of systematic reviews including the same studies within their respective reviews. Furthermore, some of the outcomes had high levels of heterogeneity. Surgeons being at different stages of the learning curve in terms of skills/experience and variability in disease status/severity amongst patients are some factors that can account for this. Finally, little evidence is available on longer-term outcomes, which inhibits the ability to make conclusions regarding prognostic comparisons.

## CONCLUSION

However, future research should include studies with longer follow-up periods to shed light on long-term prognostic outcomes. In addition, randomised trials are needed to solidify the findings of the existing evidence base. Further research would also benefit from performing more patient sub-group analyses, dividing patients according to disease status/indication for pancreatectomy in order to reduce levels of heterogeneity.

This overview of systematic reviews found RDP to have potential advantages over LDP in terms of lower rates of conversion to open surgery, higher rates of spleen preservation and shorter hospital stay whilst maintaining comparability in most other outcomes. Overall, RDP appears to be a safe and efficacious alternative to LDP and as the implementation of robotic surgery increases in the coming years, it may become the preferred approach.

#### COMPETING INTEREST:

The authors declared no conflict of interest.

# **AUTHORS' CONTRIBUTION:**

AUK, AK: Study conception, design, analysis, and interpretation of results.

AUK, AD: Data collection, drafting, and manuscript preparation. All authors approved the final version of the manuscript to be published.

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