Impact of diabetes mellitus on clinical outcomes of pancreatic cancer after surgical resection: A systematic review and meta-analysis

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Abstract

Background and objective
Diabetes mellitus (DM) is a risk factor for pancreatic cancer but its impact on postoperative outcomes and long-term survival after cancer resection remains controversial. A meta-analysis of published studies was conducted to address this issue.

Methods
An extensive electronic search of four databases was performed for relevant articles. Data were processed for meta-analysis using Review Manager version 5.1.

Results
Seventeen observational studies involving 5407 patients were subjected to the analysis. Overall morbidity or any type of complications and mortality were comparable between diabetic and non-diabetic subjects. Overall DM has a significant negative impact on survival (risk ratio [RR], 1.24, 95% confidence interval [CI], 1.05–1.45; \( P = 0.01 \)). Stratification by the type of DM revealed that new-onset DM (≤2 years duration, RR, 1.54, 95% CI, 1.24–1.91; \( P < 0.001 \)) but not long-standing DM (≥2 years duration, RR, 1.74, 95% CI, 0.86–3.52; \( P = 0.12 \)) was associated with reduced survival.

Conclusions
Diabetes mellitus does not affect perioperative outcomes in patients undergoing surgery for pancreatic cancer. However, new-onset DM confers a negative impact on survival of pancreatic cancer in patients undergoing surgical resection.
**Introduction**

Pancreatic cancer is a deadly disease, causing about 227,000 deaths worldwide every year. The exceptionally high mortality confers it as the 4th or 5th most frequent cause of cancer-related deaths in most developed countries [1]. Identification of etiological factors could enable early detection of pancreatic cancer so that it would be more amenable to treatment. One potentially important risk factor for this malignancy is diabetes mellitus (DM). A meta-analysis of 88 studies showed a strong association between DM and pancreatic cancer development (pooled odds ratio (OR), 1.97, 95% confidence interval [CI], 1.78–2.18) [2]. Hyperinsulinemia and insulin-resistance have been proposed as potential biologic mechanisms.

Pancreatectomy is the only treatment that can offer long-term survival in patients with pancreatic cancer at present. Some publications have reported that DM is associated with an increased risk of postoperative complications or worse survival outcomes following resection of pancreatic cancer [3–5], but others have failed to demonstrate such an association [6–8]. In the light of this controversy, we made a meta-analysis of published studies to address this issue.

**Materials and methods**

**Study selection**

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [9]. An electronic search of the literature was conducted in PubMed, Web of Science, Cochrane Library, and China National Knowledge Infrastructure from the time of inception to June 2016, using the following terms: “pancreatic cancer”, “diabetes mellitus”, “pancreatic resection”, “pancreaticoduodenectomy”, “post-operative outcomes”, and “prognosis”. Manual search of reference lists of all retrieved articles was carried out to identify additional studies.

**Criteria for inclusion and exclusion**

Published studies in the English or Chinese language comparing outcomes in DM and non-DM patients undergoing surgical resection with curative intent for pancreatic cancer were included. Letters, reviews, abstracts, editorials, expert opinions, non-English language papers, animal or in vitro studies, studies lacking control groups, studies with a small sample size (<10 in number), studies evaluating treatment in patients with unresectable diseases, and studies that contained patients with other periampullary adenocarcinomas (duodenal, ampullary, and biliary) without separate assessments were excluded.

**Data extraction and outcomes of interest**

Two reviewers (XL and YZ, respectively) independently extracted relevant data regarding the characteristics of study and outcomes of interest from each selected article by using standardized data extraction forms. Discrepancies were resolved by discussion until consensus was achieved.

The outcomes of interest analyzed included (a) clinicopathologic characteristics; (b) postoperative morbidity and mortality; and (c) overall survival (OS).

**Assessment of methodological quality**

The methodological quality of the included studies was assessed by using the Newcastle-Ottawa Scale. Scores were assigned for patient selection, comparability of the study groups, and outcome assessment [10].
Statistical methods

The effect measures estimated were OR with a 95% CI for dichotomous variables and weighted mean difference (WMD) with a 95% CI for continuous data. The relative risk ratio (RR) with 95% CI was used to assess the prognostic value of DM, where an observed RR > 1 implied a worse survival for DM group. To do this, the hazard ratio (HR) was directly considered as RR. To assess heterogeneity across studies, the $I^2$ statistic was calculated and a value > 50% was interpreted as statistically significant. A funnel plot based on the survival outcome was conducted to explore the possibility of publication bias. Statistical analyses were performed with Review Manager version 5.1 (The Cochrane Collaboration, Software Update, Oxford). A value of $P < 0.05$ was considered statistically significant.

Results

Selection of studies

Fig 1 presents the flowchart of selection for study. Among 4238 references identified by the initial search, 17 [3–8, 11–21] were finally met the inclusion criteria and suitable for analysis. The main characteristics of these 17 studies are summarized in Table 1. Most reports were conducted in the United States (n = 7) and Asia (n = 7), followed by Europe (n = 3). Of the two studies conducted at the same institution [4, 5], the former mainly assessed the impact of DM.

Fig 1. Flow diagram of included studies.

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on long-term survival, and the latter mainly assessed the impact of DM on perioperative morbidity and mortality. All identified studies were observational studies involving a total of 5407 patients, including 1669 in DM group and 3738 in non-DM group. The sample size of these studies varied from 83 to 1071 patients. The percentage of DM ranged from 8.8% to 56.3%. Details regarding DM definition were described in 13 articles [4,5,7,8,13–21]. Operation types were presented in 13 articles covering 4108 patients [3–5,7,8,11,12,16–21]. In total, 3333 (81.3%) patients underwent pancreaticoduodenectomy, 576 (14.0%) patients underwent left pancreatectomy, and 199 (4.7%) patients underwent total pancreatectomy.

Meta-analysis

Table 2 shows the results for the outcomes.

Compared with non-DM patients, DM patients had higher prevalence of male sex (OR, 0.81, 95% CI, 0.69–0.95; \( P = 0.01 \)) and greater body mass index (WMD, 1.45, 95% CI, 0.60–
2.30; \( P < 0.001 \)). There was no significant difference in age, smoking history and the presence of jaundice between the two groups. The operative variables including operation type, duration of surgery and transfusion were comparable between the two groups. Pathologically, DM patients had significantly higher prevalence of poor differentiation (OR, 1.22, 95% CI, 1.02–1.47; \( P = 0.03 \)) and hard pancreatic texture (OR, 3.48, 95% CI, 2.34–5.18; \( P < 0.001 \)) and were more likely to have larger tumor sizes (WMD, 0.27, 95% CI, 0.12–0.42; \( P < 0.001 \)). There was no significant difference in tumor location, lymph node involvement, perineural invasion, lymphovascular invasion, cancer stage, and the margin status between the two groups.

Table 2. Meta-analysis of short and long-term outcomes.

| Outcome of interest | No. of studies | No. of patients | OR/WMD  | 95% CI  | \( P \)-value | \( I^2 \) (%) |
|---------------------|---------------|----------------|---------|---------|--------------|-------------|
| **Characteristics of patients** |               |                |         |         |              |             |
| Gender              | 10            | DM = 1071, Non-DM = 1763 | 0.81    | 0.69, 0.95 | 0.01         | 0           |
| Age                 | 7             | DM = 764, Non-DM = 1246 | 1.66    | -0.66, 3.17 | 0.20         | 76          |
| Body mass index     | 3             | DM = 472, Non-DM = 446 | 1.45    | 0.60, 2.30 | <0.001       | 56          |
| Smoking history     | 3             | DM = 511, Non-DM = 830 | 0.97    | 0.75, 1.25  | 0.80         | 24          |
| Jaundice            | 5             | DM = 535, Non-DM = 1239 | 0.97    | 0.70, 1.34  | 0.85         | 52          |
| Type of operation   | 6             | DM = 647, Non-DM = 1029 | 1.15    | 0.89, 1.49  | 0.28         | 0           |
| Duration of surgery (min) | 7    | DM = 566, Non-DM = 1103 | -4.38   | -16.38, 7.62 | 0.47         | 0           |
| Blood transfusion   | 3             | DM = 313, Non-DM = 687 | 1.12    | 0.81, 1.56  | 0.50         | 0           |
| Tumor site          | 6             | DM = 645, Non-DM = 921 | 1.21    | 0.80, 1.81  | 0.37         | 58          |
| Tumor size          | 8             | DM = 744, Non-DM = 1217 | 0.27    | 0.12, 0.42  | <0.001       | 14          |
| Node involvement    | 4             | DM = 448, Non-DM = 940 | 1.09    | 0.85, 1.38  | 0.50         | 12          |
| Poor differentiation | 7            | DM = 920, Non-DM = 1705 | 1.22    | 1.02, 1.47  | 0.03         | 49          |
| Perineural invasion | 6             | DM = 645, Non-DM = 1492 | 1.27    | 0.85, 1.90  | 0.24         | 57          |
| Lymphovascular invasion | 6    | DM = 645, Non-DM = 1492 | 1.18    | 0.96, 1.45  | 0.12         | 0           |
| Stage               | 4             | DM = 592, Non-DM = 773 | 0.75    | 0.49, 1.15  | 0.18         | 10          |
| Hard pancreatic texture | 4     | DM = 430, Non-DM = 904 | 3.48    | 2.34, 5.18  | <0.001       | 56          |
| Positive margin     | 5             | DM = 732, Non-DM = 1300 | 1.18    | 0.93, 1.48  | 0.17         | 0           |
| **Postoperative outcomes** |           |                |         |         |              |             |
| Overall morbidity   | 4             | DM = 403, Non-DM = 796 | 0.90    | 0.59, 1.39  | 0.65         | 54          |
| Pancreatic fistula  | 6             | DM = 453, Non-DM = 914 | 0.88    | 0.50, 1.54  | 0.65         | 65          |
| ISGPF B +C fistula  | 2             | DM = 236, Non-DM = 617 | 0.69    | 0.20, 2.44  | 0.57         | 65          |
| Delayed gastric emptying | 6   | DM = 453, Non-DM = 914 | 1.08    | 0.75, 1.55  | 0.69         | 0           |
| Abdominal collection or abscess | 3    | DM = 313, Non-DM = 687 | 0.84    | 0.53, 1.35  | 0.48         | 0           |
| Biliary fistula     | 2             | DM = 197, Non-DM = 552 | 0.48    | 0.14, 1.61  | 0.24         | 50          |
| Wound infection     | 2             | DM = 193, Non-DM = 205 | 1.11    | 0.67, 1.85  | 0.68         | 0           |
| Cardiac complications | 3          | DM = 317, Non-DM = 718 | 1.53    | 0.83, 2.80  | 0.17         | 31          |
| Respiratory complications | 4   | DM = 394, Non-DM = 785 | 0.89    | 0.54, 1.46  | 0.64         | 0           |
| Renal dysfunction   | 3             | DM = 317, Non-DM = 715 | 1.75    | 0.96, 3.18  | 0.07         | 17          |
| Mortality           | 3             | DM = 317, Non-DM = 715 | 1.60    | 0.58, 4.42  | 0.36         | 0           |
| **Overall survival** |               |                |         |         |              |             |
| Overall DM          | 11            | DM = 1103, Non-DM = 2635 | 1.24\textsuperscript{a} | 1.05, 1.45 | 0.01         | 64          |
| Long-standing DM    | 3             | DM = 79, Non-DM = 540 | 1.74\textsuperscript{a} | 0.86, 3.52 | 0.12         | 79          |
| New-onset DM        | 3             | DM = 208, Non-DM = 540 | 1.54\textsuperscript{a} | 1.24, 1.91 | <0.001       | 0           |

OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; ISGPF, International Study Group of pancreatic fistula; DM, diabetes mellitus \( ^a \) risk ratio.

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On postoperative outcomes analysis, diabetics were not at increased risk for development of overall morbidity (OR, 0.90, 95% CI, 0.59–1.39; \(P = 0.65\)), pancreatic fistula (OR, 0.88, 95% CI, 0.50–1.54; \(P = 0.65\)), delayed gastric emptying (OR, 1.08, 95% CI, 0.75–1.55; \(P = 0.69\)) (Fig 2), as well as other complications and mortality.

The result of analysis on survival showed that DM had a significant negative impact on prognosis (RR, 1.24, 95% CI, 1.05–1.45; \(P = 0.01\)) (Fig 3). Subsequent analyses were restricted to nine studies [3,5, 11–17,20] that reported multivariate-adjusted estimates yielded similar results (RR, 1.35, 95% CI, 1.13–1.62; \(P = 0.001\)). Stratification by the type of DM revealed that new-onset DM (<2 years duration, RR, 1.54, 95% CI, 1.24–1.91; \(P < 0.001\)) but not long-standing DM (>2 years duration, RR, 1.74, 95% CI, 0.86–3.52; \(P = 0.12\)) was associated with reduced survival.

**Publication bias**

A funnel plot demonstrated that two of the studies fell outside the limits of the 95% CI for the impact of overall DM on survival, suggesting the presence of publication bias (Fig 4).

**Discussion**

Diabetes mellitus is reported to be associated with increased events of cardiovascular and renal dysfunction and have an adverse effect on postoperative outcomes of vascular, hepatic and gastric surgeries [22–24]. In the field of pancreatic surgery, Srivastava et al. [25] found that DM was a risk factor associated with an increased incidence of pancreatic fistula in their 120
patients with pancreatic and periampullary tumors who underwent pancreaticoduodenectomy (OR, 4.60, 95% CI, 1.23–17.18). On the other hand, DeOliveira et al. [26] reported that DM was not a significant indicator for increased occurrence of overall complications or any type of complications in their 633 patients with various benign and malignant diseases after pancreaticoduodenectomy. These conflicting results might be partially explained by the heterogeneous patient groups studied. By limiting analysis to patients undergoing resection for pancreatic cancer, a condition with a low risk of pancreatic fistula compared with other histologic diagnoses [27], the current study shows that the incidence of overall postoperative morbidity and cardiovascular and renal complications are comparable in diabetic and nondiabetic patients. This may partially reflect careful patient selection for operation and current perioperative management for patients at high risk.

Pancreatic fistula is the principal complication related to pancreatic surgery and may cause fatal consequences. A soft pancreatic texture and a small pancreatic duct (<3 mm) are well recognized as risk factors predisposing the development of pancreatic fistula [28]. Our analysis showed that diabetic patients usually had a low frequency of soft pancreatic texture as compared with non-diabetic patients. Furthermore, the frequency of a small pancreatic duct or diameter of the pancreatic duct was found to be similar between diabetic and non-diabetic patients [5,8]. Not surprisingly, we failed to demonstrate any difference in the rate and severity of pancreatic fistula between the two groups.

The prognostic value of DM in pancreatic cancer is disputable. Some investigators identified no significant survival difference between diabetic and nondiabetic patients [29,30], while others noted that survival was reduced in DM cohorts compared with nondiabetic group [31,32]. However, most patients in these studies suffered from unresectable tumors, nor was subset analysis for survival carried out on the basis of surgical cohorts. A previous published meta-analysis restricted to patients with resectable tumors included 8 studies and found that DM was associated with a worse OS after curative resection of pancreatic cancer (HR, 1.32, 95% CI, 1.46–1.60) [33]. Similarly, the detrimental effect of DM on prognosis is also demonstrated in the present update. Our strengths lie within the addition of more recent four published studies [15,17,20,21] and therefore increase the power of the estimates, providing further validation for these findings. The subpopulation of DM patients was characterized by more prevalence of comorbidities and larger tumor size, and hence may have contributed to a confounding effect. However, restricting the analysis to studies that reported multivariate-adjusted estimates did not alter the overall meta-analysis results, meaning that DM itself is an unfavorable prognostic factor rather than a confounder.

Stratification according to the duration of DM showed that new-onset DM is significantly associated with reduced survival, while long-standing DM does not affect OS significantly. An
epidemiological study [2] that examined the relationship between DM and pancreatic cancer also showed a strong association between new-onset DM and survival of pancreatic cancer patients, as compared with long-standing DM. There is evidence that new-onset DM in pancreatic cancer is likely a paraneoplastic phenomenon mediated by tumor-secreted products [34]. It is plausible that the same mechanism by which DM may cause pancreatic cancer may also accelerate pancreatic cancer progression and affect survival.

Owing to the positive link of DM with pancreatic cancer, anti-diabetic drugs may play a role in the prevention and treatment of pancreatic cancer. Experimental evidence has demonstrated that metformin, a common antidiabetic drug in the treatment of DM2, can inhibit the growth of pancreatic cancer cells via a mechanism related to its effect on disrupting crosstalk between insulin/insulin-like growth factor 1 (IGF1) and G protein-coupled receptor (GPCR) signaling pathways, a system implicated in autocrine-paracrine stimulation of a variety of malignancies, including pancreatic cancer [35]. A recent study of 171 pancreatic cancer patients who underwent surgical resection showed that metformin use was associated with better overall survival (\(P = 0.035\)) [36]. But as the study was limited to its retrospective design, future prospective research would be potentially meaningful.

The main limitation of this meta-analysis is that all included studies were observational studies that related to recall and information bias. Patient characteristics, operative procedures, perioperative care, and follow-up protocols varied widely between the included studies. These factors may affect heterogeneity of the outcomes. In addition, the prognostic significance of new-onset DM is likely to be underestimated due to the small number of patients. Further studies with larger patient samples are warranted.

Conclusions
In conclusion, DM does not seem to affect perioperative outcomes in patients undergoing surgery for pancreatic cancer. However, new-onset DM confers a negative impact on survival of pancreatic cancer in patients undergoing surgical resection.

Supporting information
S1 File. PRISMA 2009 checklist.

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Author contributions
Conceptualization: XL YZ.
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Investigation: YL.
Methodology: LW WQ.
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Supervision: YZ.
Validation: YZ.
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References

1. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis. 2010; 28:645–656. doi: 10.1159/000320068 PMID: 21088417

2. Batabyal P, Vander Hoom S, Christofi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol. 2014; 21:2453–2462. doi: 10.1245/s10434-013-3625-6 PMID: 24609291

3. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcinoma of the pancreas. Br J Surg. 1996; 83:625–31. PMID: 8689203

4. Chu CK, Mazo AE, Goodman M, Egnatashvili V, Sarmiento JM, Staley CA, et al. Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. Ann Surg Oncol. 2010; 17:502–513. doi: 10.1245/s10434-009-0789-6 PMID: 19885697

5. Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. J Am Coll Surg. 2010; 210:463–473. doi: 10.1016/j.jamcollsurg.2009.12.029 PMID: 20347739

6. Olson SH, Chou JF, Ludwig E, O'Reilly E, Allen PJ, Jarnagin WR, et al. Allergies, obesity, other risk factors and survival from pancreatic cancer. Int J Cancer. 2010; 127:2412–2419. doi: 10.1002/ijc.25240 PMID: 20143395

7. Dandona M, Linehan D, Hawkins W, Strasberg S, Gao F, Wang-Gillam A. Influence of obesity and other risk factors on survival outcomes in patients undergoing pancreaticoduodenectomy for pancreatic cancer. Pancreas. 2011; 40:931–937. doi: 10.1097/MPA.0b013e3182015a9b1 PMID: 21747317

8. Mallego G, Mazzarella F, Malpaga A, Marchegiani G, Salvia R, Bassi C, et al. Diabetes mellitus does not impact on clinically relevant pancreatic fistula after partial pancreatic resection for ductal adenocarcinoma. Surgery. 2013; 153:641–650. doi: 10.1016/j.surg.2012.10.015 PMID: 23796976

9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6:e1000097. doi: 10.1371/journal.pmed.1000097 PMID: 19621072

10. Athanasiou T, Al-Ruzzeh S, Kumar P, Crossman MC, Amrani M, Pepper JR, et al. Off-pump myocardial revascularization is associated with less incidence of stroke in elderly patients. Ann Thorac Surg. 2004; 77:745–753. doi: 10.1016/j.athoracsur.2003.07.002 PMID: 14759484

11. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobøl O, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg. 2011; 254:311–319. doi: 10.1097/SLA.0b013e31821f4d334 PMID: 21686835

12. Barbas AS, Turley RS, Cetta EP, Reddy SK, Blazer DG 3rd, Clary BM, et al. Comparison of outcomes and the use of multimodality therapy in young and elderly people undergoing surgical resection of pancreatic cancer. J Am Geriatr Soc. 2012; 60:344–350. doi: 10.1111/j.1532-5415.2011.03785.x PMID: 22211710

13. Ben Q, Xu M, Jiang Y, Yuan Y, Wang-Gillam A, et al. Clinical profiles and long-term outcomes of patients with pancreatic ductal adenocarcinoma and diabetes mellitus. Diabetes Metab Res Rev. 2012; 28:169–176. PMID: 22423386

14. Sahin IH, Shama MA, Tanaka M, Abbuzzese JL, Curley SA, Hassan M, et al. Association of diabetes and perineural invasion in pancreatic cancer. Cancer Med. 2012; 1:357–362. doi: 10.1002/cam4.43 PMID: 23342285

15. He XY, Li JF, Yao WY, Yuan YZ. Resolution of new-onset diabetes after radical pancreatic resection predicts long-term survival in patients with pancreatic ductal cell adenocarcinoma. Ann Surg Oncol. 2013; 19:39–49. doi: 10.1245/s10434-013-3096-2 PMID: 23943021

16. Zheng SR, Lu CD, Zhou XH, Li H, Qiu F, Ye H, et al. Preoperative diabetes mellitus and postoperative morbidity of pancreaticoduodenectomy for pancreatic adenocarcinoma. Chin J Gen Surg. 2013; 28:649–65.
17. Hart PA, Law RJ, Frank RD, Bamlet WR, Burch PA, Petersen GM, et al. Impact of diabetes mellitus on clinical outcomes in patients undergoing surgical resection for pancreatic cancer: a retrospective, cohort study. Am J Gastroenterol. 2014; 109:1484–1492. doi: 10.1038/ajg.2014.193 PMID: 25070053

18. Xu CX, Tian WJ. Impact of diabetes mellitus and postoperative blood glucose level on the prognosis of pancreatic carcinoma. Chinese Journal of Hepatobiliary Surgery. 2015; 21:761–764.

19. Duan CY, Wang X. Impact of diabetes on early complications after pancreactico-duodenectomy in patients with pancreatic cancer. Clinical Medicine of China. 2016; 32:160–164.

20. Lee W, Yoon YS, Han HS, Cho JY, Choi Y, Jang JY, et al. Prognostic relevance of preoperative diabetes mellitus and the degree of hyperglycemia on the outcomes of resected pancreatic ductal adenocarcinoma. J Surg Oncol. 2016; 113:203–208. doi: 10.1002/jso.24133 PMID: 26799261

21. Zhu XG, Jiang FP, Xie HB, Tang YY. The Effects of Diabetes Mellitus on prognosis of pancreatic cancer patients after radical operation. Anti-tumor Pharmacy 2016; 6:217–220.

22. Neumayer L, Hosokawa P, Itani K, El-Tamer M, Henderson WG, Khuri SF. Multivariant predictors of postoperative surgical site infection after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007; 204:1178–1187. doi: 10.1016/j.jamcollsurg.2007.03.022 PMID: 17544076

23. Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. J Gastrointest Surg. 2002; 6:88–94. PMID: 11986023

24. Tsai MS, Wang YC, Kao YH, Jeng LB, Kao CH. Preexisting Diabetes and Risks of Morbidity and Mortality After Gastrectomy for Gastric Cancer: A Nationwide Database Study. Medicine (Baltimore). 2015; 94:e1467.

25. Srivastava S, Sikora SS, Pandey CM, Kumar A, Saxena R, Kapoor VK. Determinants of pancreaticocentric anastomotic leak following pancreactico-duodenectomy. ANZ J Surg. 2001; 71:511–515. PMID: 11527259

26. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, et al. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreactico-duodenectomy. Ann Surg. 2006; 244:931–937. doi: 10.1097/01.sla.0000246856.03918.9a PMID: 17122618

27. Pratt WB, Callery MP, Vollmer CM Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. World J Surg. 2008; 32:419–428. doi: 10.1007/s00268-007-9388-5 PMID: 18175170

28. Pessaux P, Sauvanet A, Mariette C, Paye F, Muscari F, Cunha AS, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreactico-duodenectomy: prospective multicenter randomized trial. Ann Surg. 2011; 253:879–885. doi: 10.1097/SLA.0b013e31821219af PMID: 21368658

29. Talar-Wojnarowska R, Gasiorowska A, Strzelczyk J, Janiak A, Malecka-Panas E. Prognostic factors in the operative and palliative treatment of pancreatic cancer. Neoplasma. 2003; 50:383–387. PMID: 14628094

30. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. Cancer Causes Control. 1998; 9:403–410. PMID: 9794172

31. Wakasugi H, Funakoshi A, Iguchi H. Clinical observations of pancreatic diabetes caused by pancreatic carcinoma, and survival period. Int J Clin Oncol. 2001; 6:50–54. PMID: 11706528

32. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. Cancer Causes Control. 1998; 9:403–410. PMID: 9794172

33. Walter U, Kohlert T, Rahbari NN, Weitz J, Welsch T. Impact of preoperative diabetes on long-term survival after curative resection of pancreatic adenocarcinoma: a systematic review and meta-analysis. Ann Surg Oncol. 2014; 21:1082–1089. doi: 10.1245/s10434-013-3415-6 PMID: 24322532

34. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008; 134:981–987. doi: 10.1053/j.gastro.2008.01.039 PMID: 18395079

35. Kisfalvi K, Eibl G, Sinnett-Smith J, Rozengurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. Cancer Res. 2009; 69:6539–6545. doi: 10.1158/0008-5472.CAN-09-0418 PMID: 19679549

36. Kozak MM, Anderson EM, von Eyben R, Pai JS, Poultsides GA, Visser BC, et al. Statin and Metformin Use Prolongs Survival in Patients With Resectable Pancreatic Cancer. Pancreas. 2016; 45:64–70. doi: 10.1097/MPA.0000000000000470 PMID: 26474429