Safety and efficacy of robot-assisted versus open pancreaticoduodenectomy: a meta-analysis of multiple worldwide centers

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Abstract
The objective of the study is to compare the safety and efficacy of robot-assisted pancreaticoduodenectomy (PD) with open PD. The PubMed, EMBASE and Cochrane Library databases were searched for the literature available from their respective inception dates up to May 2020 to find studies comparing robot-assisted pancreaticoduodenectomy (RPD) with open pancreaticoduodenectomy (OPD). The RevMan 5.3 statistical software was used for analysis to evaluate surgical outcome and oncology safety. The combination ratio (RR) and weighted mean difference (WMD) and their 95% confidence intervals (CIs) were calculated using fixed-effect or random effect models. 18 cohort studies from 16 medical centers were eligible with a total of 5795 patients including 1420 RPD group patients and 4375 OPD group patients. The RPD group fared better than the OPD group in terms of estimated blood loss (EBL) (WMD = −175.65, 95% CI (−251.85, −99.44), \(P<0.00001\)), wound infection rate (RR = 0.60, 95% CI (0.44, 0.81), \(P=0.001\)), reoperation rate (RR = 0.61, 95% CI (0.41, 0.91), \(P=0.02\)), hospital day (WMD = −2.95, 95% CI (−5.33, −0.56), \(P=0.02\)), intraoperative blood transfusion (RR = 0.56, 95% CI (0.42, 0.76), \(P=0.0001\)), overall complications (RR = 0.78, 95% CI (0.64, 0.95), \(P=0.01\)), and clinical postoperative pancreatic fistula (POPF) (RR = 0.54, 95% CI (0.41, 0.70), \(P<0.00001\)). In terms of lymph node clearance (WMD = 0.48, 95% CI (−2.05, 3.02), \(P=0.71\)), R0 rate (RR = 1.05, 95% CI (1.00, 1.11), \(P=0.05\)), postoperative pancreatic fistula (RR = 1, 95% CI (0.85, 1.19), \(P=0.97\)), bile leakage (RR = 0.99, 95% CI (0.54, 1.83), \(P=0.98\)), delayed gastric emptying (DGE) (RR = 0.79, 95% CI (0.60, 1.03), \(P=0.08\)), 90-day mortality (RR = 0.82, 95% CI (0.62, 1.19), \(P=0.19\)), and severe complications (RR = 0.98, 95% CI (0.71, 1.36), \(P=0.91\)), and there were no significant differences between the two groups. Robotic surgery was inferior to open surgery in terms of operational time (WMD = 80.85, 95% CI (16.09, 145.61), \(P=0.01\)). RPD is not inferior to OPD, and it is even more advantageous for EBL, wound infection rate, reoperation rate, hospital stay, intraoperative transfusion, overall complications and clinical POPF. However, these findings need to be further verified by high-quality randomized controlled trials.

Keywords Complications · Open surgery · Pancreaticoduodenectomy · Robotic surgery · Meta-analysis

Introduction
Pancreaticoduodenectomy is one of the most complicated operations in abdominal surgery and is characterized by marked trauma and a high incidence of complications. In
2003, Giulianotti et al. [1] first reported Da Vinci-assisted robotic pancreaticoduodenectomy (RPD) which is a more complicated procedure than traditional surgery. Then a lot of effort has been made in these first robotic PDs, such as avoiding pancreatic anastomosis and conducting duct occlusion. The Da Vinci robot has the following unique advantages: (1) the operation field of vision can be magnified up to 10×, providing a naked-eye, 3D, high-resolution image for the operator; (2) the end of the device simulates the wrist: it is flexible and controllable, the movement can be scaled reasonably, and it can accurately complete various operations and eliminate shaking. These advantages are incomparable to those of traditional laparotomy and laparoscopic surgery. However, the safety and effectiveness of this robot method have not been fully determined. In the past 10 years, many retrospective studies have reported the efficacy of both approaches in PD. Therefore, we conducted this meta-analysis to evaluate the safety and efficacy of robot-assisted PD and open PD in the treatment of pancreatic diseases.

Data and methods

Retrieval strategy

We searched the PubMed, MEDLINE, and Cochrane Library by computer, and limited the search deadline to May 2020. The search terms used were ((open) OR laparotomy) AND ((pancreaticoduodenectomy) OR pancreatectomy) AND ((robotic) OR robot-assisted). The Boolean operators “OR” and “AND” for each keyword were used. The reference lists of identified literatures were also searched manually. In cases of duplicated studies, only the latest study, with the largest sample size and the highest quality, was selected. If a literature involved a study of patients with different types of surgery or operation times, it was still included in the analysis as an independent study.

Inclusion criteria

The following studies were included: (1) Reports of patients undergoing pancreaticoduodenectomy. (2) Original research papers, including comparative analysis of various indicators of the two surgical methods, including randomized control studies, and prospective and retrospective cohort studies. (3) Reports with any study sample size. (4) Reports with any length of follow-up. Study indicators included operation time, EBL, wound infection rate, reoperation rate, hospital stay, intraoperative transfusion, POPF, clinical POPF, R0 rate, retrieved lymph node, overall complications, bile leakage rate, DGE, 90-day mortality, and severe complications.

Exclusion criteria

(1) Those with incomplete information, those for which it was impossible to extract data effectively or for which contacting the author yielded no reply, duplicated reports. (2) Non-robotic surgery, such as laparoscopic surgery. (3) Non-PD surgery, such as central and distal pancreatectomy. (4) Review studies, case reports, and animal experiments.

This meta-analysis included prospective and retrospective cohort studies. In all the included studies, CSs was evaluated according to the Newcastle–Ottawa scale (NOS), specifically including study population selection, comparability, exposure evaluation, or outcome evaluation. The semi-quantitative star system was adopted for the evaluation of document quality by NOS, with a full score being 9 stars. The details are attached to Online Appendix file 1.

Statistical analyses

The Review Manager 5.3 software was used for meta-analysis. For binary data, relative risk (RR) and its 95% confidence interval (CI) were used, and for continuous data, the weighted mean difference (WMD) and its 95% CI were used to represent the combined statistics. Heterogeneity among the included studies was qualitatively evaluated using a $\chi^2$-based $Q$ test. $P$ values less than 0.05 showed statistically significant heterogeneity across the studies. The level of heterogeneity among studies was evaluated using $I^2$ statistics. $I^2 < 30\%$ was considered to indicate low heterogeneity; for these studies, a fixed-effects model was applied. Moreover, $30\% \leq I^2 \leq 60\%$ represented moderate heterogeneity, and $I^2 > 60\%$ was considered to indicate high heterogeneity. A random-effects model was applied when $I^2 \geq 30\%$. Sensitivity analysis was performed by removing one study at a time to assess whether the results could have been markedly affected by any single study. The results with less heterogeneity between the studies were selected if results were reversed after sensitivity analysis. Deleted literature studies are described in “Results”. Funnel plot was used to qualitatively evaluate publication bias (Online Appendix file 2). Stata software (version SE15.0) was used to calculate Begg’s test and Egger’s test for quantitative evaluation of publication bias of the included studies, with the significant level limited to 0.05. The details are attached to Online Appendix file 3.
Results

Literature search results

A total of 25 articles [2–26] were retrieved, of which 18 articles [2, 4–8, 10, 12–15, 17–20, 22, 23, 25] were included in the analysis. The flowchart of the literature screening is shown in Fig. 1. There were 11 cohort studies from prospective databases and 7 cohort studies from retrospective databases. A total of 5795 patients were included in the 18 articles, comprising 1420 patients in the RPD group and 4375 cases in the OPD group.

Data synthesis and analysis

In this study, 15 postoperative efficacy outcomes of RPD and OPD were analyzed, and sensitivity analysis was performed for each outcome. The outcomes are shown in Table 1. Subgroup analysis was conducted according to whether studies were prospective, retrospective, or propensity score matching (PSM) cohort, as shown in Table 2. Table 3 shows the basic characteristics and quality evaluation of the included documents.

Comparison of operation time

Nine studies [4–6, 8, 12, 15, 17, 22, 25] reported the operation time. There was a high degree of
heterogeneity ($I^2 = 96\%, \ P < 0.00001$) among studies. Using a random-effects model, the WMD was 80.85 (95% CI 16.09–145.61; $P = 0.01$). The operation time in the RPD group was significantly longer than that in the OPD group. Subgroup analysis showed that, in the retrospective cohort studies, the operation time of the RPD group was significantly longer than that of the OPD group ($WMD = 120.4, 95\% \ CI − 16.02 ~ 256.83, \ P = 0.08$) and the difference was significant. In the prospective cohort study, the operation time in the RPD group was not significantly different from that in the OPD group ($WMD = 57.52, 95\% \ CI − 30.98 ~ 146.02, \ P = 0.2$) (Fig. 2a).

### Comparison of estimated blood loss

Nine studies [4, 6, 8, 10, 12, 15, 17, 22, 25] reported estimated blood loss (EBL). There was a high degree of heterogeneity among the studies ($I^2 = 82\%, \ P < 0.00001$). Using the random-effects model, the combined WMD was $− 175.65, 95\% \ CI − 251.85, − 99.44, \ P < 0.00001$, the EBL in the RPD group was significantly less than that in the OPD group. Subgroup analysis showed that in both retrospective and prospective cohort studies, the EBL in the RPD group was significantly less than that in the OPD group ($WMD = − 136.55, 95\% \ CI − 230.64, − 42.45, \ P = 0.004$; and $WMD = − 222.8, 95\% \ CI − 361.50, − 84.10, \ P = 0.0002$, respectively) (Fig. 2b).

### Comparison of intraoperative blood transfusion

Nine studies [3–5, 7, 8, 11, 13–15] reported the rate of transfusion. There was moderate heterogeneity among these studies ($I^2 = 36\%, \ P = 0.13$). Using a random-effects model, the combined RR was 0.56, 95% CI (0.42, 0.76), $P = 0.0001$, and the rate of transfusion in the RPD group was significantly lower than that in the OPD group. After sensitivity analysis, the meta-results did not show any reversal changes. However, when Cai et al. [14] was eliminated, the heterogeneity was significantly reduced ($I^2 = 0\%, \ P = 0.43$), the fixed-effects model yielded an RR of 0.65, 95% CI (0.50, 0.86), $P = 0.002$, and the statistically significant difference remained. In both retrospective and prospective cohort studies, there was a statistically significant difference in the number of transfusion between the RPD group and the OPD group (RR = 0.69, 95% CI 0.48, 0.99, $P = 0.04$; RR = 0.48, 95% CI 0.31, 0.75, $P = 0.001$, respectively) (Fig. 2c).

### Postoperative hospital stay

Ten studies [4–6, 10, 12, 15, 17, 19, 22, 25] reported the postoperative hospital stay. There was a high degree of heterogeneity among the studies ($I^2 = 87\%, \ P < 0.00001$). Using a random-effects model, the combined WMD was $− 2.95, 95\% \ CI − 5.33, − 0.56, \ P = 0.02$; there was no statistically significant difference between the RPD group and the OPD group. Subgroup analysis showed
that in the retrospective or PSM cohort studies, the hospital stay in the RPD group was significantly shorter than that in the OPD group (WMD = −5.35, 95% CI (−9.89, −0.81), P = 0.02; WMD = −3.04, 95% CI (−5.28, −0.81), P = 0.008, respectively). In the prospective cohort studies, there was no significant difference between the RPD and OPD groups (Fig. 2d).

### Table 2 Meta-analysis results of subgroup analysis in measured outcomes

| Measured outcomes       | Subgroup analysis | No. studies | No. patients RPD | No. patients OPD | Heterogeneity test | Model | RR / WMD | 95% CI | P       |
|-------------------------|-------------------|-------------|------------------|------------------|--------------------|--------|-----------|--------|---------|
| Operative time (min)    | R                 | 4           | 243              | 290              | <0.00001           | Random | 120.4     | −16.02, 256.83 | 0.08    |
|                         | P                 | 5           | 225              | 308              | <0.00001           | Random | 57.52     | −30.98, 146.02 | 0.2     |
| Estimated blood loss (ml)| R                 | 4           | 243              | 290              | 0.002              | Random | −136.55   | −230.64, −42.45 | 0.004   |
|                         | P                 | 5           | 167              | 309              | <0.00001           | Random | −222.80   | −361.50, −84.10 | 0.0002  |
| Hospital day (days)     | R                 | 4           | 243              | 290              | 0.0003             | Random | −5.35     | −9.89, −0.81   | 0.02    |
|                         | P                 | 6           | 372              | 467              | <0.00001           | Random | −1.67     | −4.92, 1.59    | 0.32    |
|                         | PSM               | 3           | 390              | 525              | 0.11               | Random | −3.04     | −5.28, −0.81   | 0.008   |
| Retained lymph nodes    | R                 | 2           | 48               | 95               | 0.06               | Random | 2.22      | −6.63, 2.19    | 0.32    |
|                         | P                 | 4           | 174              | 122              | 0.07               | Random | 1.84      | −0.75, 4.42    | 0.16    |
| R0 rate                 | R                 | 5           | 327              | 285              | 0.42               | Fixed  | 1.04      | 0.98, 1.10     | 0.25    |
|                         | P                 | 8           | 262              | 228              | 0.52               | Fixed  | 1.08      | 0.98, 1.19     | 0.1     |
|                         | PSM               | 4           | 265              | 269              | 0.49               | Fixed  | 1.02      | 0.95, 1.09     | 0.59    |
| Overall complication    | R                 | 3           | 130              | 82               | 0.02               | Random | 0.6       | 0.23, 1.56     | 0.29    |
|                         | P                 | 8           | 431              | 528              | 0.27               | Fixed  | 0.94      | 0.84, 1.06     | 0.31    |
|                         | PSM               | 4           | 247              | 384              | 0.14               | Random | 0.98      | 0.77, 1.25     | 0.87    |
| POPF                    | R                 | 6           | 281              | 343              | 0.55               | Fixed  | 1.1       | 0.84, 1.44     | 0.5     |
|                         | P                 | 9           | 756              | 663              | 0.74               | Fixed  | 0.96      | 0.78, 1.18     | 0.7     |
|                         | PSM               | 4           | 269              | 271              | 0.7                | Fixed  | 1.08      | 0.75, 1.54     | 0.69    |
| Delayed gastric emptying| R                 | 3           | 227              | 274              | 0.36               | Fixed  | 1.07      | 0.49, 2.37     | 0.86    |
|                         | P                 | 8           | 322              | 407              | 0.35               | Fixed  | 0.73      | 0.56, 0.97     | 0.03    |
|                         | PSM               | 5           | 320              | 457              | 0.1                | Random | 0.72      | 0.31, 1.65     | 0.44    |
| Wound infection         | R                 | 3           | 227              | 274              | 0.48               | Fixed  | 0.67      | 0.49, 0.92     | 0.01    |
|                         | P                 | 5           | 164              | 159              | 0.73               | Fixed  | 0.28      | 0.10, 0.79     | 0.02    |
|                         | PSM               | 3           | 245              | 245              | 0.46               | Fixed  | 0.66      | 0.48, 0.90     | 0.009   |
| Mortality               | R                 | 4           | 243              | 243              | 0.73               | Fixed  | 0.73      | 0.3, 1.77      | 0.48    |
|                         | P                 | 10          | 935              | 975              | 0.31               | Fixed  | 0.84      | 0.62, 1.13     | 0.25    |
|                         | PSM               | 5           | 448              | 583              | 0.5                | Fixed  | 1.01      | 0.69, 1.47     | 0.97    |
| Reoperation             | R                 | 2           | 207              | 254              | 0.71               | Fixed  | 0.58      | 0.25, 1.31     | 0.19    |
|                         | P                 | 7           | 635              | 589              | 0.49               | Fixed  | 0.63      | 0.40, 0.98     | 0.04    |
| Transfusion             | R                 | 3           | 150              | 102              | 0.76               | Fixed  | 0.69      | 0.48, 0.99     | 0.04    |
|                         | P                 | 6           | 667              | 576              | 0.12               | Random | 0.48      | 0.31, 0.75     | 0.001   |
| Clinical PF             | R                 | 2           | 205              | 220              | 0.23               | Fixed  | 0.61      | 0.36, 1.03     | 0.06    |
|                         | P                 | 6           | 764              | 858              | 0.6                | Fixed  | 0.5       | 0.36, 0.71     | <0.0001 |
|                         | PSM               | 3           | 389              | 439              | 0.85               | Fixed  | 0.63      | 0.42, 0.96     | 0.03    |
| Severe complications    | R                 | 3           | 140              | 107              | 0.78               | Fixed  | 0.75      | 0.33, 1.71     | 0.5     |
|                         | P                 | 3           | 210              | 215              | 0.71               | Fixed  | 1.04      | 0.73, 1.49     | 0.84    |
|                         | PSM               | 3           | 196              | 198              | 0.64               | Fixed  | 1.01      | 0.70, 1.46     | 0.96    |

RPD robot-assisted pancreaticoduodenectomy, OPD open pancreaticoduodenectomy, P review of prospectively collected databases, R review of retrospective databases, PSM propensity score matching, No. number of, POPF postoperative pancreatic fistula, PF pancreatic fistula, CI confidence interval.

Number of retrieved lymph nodes

Six studies [4–6, 8, 12, 17] reported the number of retrieved lymph nodes. There was moderate heterogeneity among the studies (I² = 72%, P = 0.003). Using the random-effects model, WMD was 0.48, 95% CI (−2.05, 3.02), P = 0.71, and there was no statistically significant difference between
### Table 3  Basic characteristics and quality evaluation of the included documents

| Study          | Country | Organization                                                                 | Period          | Types | Case | Age       | OPD         | Malignant (%) | Gender (m/f) | Quality |
|----------------|---------|-------------------------------------------------------------------------------|-----------------|-------|------|-----------|-------------|---------------|-------------|---------|
| Baimas-George 2020 [2] | USA     | Department of General Surgery, Carolinas Medical Center                        | 2008–2019       | PSM(P) | 38 vs. 38 | 66 (38–84) | 68 (42–81) | 100 vs. 100 | 16/22 | 16/22     | 8       |
| Bao 2014 [4]    | USA     | Stony Brook University Medical Center, NK                                      | 2009–2011       | R     | 39 vs. 38 | 68.0 ± 11.2 | 67.7 ± 12.5 | 68 vs. 93    | 13/15 | 13/15     | 7       |
| Buchs 2011 [6]  | USA     | Division of General, Minimally Invasive and Robotic Surgery                   | 2002–2010       | P     | 44 vs. 39 | 63 ± 14.5  | 56 ± 15.8  | 75.0 vs. 69.2 | 22/22 | 14/25     | 8       |
| Cai 2019 [7]    | China   | Department of Hepatobiliary and Pancreatic Surgery, First Affiliated Hospital, Sun Yat-sen University, Guangzhou | 2011–2018       | P     | 460 vs. 405 | 66.5 ± 11.0 | 67.5 ± 10.7 | NA            | 253/207 | 211/194   | 7       |
| Chalikonda 2012 [8] | USA     | Department of general Surgery, Cleveland Clinic Foundation                   | 2009–2010       | p     | 30 vs. 30 | 62          | 61          | 53.3 vs. 53.3 | 16/14 | 16/14     | 7       |
| Gall 2020 [10]  | UK      | HPB Surgical Unit, Dept. of Surgery & Cancer Imperial College London          | 2017–2019       | P     | 25 vs. 37 | 60.93 ± 12.52 | 62.23 ± 10.76 | NA            | 16/19 | 21/16     | 8       |
| Ielpo 2019 [12] | Spain   | Sanchinarro University Hospital, San Pablo CEU University of Madrid           | 2008–2016       | P     | 17 vs. 17 | 66.8 ± 9.5  | 61.4 ± 11.9 | 88.2 vs. 100 | 89    | 10/7      | 7       |
| Boggi 2016 [5]  | Italy   | Division of General and Transplant Surgery, University of Pisa               | 2008–2014       | P     | 83 vs. 36 | 58 (21–84)  | 4.8 vs. 16.7 | 77/123        | 8     | 8         |
Table 3 (continued)

| Study       | Country | Organization                                                                 | Period       | Types    | Case     | Case Age | OPD       | OPD Age    | Malignant (%) | Gender (m/f) | Quality |
|-------------|---------|------------------------------------------------------------------------------|--------------|----------|----------|----------|-----------|------------|---------------|--------------|---------|
| Kauffmann 2019 [14] | Italy   | Division of General and Transplant Surgery, University of Pisa                | 2014–2017    | PSM(P)   | 24 vs. 26 | 65 (58.5–74.75) | 72.5 (59.75–78.75) | NA           | 10/10 | 13/11 | 7      |
| Kim HS 2018 [15]   | Korea   | Seoul National University College of Medicine                                | 2015–2017    | PSM(P)   | 51 vs. 186 | 60.7 ± 11.9 | 65.4 ± 10.1 | 96 vs. 93   | 24/27 | 108/78 | 8      |
| Lai 2012 [17]      | China   | Pamela Youde Nethersole Eastern Hospital, Hong Kong                          | 2000–2012    | R        | 20 vs. 67  | 66.4 ± 11.9 | 62.1 ± 11.2 | 75 vs. 79   | 12/8  | 38/29  | 8      |
| Marino 2019 [18]   | Italy   | Department of Surgery, Palermo University                                    | 2014–2016    | P        | 35 vs. 35  | 60.4 (43–72) | 62.3 (45–73) | 45.7 vs. 37.1 | 19/16 | 15/20  | 8      |
| McMillan 2017 [19] | USA     | University of Pittsburgh Medical Center                                      | 2003–2015    | PSM(P)   | 185 vs. 2661 | 64 (56–72) | NA        | 46.7 vs. 46.7 | 51.5% male | 8      |
| Mejia 2020 [20]    | USA     | Methodist Dallas Medical Center                                              | 2013–2019    | R        | 102 vs. 54 | 66± 10.6 | 61.7 ± 14.1 | 80.4 vs. 81.5 | 53/49 | 30/24  | 8      |
| Jin J 2019 [13]    | China   | the Pancreatic Disease Center of the Shanghai Ruijin Hospital                | 2003–2017    | R        | 39 vs. 44  | 29 (21–41) | 30 (25–38) | NA           | 3/15 | 1/32   | 7      |
| Shi 2020 [22]      | China   | the Pancreatic Disease Center of the Shanghai Ruijin Hospital                | 2017–2018    | PSM (R)  | 200 vs. 634 | 60.9 ± 11.4 | 60.1 ± 10.8 | NA           | 109/78 | 107/80 | 7      |
| Tan 2019 [23]      | Singapore | Yong Loo Lin School of Medicine                                           | 2014–2016    | PSM (R)  | 20 vs. 20  | 65 (37–82) | 64 (46–84) | 100 vs 100  | 11/9  | 11/9   | 7      |
| Zhou 2011 [25]     | China   | General Hospital of PLA Second Artillery, Beijing                           | 2009, 1–2009, 11 | R | 8 vs. 8 | 65 (48–75) | 57 (47–77) | NA           | 5/3  | 4/F    | 5      |
| Excluded studies   |         |                                                                              |              |          |           |          |            |             |                |            |        |
| Baker 2015 [3]     | USA     | Department of General Surgery, Carolinas Medical Center                     | 2012–2013    | R        | 22 vs. 49  | 63 (38–82) | 63 (26–86) | 81.2 vs.81.8 | 31/18 | 13/9   |        |
| Napoli 2017 [21]   | Italy   | Division of General and Transplant Surgery, University of Pisa              | 2007–2014    | P        | 82 vs. 227 | 61.6 (51.9–70.7) | 67.4 (59.7–74.8) | NA           | 36/46 | 125/102 |        |
Table 3 (continued)

| Study          | Country | Organization                                                                 | Period       | Types    | Case RPD vs. OPD | Age RPD | OPD | Malignant (%) | Gender (m/f) | Quality |
|----------------|---------|--------------------------------------------------------------------------------|--------------|----------|-----------------|---------|-----|---------------|--------------|---------|
| Kowalsky 2019 [16] USA | University of Pittsburgh School of Medicine | 2014–2015     | P          | 159 vs. 95 | 66.8 ± 9.8     | 67.9 ± 10.9 | 52 vs. 63 | 87/72 | 47/48 |
| Varley 2018 [24] USA | University of Pittsburgh Medical Center | 2011–2016     | P          | 133 vs. 149 | 66.3 ± 10.6     | 66.3 ± 10.6 | NA   | 64/69 | 79/70 |
| ZureiKat 2016 [26] USA | Multicenter: University of Pittsburgh School of Medicine, etc | 2011–2015     | R          | 211 vs. 817 | 67 (15–86)     | 65 (15–93) | NA   | 425/392 | 117/94 |
| Girgis M 2019 [11] USA | the National Cancer Database (NCDB) from the University of Pittsburgh Medical Center | 2011–2016     | P          | 163 vs. 198 | 66.6 ± 10.9     | 67.6 ± 10.3 | NA   | 87/76 | 105/93 |
| Chen S 2015 [9] China | Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine | 2010–2013     | P          | 60 vs. 120  | 53.6 ± 13.5     | 53.8 ± 14.3 | 63.3 vs. 63.3 | 34/26 | 65/55 |

RPD: robot-assisted pancreaticoduodenectomy, OPD: open pancreaticoduodenectomy, P: review of prospectively collected databases, R: review of retrospective databases, PSM: propensity score matching, No.: number of, NA: data not accessible, vs.: versus, Quality: quality assessment
the two operative methods. Subgroup analysis showed that there was no statistically significant difference between the RPD group and OPD group in both retrospective and prospective cohort studies (WMD = 2.22, 95% CI = −6.63, 2.19, P = 0.32; WMD = 1.84, 95% CI = −0.75, 4.42, P = 0.16, respectively) (Fig. 3a).

R0 rate

Thirteen studies [2, 4–6, 8, 10, 12, 14, 18, 20, 22, 23, 25] reported the R0 rate of the cutting edge. There was a low degree of heterogeneity (I^2 = 1%, P = 0.44) among the studies. Using the fixed-effects model, the combined RR was 1.05, 95% CI (1.01, 1.11), P = 0.05. The R0 rate of the RPD group was significantly higher than that of the OPD group. However, subgroup analysis showed that there was no statistically significant difference between the RPD group and the OPD group in the prospective or retrospective cohort studies (RR = 1.04, 95% CI 0.98, 1.10, P = 0.25; and RR = 1.08, 95% CI 0.98, 1.19, P = 0.1, respectively) (Fig. 3b).

Overall complications

Eleven studies [5, 6, 10, 12, 14, 15, 18–20, 23, 25] reported the overall complications. There was moderate heterogeneity (I^2 = 55%, P = 0.01) among the studies. Using the
random-effects model, the combined RR was 0.83, 95% CI (0.68, 1.01), \( P = 0.27 \), with no statistically significant difference. After sensitivity analysis, the meta-analysis results show reversal changes. When studies by McMillan et al. [19] was sequentially eliminated, the heterogeneity was significantly reduced (\( I^2 = 33\% \), \( P = 0.14 \)). The combined RR of the random effect model was 0.78, 95% CI (0.64, 0.95), \( P = 0.01 \), and there was statistically significant difference. Subgroup analysis showed that, in the retrospective, prospective and PSM cohort study, there was no statistically significant difference between the RPD group and OPD group (Fig. 3c).

### Bile leakage rate

Six studies [6, 12, 13, 17, 18, 22] reported the bile leakage rate. There was a low degree of heterogeneity (\( I^2 = 0\% \), \( P = 0.6 \)) among the studies. Using a fixed-effects model, the combined RR was 0.99, 95% CI (0.54, 1.83), \( P = 0.98 \). There was no statistically significant difference between the RPD
and OPD groups. Subgroup analysis showed that there was no significant difference in bile leakage rate between the RPD group and OPD group in the prospective and retrospective cohort studies (Online Appendix file 4A).

**Incidence of delayed gastric emptying**

Nine studies [2, 4–7, 9, 10, 15, 18] reported the incidence of DGE. There was a low degree of heterogeneity ($I^2 = 0\%$, $P = 0.46$) among the studies. Using the fixed-effects model, the combined RR was 0.98, 95% CI 0.60, 1.03, $P = 0.08$, and the difference was not statistically significant. Subgroup analysis showed that there was no significant difference in the incidence of DGE between the RPD group and OPD group for prospective or PSM studies (RR = 1.07, 95% CI 0.49, 2.37, $P = 0.86$; and RR = 0.72, 95% CI 0.31, 1.65, $P = 0.44$, respectively). However, DGE in the RPD group was significantly lower than that in the OPD group among the eight prospective cohort studies (Online Appendix file 4B).

**Severe complications**

Six studies [10, 13, 14, 19, 20, 23] reported the severe complications. There was a low degree of heterogeneity ($I^2 = 0\%$, $P = 0.89$) among the studies. Using the fixed-effects model, the combined RR was 0.98, 95% CI (0.71, 1.36), $P = 0.91$, with no statistically significant difference. After sensitivity analysis, the meta-analysis showed no reversal changes. Subgroup analysis showed that there was no significant difference between the RPD group and OPD group in either prospective, retrospective or PSM cohort studies (Online Appendix file 4C).

**Incidence of clinical POPF**

Nine studies [7, 10, 12–15, 18, 19, 22] reported the incidence of clinical POPF. There was moderate heterogeneity ($I^2 = 58\%$, $P = 0.58$) among the studies. Using a fixed-effects model, the combined RR was 0.54, 95% CI (0.41, 0.70), $P < 0.0001$. Subgroup analysis showed that the incidence of POPF in the RPD group was lower than that in the OPD group in prospective, retrospective and PSM cohort studies (RR = 0.61, 95% CI (0.36, 1.03), $P = 0.06$; RR = 0.61, 95% CI (0.36, 1.03), $P = 0.06$; and RR = 0.61, 95% CI (0.36, 1.03), $P = 0.06$; respectively) (Fig. 4a).

**Wound infection rate**

Eight studies [2, 6, 8, 12, 17, 18, 22, 23] reported the number of wound infection rate. There was moderate heterogeneity ($I^2 = 0\%$, $P = 0.65$) among the studies. Using the fixed-effect model, the combined RR was 0.6, 95% CI (0.44, 0.81), $P = 0.001$, with statistical significance. Subgroup analysis showed that in both the retrospective and prospective cohort studies, the wound infection rate in the RPD group was significantly lower than that in the OPD group (RR = 0.67, 95% CI 0.49–0.92, $P = 0.01$, RR = 0.28, 95% CI 0.10–0.79, $P = 0.02$, respectively) (Fig. 4b).

**Reoperation rate**

Nine studies [6–8, 10, 12, 14, 17, 18, 22] reported the reoperation rate. There was a low degree of heterogeneity ($I^2 = 0\%$, $P = 0.69$) among the studies. Using the fixed-effects model, the combined RR was 0.61, 95% CI (0.41, 0.91), $P = 0.02$, with statistical significance. Subgroup analysis showed that there was no significant difference in reoperation rate between the RPD group and the OPD group in the retrospective cohort studies (RR = 0.58, 95% CI (0.25, 1.31), $P = 0.19$). In a prospective cohort study, the rate of reoperations in the RPD group was less than that in the OPD group, and the difference was significant (RR = 0.63, 95% CI (0.40, 0.98), $P = 0.04$) (Fig. 4c).

**Incidence of POPF**

Fifteen studies [2–7, 9–15, 17, 18] reported the incidence of POPF. There was moderate heterogeneity ($I^2 = 0\%$, $P = 0.75$) among the studies. Using the fixed-effect model, the combined RR was 0.82, 95% CI (0.62, 1.10), $P = 0.19$, with no statistically significant difference. Subgroup analysis showed that there was no significant difference in POPF between the RPD group and the OPD group in the prospective, retrospective and PSM studies, respectively (Online Appendix file 5A).

**Postoperative 90-day mortality**

Fourteen studies [2, 4–8, 10, 12, 15, 18, 19, 22, 23, 25] reported postoperative 90-day mortality. There was a low degree of heterogeneity ($I^2 = 0\%$, $P = 0.53$) among the studies. Using the fixed-effects model, the combined RR was 0.82, 95% CI (0.62, 1.10), $P = 0.19$, with no statistically significant difference. Subgroup analysis showed that there was no significant difference in postoperative mortality between the RPD group and OPD group in the prospective, retrospective and PSM cohort studies (RR = 0.73, 95% CI (0.3, 1.77), $P = 0.48$; RR = 0.84, 95% CI (0.62, 1.13), $P = 0.25$; RR = 1.01, 95% CI (0.69, 1.47), $P = 0.97$, respectively) (Online Appendix file 5B).

**Sensitivity analysis and bias risk assessment**

Sensitivity analysis was carried out in each meta-analysis. The heterogeneity of operation time, estimated blood loss,
intraoperative blood transfusion, retrieved lymph node, and hospital day was large. After the relevant literature was removed, the heterogeneity was significantly reduced, but the results were not reversed. After the relevant literature was removed, the heterogeneity of overall complications is reduced, but the result reversed. The sensitivity analysis showed that other results were not reversed after sequential removal of each study. The funnel plots of the publications were found to be symmetrical, which suggested no publication bias. No publication bias was detected by Begg’s test and Egger’s test, except for the hospital day in the Egger’s test (Online Appendix file 3).

Discussion

Pancreatectoduodenectomy was first reported by Whipple et al. in 1935 [27]. Traditional pancreatectoduodenectomy is considered one of the most complicated operations in abdominal surgery because it involves multiple organs and complex reconstruction of the pancreatic digestive tract. At present, traditional open surgery remains the main method used. With the development of computer science and technology, a robotic (Da Vinci) surgical system has been introduced into the general surgery field, including pancreatic surgery, and has become one of the most promising surgical
techniques. However, the safety and effectiveness of this new technology have not been fully determined. Compared with OPD, robotic surgery is more dependent on surgical instruments and equipment. At present, the Da Vinci surgical robot is the only technical platform used for RPD, and the medical units that have a Da Vinci surgical robot are typically the most advanced hospitals in a region. Therefore, the equipment is homogeneous across regions, making studies comparable. Therefore, we reviewed the existing literature, conducted this meta-analysis, and evaluated the current role of robotics and open surgery in pancreatic disease.

The results of this meta-analysis showed that RPD was significantly better than open surgery in the estimated blood loss, wound infection rate, reoperation rate, postoperative hospital stay, transfusion, overall complications and clinical POPF. Additionally, no significantly different were found in the retrieved lymph node, R0 rate, bile leakage rate, delayed gastric emptying, postoperative 90-day mortality, POPF, severe complications. In terms of operation time, open surgery was better than robot surgery.

Four previous meta-analyses [28–31] discussed the safety and effectiveness of robot technology in pancreaticoduodenal surgery and concluded that pancreaticoduodenectomy is a safe and feasible alternative to open surgery. However, these meta-analyses also have some limitations. One of the limitations is that their meta-analysis included all the published literature at that time, but the data of many literature studies came from the same institution, and there may be overlap. This study provides a comprehensive and up-to-date meta-analysis, in which not only new institutions are included, but also the most recent studies with the largest sample size and highest quality from previous institutions are selected. Up to now, randomized controlled trials (RCTs) are still lacking; however, it is difficult to conduct a prospective, randomized study because of ethical issues and patients' concerns for malignant tumors. It has been pointed out that the meta-analysis of carefully designed non-randomized comparative studies of surgery may be as accurate as that of RCTs [32], and we used comparative meta-analysis, which will be better accepted as a supplementary tool for qualitative review in the medical literature [33].

Postoperative complications of pancreaticoduodenectomy are some of the most difficult problems for surgeons. Postoperative complications after pancreaticoduodenectomy occur in 40–50% of patients [34]. POPF is widely considered the most common and most dangerous complication after pancreaticectomy, which is the most important factor in death due to pancreaticoduodenectomy. Whether via a new material or new surgical technique, reducing POPF has become the focus of surgeons. The results of this meta-analysis showed that there was no significant difference between the RPD group and the OPD group in terms of POPF, while for clinical POPF, the incidence in the RPD group decreased by 47% (95% CI 29% ~ 60%), which was statistically significant. Clinical POPF, also known as BC grade POPF, requires clinical intervention; hence, the reduction of RPD will undoubtedly reduce the occurrence and development of a series of other problems. As in this meta-analysis, overall complications are also reduced.

This meta-analysis concluded that the estimated blood loss, intraoperative transfusion, and the length of stay of the RPD patients were reduced compared to those of OPD patients, but the operation time was longer for RPD than for OPD. However, there was a high degree of heterogeneity between the studies in the terms. Although the random-effects model is used to combine the effect amount, the high degree of heterogeneity will greatly weaken the interpretation of the results. The most likely reason for the marked heterogeneity is that many studies are still in the initial stage of the learning curve. In the prospective database collection study, there was no significant difference in operative time and postoperative hospital stay between the RPD group and the OPD group, while in the retrospective cohort study, there was a significant difference, but EBL’s situation was the opposite. Different types of database studies were included, which may have introduced a bias in these outcome indicators. Thus, there is a need to verify this further by better-designed, high-quality RCTs.

R0 resection and retrieved lymph node are two important prognostic factors in patients with pancreaticoduodenectomy [35]. The survival rate can be improved by increasing the number of retrieved lymph node, clarifying lymph node metastasis, and guiding postoperative treatment [36, 37]. This meta-analysis showed that the R0 resection rate and retrieved lymph node of robotic surgery were not significantly different from that of open surgery, which was consistent with the previous meta-analyses by Podda et al. [29] and Yan et al. [30], but not Zhao et al. [31]. Nevertheless, they may have partially overlapping patients, which may lead to bias. Long-term survival and tumor recurrence rates were not evaluated due to incomplete data. Therefore, it is difficult to make a reliable conclusion regarding tumor safety.

With the development of neoadjuvant chemotherapy, the current treatment strategy for pancreaticoduodenal cancer is a multidisciplinary comprehensive treatment with surgery at the core. The fibrogenic response and cytotoxicity caused by neoadjuvant chemotherapy lead to the loss of a normal tissue plane, which brings great challenges to all surgeons. Whether robotic surgery can overcome the new problems caused by new adjuvant therapy due to its unique advantages remains unclear. Some of the studies included in this meta-analysis, such as those by Baimas-George et al. [2], Cai et al. [7], Ielpo et al. [12], Marino et al. [18], Mejia et al. [20], reported the number of people who had received neoadjuvant therapy in the RPD and OPD groups; however,
Conclusions

This meta-analysis showed that RPD is superior to OPD in terms of the rate of R0, the rate of infection at the wound site, the rate of reoperation, the rate of blood transfusions required during operation, and the rate of clinical POPF; however, the operation time is longer than that of open surgery. Robot-assisted surgery is a safe and feasible alternative to OPD with regard to short outcomes. This needs to be further verified by high-quality clinical trials.

Limitations

Most of the studies included in this meta-analysis were retrospective, and there was, consequently, a risk of selection bias. In addition, RPD is a complex process and is still in its infancy; therefore, the number of cases in each study is small, and some studies reported on data obtained during the learning curve stage of these processes.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest in this work.

Research involving human participants and/or animals Not applicable.

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