Minimally invasive distal pancreatectomy: Laparoscopic versus robotic approach—A cohort study

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Funding information
Ministry of Science and Technology, Taiwan, Grant/Award Number: MOST 108-2314-B-075-051-MY3; Ministry of Health and Welfare, Grant/Award Number: MOHW111-TDU-B-221-014015; Taipei Veterans General Hospital, Grant/Award Numbers: V111C-021, V110B-023, and V111C-023

Abstract

Background and Aims: There is no consensus on the superiority of robotic distal pancreatectomy (RDP) over laparoscopic distal pancreatectomy (LDP).

Methods: Data of patients undergoing RDP and LDP were prospectively collected and compared.

Results: There were 65 RDP and 112 LDP. RDP took a shorter operation time than LDP. Overall, DP with splenectomy took a longer operation time than that with spleen preservation. This difference was only significant in LDP group. In both RDP and LDP groups, splenectomy was associated with increased blood loss, as compared with spleen preservation. No significant differences were observed in surgical morbidity between RDP and LDP. The hospital cost in RDP was almost double that of LDP, with a median of 13,404 versus 7765 USD.

Conclusion: LDP is comparable to RDP in regard to surgical outcomes. LDP with spleen preservation is highly recommended whenever possible and feasible for benign or low malignant lesions in terms of lower costs and less blood loss.

KEYWORDS
distal pancreatectomy, laparoscopic, preservation, robotic, spleen

1 | INTRODUCTION

Distal pancreatectomy has been the mainstay of surgical treatment in pancreatic body-tail tumors. This surgery, traditionally performed with an open approach, is a fairly common but technique-demanding procedure. It carries significant surgical risks and causes wound pain with a large incision. Recently, minimally invasive surgery (MIS) with the benefits of less wound pain and better cosmesis has been the trend in diverse fields. However, many surgeons still consider minimally invasive distal pancreatectomy (MIDP) a complex operation because of the difficult dissection of the pancreas deeply located in the retroperitoneum and technical problems related to vascular control. Thus, the popularization of MIS in the field of the pancreas was significantly delayed when compared to other minimally invasive surgeries. Nevertheless, two available randomized controlled trials (RCTs) were all in favor of MIDP in terms of less intraoperative blood loss and shorter length of hospital stay, without increasing morbidity and mortality, as compared with open DP.

The first laparoscopic distal pancreatectomy (LDP) in 1996 was performed by Cuscheri et al. With the refinement of surgical technique and experience gained in laparoscopic surgery, LDP has achieved oncological results comparable to open distal pancreatectomy (ODP),
but with the benefits of smaller incisions, better cosmesis, faster recovery and shorter length of hospital stay.\textsuperscript{1,5,8} Another MIS for DP is robotic distal pancreatectomy (RDP) first performed by Melvin et al.\textsuperscript{9} Several limitations of the laparoscopic approach have been overcome by da Vinci Robotic System (Intuitive Surgical, Inc.), which could provide the advanced ergonomics. Possessing the articulation of instruments with a high-quality 3-D visualization, 540 degrees of motion, 10–15 times magnification view, and tremor filtration, a robotic surgical system facilitates more complex and delicate procedures.\textsuperscript{13} Nevertheless, concerns of higher cost and longer operation time in robotic surgery have limited its widespread in many centers.\textsuperscript{1} There are some retrospective studies\textsuperscript{10–15} and systemic review/meta-analysis\textsuperscript{14,16} comparing RDP and LDP. Most of these studies reveal that LDP is comparable to RDP in terms of surgical results.

As there was no uniform conclusion reported in the literature in terms of safety and efficacy, which probably related to biases associated with patient selection or surgeon preference in these retrospective studies. Therefore, the objective of this was to compare RDP and LDP regarding the surgical outcomes and hospital costs. Both LDP and RDP procedures were performed by the same pancreatic surgeons using the same surgical principles. Biases associated with patient selection and surgeon preference were nearly eliminated in this study. The results would be truly related to the difference between these two surgical approaches solely.

2 | MATERIALS AND METHODS

Patients with pancreatic body-tail lesions undergoing LDP and RDP were identified and included in this retrospective study from our prospectively-collected computer database between February 2011 and September 2020. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB number: 2020-10-005CC). All human studies have been reviewed by the appropriate ethics committee (Taipei Veterans General Hospital IRB) and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in 2013). Informed consent was waived with the anonymity of the data in this retrospective cohort study. Patients undergoing LDP or RDP with conversion or spleen preservation by the Kimura technique for conserving splenic artery and veins\textsuperscript{17} were not included in this study. The indications for spleen preservation included benign or low-malignant lesions. All data were prospectively collected, including demographics, pathology, surgical parameters, surgical outcomes, and costs. The hospital cost referred to the total cost during the hospital stay, including pre-, intra-, and postoperative costs. Intra-operative cost referred to the cost incurred during operation including robotic instruments.

The primary study aim was to determine the superiority of RPD by comparing LPD in terms of surgical outcomes. The secondary study’s aim was to evaluate hospital costs of RPD and LPD. The surgical principles and procedures of LDP were applied in the same manner as RDP. RDP was the technique of choice before 2016. Thereafter, LDP was the major option and RDP was seldom performed due to the limited availability of da Vinci Robotic Surgical Systems, which were reserved mainly for the more complex procedure, robotic pancreatecoduodenectomy at our institute. All RDP and LPD procedures were performed using the same surgical technique by the same surgical surgeons led by YM Shyr. Warshaw technique for spleen preservation was our technique of choice for handling benign or low malignant lesions in RDP or LDP, whereas splenectomy was reserved mainly for pancreatic cancer or whenever the Warshaw technique to preserve the spleen was not feasible technically. da Vinci Robotic Systems (Intuitive Si or Xi system) were used for RDP cases. RDP technique has been previously described in detail.\textsuperscript{13} Briefly, the patient for RPD was placed in reverse Trendelenburg position and left side 15–20 degrees upward. Five ports were used for our RDP procedures, including four robotic trocars and a 12-mm accessory port. To perform RDP and spleen-preservation with the Warshaw technique, the left gastroepiploic vessels and short gastric vessels were preserved. Pancreas parenchyma was divided with tumor-free margin using Endo GIA™ with Tri-Staple™ (Covidien). The techniques for DP with splenectomy were similar except for some additional procedures in mobilizing the spleen and dividing the short gastric vessels. As the Kimura technique was considered to have oncological radicality concerns in case of malignancy and to be technique-demanding, it was not the technique of choice for our team.

Postoperative pancreatic fistula (POPF) by the International Study Group for Pancreatic Fistula was regarded as grade B and C based on the new definition revised in 2016.\textsuperscript{18} Post-pancreatectomy hemorrhages (PPH), delayed gastric emptying, and chyle leak were identified and classified according to the criteria proposed by the International Study Group of Pancreatic Surgery.\textsuperscript{19–21} Postoperative complications were graded based on the Clavien–Dindo classification.\textsuperscript{22} Radicaty of resection was categorized into three groups according to resection margin status: R0, a resection without gross and microscopic evidence of cancer at the resection margin; R1, a resection without gross and microscopic evidence of cancer, but microscopically positive cancer at the resection margin; and R2, a resection with grossly positive cancer at the resection margin.\textsuperscript{23} Surgical mortality was defined as death within 90 days after surgery.

Statistical work was carried out with Statistical Product and Service Solutions (SPSS) version 26.0 software (SPSS Inc., IBM). Categorical data were presented with numbers and percentages. Categorical data were compared by Pearson’s χ\textsuperscript{2} test. The continuous data were presented with median, range, and mean ± standard deviation (SD). Mean values of continuous data were compared using a two-tailed Student’s t-test. The tests were one- or two-sided. For all statistical analyses, a p value less than 0.05 was regarded to be statistically significant.
3 | RESULTS

There were 177 patients were identified and included for analysis, including 65 RDP and 112 LDP. No significant difference in the patient characteristics was noted between RDP and LDP groups, including sex, age, body mass index, tumor size, and primary tumors (Table 1). Pancreatic adenocarcinoma was the most common tumor in both groups, followed by serous cystadenoma.

There was a conversion in one case (1.5%) of the RDP group and four (3.6%) of LDP, \( p = 0.653 \) (Table 2). Spleen-preservation by Warshaw technique was performed in 45.9% in total, of which 53.1% in RDP and 41.7% in LDP, \( p = 0.157 \). Overall, RDP took a shorter operation time than LDP, with a median of 162 versus 210 min, \( p = 0.005 \). The median docking time for the RDP was 3.0 min, with a mean of 5 ± 7 min. However, there was no significant difference in the operation time between these two groups for either spleen-preservation, \( p = 0.078 \), or splenectomy, \( p = 0.067 \). DP with splenectomy took more operation time than that with spleen-preservation, \( p < 0.001 \), but the difference regarding the operation time between spleen-preservation and splenectomy was only significant in the LDP group, \( p = 0.003 \), not in RDP, \( p = 0.072 \). There was no significant difference in blood loss between RDP and LDP. However, splenectomy was associated with more blood loss, as compared with spleen preservation in both RDP and LDP groups. The radicality of resection was similar, with an R0 resection rate of 93.0% in the RDP group and 96.9% in the LDP, \( p = 0.328 \).

There was no surgical mortality in both groups, and surgical morbidity was of no significant difference between RDP and LDP, 31% versus 38%, \( p = 0.413 \). Most of the surgical complications were low grades by Clavien–Dindo classification in both groups, with grade 1 of 27% in RDP, and 25% in LDP, \( p = 0.367 \) (Table 3). The POPF (ISGPF grades B and C) was 22% in all patients, with 17% in RDP, and 24% in LDP, \( p = 0.340 \). No grade C pancreatic leakage occurred in our series. There was also no significant difference in PPH, wound infection, chyle leakage, and hospital stay. The hospital cost in RDP was much higher than that in LDP, with a median of 13,404 versus 7765 USD, \( p < 0.001 \). The intra-operative cost in RDP was also much higher than that in LDP, with a median of 7386 versus 2520 USD, \( p < 0.001 \).

| TABLE 1 | Demographics of patients undergoing robotic and laparoscopic distal pancreatectomy |
|----------|---------------------------------|-----------------|------------------|
|          | Total                          | RDP\(^a\)        | LDP\(^b\)        |
| Case number | 177                           | 65               | 112              |
| Gender    |                                 |                 |                  |
| Female    | 104 (58.8%)                    | 37 (56.9%)      | 67 (59.8%)      |
| Age, y/o  |                                 |                 |                  |
| Median (range) | 59 (23–85)                  | 62 (25–85)      | 58 (23–84)      |
| Mean ± SD | 57 ± 15                        | 58 ± 15          | 57 ± 16          |
| BMI,\(^d\) kg/m\(^2\) |                                 |                 |                  |
| Median (range) | 23.4 (15.9–42.4)            | 22.8 (15.9–29.4) | 23.6 (17.1–42.4) |
| Mean ± SD  | 23.9 ± 3.6                     | 23.3 ± 3.0       | 24.3 ± 3.0       |
| Tumor size, cm |                                 |                 |                  |
| Median (range) | 3.8 (0.9–15.0)               | 3.5 (1.0–15.0)  | 4.0 (0.9–13.0)  |
| Mean ± SD  | 4.4 ± 2.4                      | 4.3 ± 2.6        | 4.4 ± 2.3        |
| Primary tumor |                                 |                 |                  |
| Pancreatic adenocarcinoma | 57 (32.2%)                 | 18 (27.7%)      | 39 (34.8%)      |
| Serous cystadenoma | 36 (23.0%)                | 13 (20.0%)      | 23 (20.5%)      |
| Neuroendocrine tumor | 24 (13.6%)                | 10 (15.4%)      | 14 (12.5%)      |
| Mucinous cystic neoplasm | 24 (13.6%)               | 8 (12.3%)       | 16 (14.3%)      |
| Solid pseudopapillary tumor | 11 (6.2%)               | 4 (6.2%)        | 7 (6.3%)        |
| IPMNe\(^c\) | 8 (4.5%)                     | 4 (6.2%)        | 4 (3.6%)        |
| Chronic pancreatitis | 1 (0.6%)               | 0               | 1 (1.5%)        |
| Others    | 16 (9.0%)                      | 7 (10.8%)        | 9 (8.0%)        |

\(^a\)RDP: robotic distal pancreatectomy.
\(^b\)LDP: laparoscopic distal pancreatectomy.
\(^c\)SD: standard deviation.
\(^d\)BMI: body mass index.
\(^e\)IPMN: intraductal papillary mucinous neoplasm.
DISCUSSION

MIDP has been considered feasible and safe, and even proclaimed as a superior alternative to ODP by several retrospectively studies.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^24\)\(^–\)\(^26\) and two RCTs.\(^6\) MIS, either laparoscopic or robotic approach, has become the technique of choice for distal pancreatectomy worldwide, with the benefits of less wound pain, smaller incision, better cosmetic outcome, less blood loss, faster recovery, and shorter length of hospital stay. Although there are some technical advantages of the robotic approach that make it potentially superior to the laparoscopic approach, LDP and RDP were comparable regarding the perioperative outcomes, and no obvious advantage of one approach over the other was observed. Both LDP and RDP could achieve a similar rate of R0 resection for patients with pancreatic adenocarcinoma.\(^25\) However, currently there is no consensus or clear evidence from RCTs on which approach of MIDP, RDP, or LDP, is better.\(^27\) In this study, LDP, and RDP were performed by the same pancreatic surgeons using the same principles and procedures. At our institute, RDP had been the technique of choice until the da Vinci Robotic Surgical Systems were reserved mainly for the more complex procedure, robotic pancreaticoduodenectomy since 2016. Thereafter, RDP was seldom performed and LDP became the major option

### TABLE 2 Surgical parameters for robotic and laparoscopic distal pancreatectomy

|                                      | Total  | RDP\(^a\) | LDP\(^b\) | p value |
|--------------------------------------|--------|-----------|-----------|---------|
| Conversion                           | 5 (2.8%) | 1 (1.5%) | 4 (3.6%) | 0.653   |
| Spleen-preservation                  | 79 (45.9%) | 34 (53.1%) | 45 (41.7%) | 0.157   |

#### Operation time, min

|                                      | Total, n | RDP\(^a\) | LDP\(^b\) | p value |
|--------------------------------------|----------|-----------|-----------|---------|
| Median (range)                       | 186 (60–570) | 162 (66–570) | 210 (60–510) | 0.005   |
| Mean ± SD\(^c\)                      | 222 ± 108 | 192 ± 108 | 240 ± 102 |         |

|                                      | Spleen-preservation, n | RDP\(^a\) | LDP\(^b\) | |
|--------------------------------------|------------------------|-----------|-----------|---|
| Median (range)                       | 180 (60–450)           | 150 (66–426) | 180 (60–450) | 0.078   |
| Mean ± SD\(^c\)                      | 192 ± 90               | 168 ± 96 | 204 ± 84 |         |

|                                      | Splenectomy, n | RDP\(^a\) | LDP\(^b\) | |
|--------------------------------------|---------------|-----------|-----------|---|
| Median (range)                       | 240 (78–570)  | 180 (78–570) | 240 (78–570) | 0.067   |
| Mean ± SD\(^c\)                      | 252 ± 114     | 216 ± 120 | 264 ± 114 |         |

#### Blood loss, ml

|                                      | Total, n | RDP\(^a\) | LDP\(^b\) | p value |
|--------------------------------------|----------|-----------|-----------|---------|
| Median (range)                       | 55 (1–1200) | 50 (2–600) | 100 (1–1200) | 0.097   |
| Mean ± SD\(^c\)                      | 167 ± 223 | 131 ± 157 | 189 ± 253 |         |

|                                      | Spleen-preservation, n | RDP\(^a\) | LDP\(^b\) | |
|--------------------------------------|------------------------|-----------|-----------|---|
| Median (range)                       | 50 (5–550)             | 50 (10–500) | 50 (5–550) | 0.814   |
| Mean ± SD\(^c\)                      | 93 ± 117               | 89 ± 120 | 95 ± 116 |         |

|                                      | Splenectomy, n | RDP\(^a\) | LDP\(^b\) | |
|--------------------------------------|---------------|-----------|-----------|---|
| Median (range)                       | 130 (1–1200)  | 100 (2–600) | 135 (1–1200) | 0.180   |
| Mean ± SD\(^c\)                      | 232 ± 270     | 178 ± 182 | 259 ± 301 |         |

#### Radicality

|                                      | R0\(^d\) | R1\(^e\) | R2\(^f\) |
|--------------------------------------|----------|----------|----------|
| R0\(^d\)                             | 148 (95.5%) | 53 (93.0%) | 95 (96.9%) |
| R1\(^e\)                             | 1 (0.6%) | 1 (1.8%) | 0 |
| R2\(^f\)                             | 6 (3.9%) | 3 (5.3%) | 3 (3.1%) |

\(^a\)RDP: robotic distal pancreatectomy.
\(^b\)LDP: laparoscopic distal pancreatectomy.
\(^c\)SD: standard deviation.
\(^d\)R0: curative resection.
\(^e\)R1: microscopic residual cancer.
\(^f\)R2: gross residual cancer.
because of the limited availability of the da Vinci Robotic Surgical Systems. However, biases related to surgical skill and experience in different time periods would be inevitable, although these procedures were performed by the same pancreatic team.

With the introduction of da Vinci Robotic Systems, many surgeons have been fascinated by its high-quality 3-D visualization, enhanced dexterity of the robotic arms, and wide range of endo-wrist movements. Therefore, robotic systems with these advantages would be expected to allow fine and precise dissection and, moreover, facilitate hemostasis and suturing in complex pancreatic surgery. Some authors claimed that RDP could be associated with a lower open conversion rate, less blood loss, higher spleen preservation rate, and more harvested lymph nodes, but not all of these advantages of RDP were uniformly confirmed. Our study showed that although there was a tendency toward lower conversion rate, higher spleen preservation rate, shorter operation time, and less blood loss in the RDP group, all of them were not statistically significant, as compared with LDP. Splenectomy was associated with more blood loss, as

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TABLE 3  Surgical outcomes for robotic and laparoscopic distal pancreatectomy

|                      | Total | RDP  | LDP  | p value |
|----------------------|-------|------|------|---------|
| Case number          | 172   | 64   | 108  |         |
| Surgical mortality   | 0     | 0    | 0    | 1.000   |
| Surgical morbidity   | 61 (36%) | 20 (31%) | 41 (38%) | 0.413   |
| Clavien–Dindo        |       |      |      |         |
| classification       |       |      |      |         |
| Grade 0              | 111 (65%) | 44 (69%) | 67 (62%) | 0.367   |
| Grade I              | 44 (26%) | 17 (27%) | 27 (25%) |         |
| Grade II             | 10 (6%)  | 2 (3%)  | 8 (7%)  |         |
| Grade III            | 7 (4%)   | 1 (2%)  | 6 (6%)  |         |
| Grade IV             | 0       | 0      | 0      |         |
| Grade V (death)      | 0       | 0      | 0      |         |
| POPF<sup>c</sup>     |       |      |      |         |
| ISGPF<sup>d</sup> grades B and C | 37 (22%) | 11 (17%) | 26 (24%) | 0.340   |
| PPH<sup>e</sup>      |       |      |      |         |
| ISGSP<sup>f</sup> grades B and C | 4 (2%)   | 1 (2%)  | 3 (3%)  | 1.000   |
| Wound infection      | 3 (2%)  | 0      | 3 (3%)  | 0.295   |
| Chyle leakage        | 23 (13%) | 10 (16%) | 13 (12%) | 0.498   |
| Hospital stay, days  |         |       |       |         |
| Median (range)       | 10 (3–66) | 9 (4–56) | 11 (3–66) | 0.687   |
| Mean ± SD<sup>g</sup> | 13 ± 10 | 13 ± 10 | 13 ± 9  |         |
| Hospital cost, USD<sup>h</sup> |         |       |       |         |
| Median (range)       | 10,729 (917–26,157) | 13,404 (10,260–26,157) | 7765 (917–10,773) | <0.001 |
| Mean ± SD            | 10,953 ± 4522 | 14,618 ± 3480 | 8523 ± 3391 |         |
| Intra-operative cost, USD<sup>i</sup> |         |       |       | <0.001 |
| Median (range)       | 2974 (173–10,015) | 7386 (679–10,015) | 2520 (173–5007) |         |
| Mean ± SD            | 4310 ± 2425 | 7036 ± 1462 | 2557 ± 634 |         |

<sup>a</sup>RDP: robotic distal pancreatectomy.
<sup>b</sup>LDP: laparoscopic distal pancreatectomy.
<sup>c</sup>POPF: postoperative pancreatic fistula.
<sup>d</sup>ISGPF: International Study Group of Pancreatic Fistula.
<sup>e</sup>PPH: post-pancreatectomy hemorrhage.
<sup>f</sup>ISGSP: International Study Group of Pancreatic Surgery.
<sup>g</sup>SD: standard deviation.
<sup>h</sup>USD: United States dollar.

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compared with spleen-preservation with the Warshaw technique in both LDP and RDP groups in this study. Warshaw technique has gained the favor of some surgeons due to its simplicity with shorter operation time, less blood loss, and shorter hospitalization, as compared with the Kimura technique which appears to be tedious and risky for bleeding. Technical and oncological concerns are the reasons for our team to use the Warshaw technique for preserving the spleen, because the Kimura technique by preserving the splenic vessels appears to be tedious technique demanding, risky in hemostasis, and could be difficult and even impossible in chronic pancreatitis or obesity. Moreover, it might compromise the oncological radicality of a malignant lesion with a close or positive resection margin along the preserved splenic vessels by the Kimura technique. There is no significant difference regarding the surgical risks and outcomes between RDP and LDP, including overall surgical morbidity, the severity of complications based on Clavien-Dindo classification, POPF, PPH, wound infection, chyle leakage, hospital stay, and resection radicality of the tumor by our study. There is no surgical mortality in both RDP and LDP groups in our series. Many authors also reported similar findings like ours. Technically, RDP and LDP are comparable in terms of feasibility and safety.

Robotic surgery has been blamed for its longer operation time in many surgical fields including RDP, because of additional time for docking the robotic machine and changing robotic working instruments. However, this concern did not occur in our study, and a shorter operation time of RDP was observed (a median of 162 vs. 210 min, \( p = 0.005 \)). The median docking time for the RDP was only 3.0 min, with a mean of 5 ± 7 min. This discrepancy could be a reflection of experience accumulation and teamwork because multiple pancreatic surgeons were involved in each robotic pancreatic surgery at our institute. High cost was the major barrier to the widespread adoption of robotic surgery. In this study, the hospital cost of RDP was almost double that of LDP (a median of 13,404 vs. 7765 USD, \( p < 0.001 \)). Thus, when choosing the type of MIS adopted, the cost would be a major factor to consider if patients had to pay an additional amount for robotic surgery. Although the cost of robotic surgery could vary between institutions and countries, nevertheless, it is uniformly higher than conventional laparoscopic surgery.

The limitation of this study is that this study is a retrospective and unmatched comparison between two techniques done by the same surgical team in two different time periods. Thus, the biases related to surgical skill and experience in different time periods would be inevitable, although propensity matching analysis has been claimed to minimize the selection bias that occurred in this retrospective study.

5 | CONCLUSION

Both RDP and LDP are technically feasible and safe, and they are comparable in terms of surgical outcomes including conversion, blood loss, the radicality of tumor resection, hospital stay, and surgical morbidities such as POPF, PPH, chyle leakage, and wound infection. LDP costs much less, but takes more time, as compared with RDP. Spleen-preservation takes less time in the LDP group, and less blood loss in both LDP and RDP, as compared with splenectomy. Thus, both robotic and laparoscopic surgeries work equally well for DP. Nevertheless, whenever possible and feasible for those benign or low malignant lesions, LDP with spleen-preservation by the Warshaw technique is highly recommended in terms of lower cost and less blood loss. Although biases associated with patient selection and surgeon preference could be nearly eliminated, this study would have some unavoidable limitations as a retrospective cohort study comparing RDP and LDP performed during different time periods.

**AUTHOR CONTRIBUTIONS**

Hon-Fan Lai: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; validation; writing – original draft; writing – review and editing. Yi-Ming Shyr: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. Bor-Shian Shyr: Conceptualization; data curation; methodology; resources; software; validation; writing – review and editing. Shih-Chin Chen: Conceptualization; data curation; formal analysis; investigation; supervision; validation. Shin-E Wang: Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; supervision; writing – review and editing. Bor-Uei Shyr: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – review and editing.

**ACKNOWLEDGMENTS**

This study was financially supported by the Taipei Veterans General Hospital (V111-C-021, V110B-023, and V111-C-023), the Ministry of Health and Welfare (MOHW111-TDU-B-221-014015), and the Ministry of Science and Technology (MOST 108-2314-B-075-051-MY3).

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**TRANSPARENCY STATEMENT**

Bor-Uei Shyr affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**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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How to cite this article: Lai H-F, Shyr Y-M, Shyr B-S, Chen S-C, Wang S-E, Shyr B-U. Minimally invasive distal pancreatectomy: Laparoscopic versus robotic approach—A cohort study. Health Sci. Rep. 2022;5:e712.
doi:10.1002/hsr2.712