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Systematic review and meta-analysis of the impact of deviations from a clinical pathway on outcomes following pancreatoduodenectomy

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Abstract

BACKGROUND

Enhanced recovery after surgery is steadily gaining importance in patients undergoing pancreatic surgery, including pancreatoduodenectomy (PD). While clinical pathways targeting enhanced-recovery can achieve their intended outcome in reducing length of stay, compliance to these pathways, and their relevance is poorly understood. The aim of this systematic review was to assess the impact of deviations from/non-compliance to a clinical pathway on post-PD outcomes.

AIM

To assess the impact of deviations from/non-compliance to a clinical pathway on post-PD outcomes.

METHODS

A systematic review of major reference databases was undertaken, according to preferred reporting items for systematic reviews and meta-analysis guidelines,

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between January 2000 and November 2020 relating to compliance with clinical pathways and its impact on outcomes in patients undergoing PD. A meta-analysis was performed using fixed-effects or random-effects models.

RESULTS

Eleven studies including 1852 patients were identified. Median overall compliance to all components of the clinical pathway was 65.7% [interquartile range (IQR): 62.7%-72.3%] with median compliance to post-operative parameters of the clinical pathway being 44% (IQR: 34.5%-52.25%). Meta-analysis using a fixed-effects model showed that $\geq 50\%$ compliance to a clinical pathway predicted significantly fewer post-operative complications [pooled odds ratio (OR): 9.46, 95% confidence interval (CI): 5.00-17.90; $P < 0.00001$] and a significantly shorter length of hospital stay [pooled mean difference (MD): 4.32, 95%CI: -3.88 to -4.75; $P < 0.0001$]. At 100% compliance which was associated with significantly fewer post-operative complications (pooled OR: 11.25, 95%CI: 4.71-26.84; $P < 0.00001$) and shorter hospital stay (pooled MD of 4.66, 95%CI: 2.81-6.51; $P < 0.00001$).

CONCLUSION

Compliance to post-PD clinical pathways remains low. Deviations are associated with an increased risk of complications and length of hospital stay. Understanding the relevance of deviations to clinical pathways post-PD presents pancreatic surgeons with opportunities to actively pursue an enhanced-recovery of their patients.

Key Words: Outcomes; Morbidity; Mortality; Quality; Surgery; Recovery

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Core Tip: Compliance to post-pancreatoduodenectomy clinical pathways remains low. Deviations are associated with an increased risk of complications and length of hospital stay. Understanding the relevance of deviations to clinical pathways post-pancreatoduodenectomy presents us with opportunities to actively pursue an enhanced-recovery of our patients.

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INTRODUCTION

Pancreatic surgery is technically challenging and complex with a high risk of morbidity^[1]. There exists a wide variability in outcomes of pancreatic surgery even amongst high-volume providers^[2] which can be traced back to variations in quality and its indicators^[3]. A key strategy proven to improve outcomes following pancreatic surgery, especially pancreatoduodenectomy (PD), has been standardization not only in the technique of pancreatico-enteric anastomosis^[4], but even peri-operative processes^[1], including the development of post-operative clinical pathways^[5].

Clinical pathways are standardized care plans for individual clinical problems that detail essential steps in patient care bearing in mind the expected postoperative course with the overall aim of improving outcomes^[6]. These pathways fall under the broad umbrella of enhanced recovery after surgery (ERAS®) protocols, an evidence-based concept propounded by Bardram *et al*^[7]. Pancreatic surgeons were amongst the last to integrate ERAS® pathways into perioperative patient care^[8] with the perceived inertia partly attributable to the complexity of the surgery and partly due to the high post-operative morbidity. There is now a steadily growing body of literature supporting the relevance and benefit of pathways targeting enhanced recovery on outcomes following PD in comparison to conventional care^[9]. However, auditing our own clinical pathway

post-PD led us to the realization that while the pathway helped us achieve a reduced length of stay^[5], the compliance to all parameters was low^[6] with increasing deviations portending complications and readmissions. These observations have been published by others, as well^[10]. Thus, in pancreatic surgery and especially PD, it is imperative that we investigate compliance to protocols, as well as the impact of deviations from clinical pathways^[11] because herein lies the potential to improve early detection of complications with the potential to treat them in a systematic and prompt fashion preventing death^[12] due to a “failure to rescue”^[13].

MATERIALS AND METHODS

Search strategy

A literature search was performed on MEDLINE, SCOPUS, EMBASE, and Google Scholar databases for the articles published between January 2000 and November 2020 relating to compliance with clinical pathways and its impact on outcomes in patients undergoing PD. Articles were searched using Medical Education Subject Headings keywords: “Enhanced recovery OR Clinical pathways”, “Adherence OR Compliance”, “Deviations”, Pancreaticoduodenectomy OR Pancreatoduodenectomy, “Pancreatic cancer OR Pancreatic carcinoma OR Pancreatic adenocarcinoma”. Preferred reporting items for systematic reviews and meta-analysis guidelines (<http://www.prisma-statement.org>) were followed for searching and reporting of articles.

Study selection

Two authors (Jonnada PK and Karunakaran M) independently assessed titles and abstracts for eligibility. We perused the reference lists of articles and “related articles” function for similar additional articles. All the screened articles were assessed for eligibility, and any disagreement was fixed through mutual discussion. The accuracy of the extracted data was adjudicated further by a third author.

Inclusion criteria: (1) Studies conducted on patients undergoing PD with a clearly defined clinical pathway for post-operative care; and (2) Study should report on the patient compliance to the clinical pathway and impact of deviations from the pathway, or lack of compliance on outcomes in terms of adverse events and/or duration of hospitalization.

Exclusion criteria: (1) Did not report on compliance; (2) Did not report on the number of patients with a pre-defined level of compliance suffering adverse events and/or was impossible to calculate; and (3) Non-English language studies.

Quality assessment

Methodological quality of the studies was assessed independently by two authors (Jonnada PK and Karunakaran M) using Newcastle-Ottawa Scale^[14] and final scores were reached by general consensus. A study was considered to be of poor quality if it did not meet more than one criterion in the selection domain, if there was no score in the compatibility domain, and if it did not meet more than one of the criteria in the outcome domain. The Cochrane Collaboration’s tool^[15] for assessing risk of bias in individual studies was also used by the two independent authors and conflicts were resolved with mutual discussion.

Data extraction

A standardized data extraction form was used for data entry and analysis. Study selection process and preferred reporting items for systematic reviews and meta-analysis flow diagram for identifying studies are shown in [Figure 1](#). For included studies, two authors (Jonnada PK and Karunakaran M) extracted the data using the agreed form. For each study that fulfilled the criteria, the following information was extracted: Name of the first author; year of publication; study setting; design of the study; duration of the study; geographical setting; age of patient; total sample; level of compliance to the intended clinical pathway; prevalence of deviation from the clinical pathway; impact of deviation from the clinical pathway on post-operative complications and length of hospital stay.

Data analysis and statistical methods

The statistical analysis was performed using RevMan software, version 5.3 (Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark). Continuous

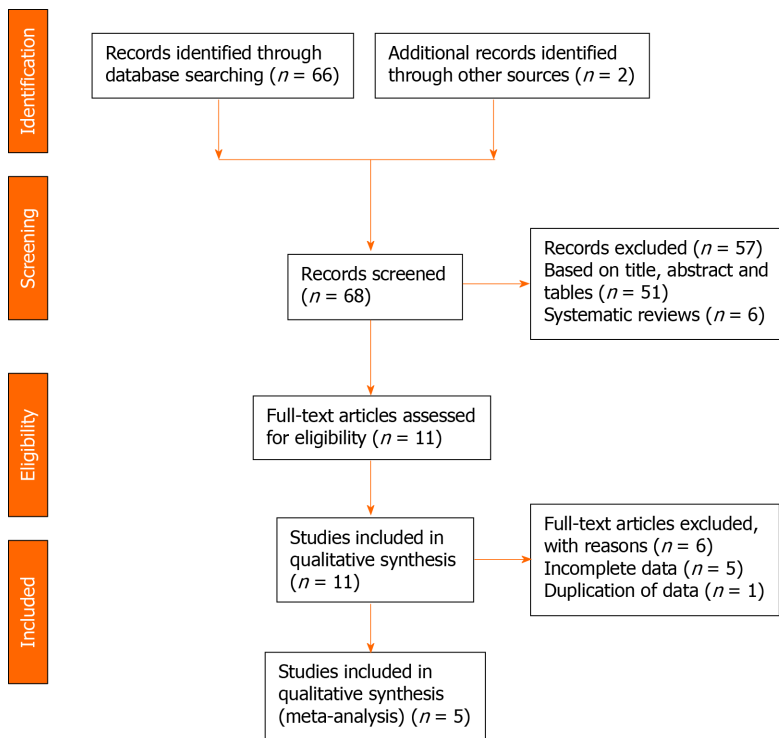


Figure 1 Preferred reporting items for systematic reviews and meta-analysis guidelines diagram.

variables were analyzed by the odds ratio (OR), and 95% confidence interval (CI) was recorded. Random variables were analyzed by the mean difference (MD), and 95% CI was recorded. Heterogeneity was evaluated using χ^2 and I^2 tests. I^2 of 0-40%, 30%-60%, 50%-70%, and > 75% represent low, moderate, substantial, and considerable heterogeneity, respectively. Studies with a P value of < 0.1 and I^2 > 50% indicated substantial heterogeneity. A random-effects model was used for assessment of the pooled OR if significant heterogeneity existed in the fixed-effects model. Else, the fixed-effects model was used with P > 0.10 and I^2 < 25%. The Z test was used to determine the pooled OR, and the significance was set to reject the null hypothesis at P < 0.05. Funnel plots were undertaken to consider possible bias. Compliance rates were expressed as median [interquartile range (IQR)].

RESULTS

The search yielded a total of 68 articles of which 57 were excluded based on the inclusion and exclusion criteria and following the screening of titles and abstracts (Figure 1). After excluding duplicates, the reviewers identified 11 studies^[6,10,16-24] for further analysis. The studies included in the analysis were published between January 2010 and November 2020. The sample sizes of the included studies ranged from 82 to 394 patients. Within these 11 studies^[6,10,16-24], a total of 1852 patients underwent PD and were managed according to their respective institutional clinical pathways. Eight studies^[6,10,17-19,22-24] stratified patients according to a specific, albeit arbitrary, level of compliance and compared their immediate post-operative outcomes. The characteristics, methodology and conclusions of the included studies are provided in Tables 1 and 2. The included clinical pathways were quite heterogeneous in terms of the parameters used (Supplementary Table 1). Out of the 11 studies, 5 of them^[6,17,18,22,24] were included in the meta-analysis (Figure 1). The methodological quality of all included manuscripts was deemed acceptable as per Newcastle-Ottawa Scale.

Included studies

The 11 studies analyzed (Table 1) included 6 prospective^[10,16,17,21-23] and 5 retrospective^[6,18-20,24] studies all published since 2014. There were 2 publications from India^[11,23], Canada^[18,20] and Italy^[16,22], and 1 each from Switzerland^[19], Israel^[21], Sweden^[24] and Greece^[24], all from single centers, with 1 publication from multiple centers in Europe^[10]. The median overall compliance to all components of the clinical pathway

Table 1 Summary of studies included in the analysis along with details of the clinical pathway, compliance and comparison between groups

Ref.	Study design	n	Age (yr)	Number of clinical pathway factors	Overall compliance (%)	Comparison groups (% of compliance)	NOS
Braga <i>et al</i> ^[16] , 2014	Prospective	115	69 (61-74)	12 (4 Pre- + 3 Intra- + 5 Post-op)	NA	No group stratification	-
Zouros <i>et al</i> ^[17] , 2016 ¹	Prospective	75	65.9 ± 10.5	5 (Post-op)	NA	100% (n = 53) vs < 100% (n = 22)	7
Kagedan <i>et al</i> ^[18] , 2017 ¹	Retrospective	82	65 (56-74)	4 (Post-op)	NA	100% (n = 134) vs < 100% (n = 134)	6
Tremblay St-Germain <i>et al</i> ^[20] , 2017	Retrospective	83	65 (29-85)	8 (Post-op)	NA	No group stratification	-
Agarwal <i>et al</i> ^[23] , 2018	Prospective	394	55 (18-81)	13 (6 Pre + 4 Intra- + 3 Post-op)	84	≥ 80% (n = 278) vs < 80% (n = 116)	-
Williamsson <i>et al</i> ^[24] , 2019 ¹	Retrospective	160	66-69	8 (Post-op)	52	≥ 50% (n = 134) vs < 50% (n = 26)	7
Karunakaran <i>et al</i> ^[6] , 2020 ¹	Retrospective	162	59 (19-84)	8 (Post-op)	53	≥ 50% (n = 98) vs < 50% (n = 64)	7
Roulin <i>et al</i> ^[10] , 2020	Prospective	390	65.3 ± 11.6	19 (7 Pre + 3 Intra- + 9 Post-op)	62 (30 for post-operative components)	≥ 70% (n = 85) vs < 70% (n = 305)	-
Tankel <i>et al</i> ^[21] , 2020	Prospective	97	68 (17-85)	7 (Post-op)	NA	No group stratification	-
Capretti <i>et al</i> ^[22] , 2020 ¹	Prospective	205	64.7 ± 13.7	16 (5 Pre + 5 Intra- + 6 Post-op)	68.4	100% (n = 52) vs < 100% (n = 152)	7
St-Amour <i>et al</i> ^[19] , 2020	Retrospective	89	68 (61-73)	NA	63 (36 for post-op)	≥ 67% vs < 67%	-

¹Included in the meta-analysis. NOS: Newcastle–Ottawa scale; NA: Not available.

was 65.7% (IQR: 62.7%-72.3%) with median compliance to post-operative parameters of the clinical pathway being 44% (IQR: 34.5%-52.25%) in the 4 included studies that reported the values.

Table 2 provides an overview of the morbidity^[25], mortality and readmission rates in the various studies included in the analysis along with the length of stay and impact of deviations from/compliance to the clinical pathway parameters. The major effects of deviations from clinical pathways are on length of stay and complications. These aspects have been addressed in further detail in the meta-analysis below.

The rates of adherence to individual parameters within the clinical pathways in the various studies are presented in **Supplementary Table 1**.

Impact of deviations/non-compliance from clinical pathway on post-operative outcomes

The results of meta-analysis using a fixed-effects model showed that less frequent the deviation from clinical pathway objectively (expressed as ≥ 50% compliance with the prescribed parameters) resulted in significantly fewer post-operative complications (pooled OR: 9.46, 95%CI: 5.00-17.90; $P < 0.00001$) (**Figure 2A**). There was moderate heterogeneity ($I^2 = 60\%$ and $P = 0.11$) between the included studies. Patients with a 100% compliance demonstrated a significantly reduced risk of complications (pooled OR: 11.25, 95%CI: 4.71-26.84; $P < 0.00001$) (**Figure 2B**). There was no heterogeneity ($I^2 = 0\%$; $P = 0.80$) between the included studies.

Patients with ≥ 50% compliance with the prescribed parameters also had a significantly shorter length of hospital stay (pooled MD: 4.32, 95%CI: -3.88 to -4.75; $P < 0.0001$) (**Figure 3A**). There was moderate heterogeneity ($I^2 = 52\%$ and $P = 0.15$). A 100% compliance to the pathway resulted in a significantly reduced hospital stay (pooled MD of 4.66, 95%CI: 2.81-6.51; $P < 0.00001$) (**Figure 3B**). However, there was significant heterogeneity between the included studies ($I^2 = 90\%$ and $P < 0.00001$).

There was minimal publication bias in the included studies as assessed by funnel plots (**Figures 2 and 3**).

Table 2 Summarising the morbidity, mortality and readmission rates along with length of stay and impact of deviations on these outcomes

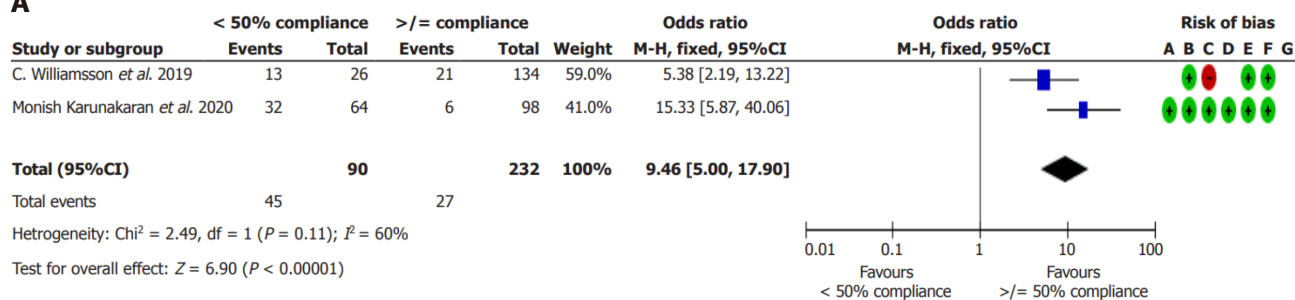
Ref.	Length of stay ¹ (d)	Complications (%)		Mortality (%)	Readmissions (%)	Impact of deviations/non-compliance to clinical pathway
		Overall	≥ CD 3			
Braga <i>et al</i> ^[16]	14.6 ± 9.8	60	20	3.5	12.2	Significantly lower deviations in patients with uneventful post-operative course; Lower compliance correlated with severity of postoperative complications; Low compliance to early oral feeding most likely to be associated with postoperative complications
Zouros <i>et al</i> ^[17]	9.7 ± 5.6	34.7	14.7	4	6.7	< 100% compliance associated with significantly higher rates of postoperative complications (72.7% <i>vs</i> 20.8%; <i>P</i> < 0.001)
Kagedan <i>et al</i> ^[18]	9 (7-14)	NA	NA	0.8	16	< 100% compliance associated with longer length of stay (13 <i>vs</i> 7 d, <i>P</i> < 0.001) and greater mean total cost of the index postoperative hospitalization (\$20392.81 CAD <i>vs</i> \$10562.28 CAD, <i>P</i> < 0.002)
Tremblay St-Germain <i>et al</i> ^[20]	8 (4-35)	67.5	29	0	22 ²	Failure to remove urinary catheter by POD 3, and initiate solid diet ≤ POD 4 (<i>P</i> < 0.01 and <i>P</i> < 0.001, respectively), more likely to have prolonged length of stay (> 8 d)
Agarwal <i>et al</i> ^[23]	12 (4-78)	63.2	33.2	3.5	7.8	< 80% compliance associated with significantly increased major complications (44% <i>vs</i> 28.7%, <i>P</i> < 0.004), CR-POPF (32.7% <i>vs</i> 20.8%, <i>P</i> < 0.012), longer length of stay [15 (4-61) <i>vs</i> 11 (5-78), <i>P</i> < 0.001], re-explorations (17.2% <i>vs</i> 6.8%, <i>P</i> < 0.002), escalation of antibiotics (24.1% <i>vs</i> 14.7%, <i>P</i> < 0.025) and mortality (6.8% <i>vs</i> 2.1%, <i>P</i> = 0.021)
Williamsson <i>et al</i> ^[24]	12 (6-97)	69.4	21.25	1.25	16.25 ²	< 50% compliance associated with delayed discharge [10 (6-77) <i>vs</i> 23 (8-97) d] and higher incidence of CD ≥ 3A complications [21 (16%) <i>vs</i> 13 (50%)]; ≥ 90% (<i>n</i> = 13) compliance had a median discharge of POD 8 (7-9) and no complication ≥ CD3A
Karunakaran <i>et al</i> ^[6]	10.8 ± 5.8	71	23.5	6.2	23.7 ²	< 50% compliance significantly higher risk of complications [DGE (79.7% <i>vs</i> 19.4%, <i>P</i> = 0.0001); POPF (22.2% <i>vs</i> 8.1%, <i>P</i> < 0.025); CD 3/4 complications (37.5% <i>vs</i> 6.1%, <i>P</i> < 0.0001)], longer length of stay (14 <i>vs</i> 10.8 d, <i>P</i> < 0.0001), 90-d readmissions (40.7% <i>vs</i> 14.3%, <i>P</i> = 0.0001) and mortality (14.1% <i>vs</i> 1%, <i>P</i> < 0.003)
Roulin <i>et al</i> ^[10]	14 (9-22)	83.7	36.9	3.1	11.3	< 70% compliance significantly increased length of stay [15 (10-23) <i>vs</i> 11 (7-16) d, <i>P</i> < 0.001], and overall (88.9% <i>vs</i> 78.8%, <i>P</i> < 0.029) and major (43.6 <i>vs</i> 28.2, <i>P</i> < 0.012) complications (especially respiratory and infectious)
Tankel <i>et al</i> ^[21]	14 (6-100)	NA	21.6	2.1	28.9	< 100% compliance had a longer length of stay ≥ 14 d
Capretti <i>et al</i> ^[22]	14.1 ± 8.6	54.6	15.6	1	3.4	Sum of failed ERP components/deviations significantly correlated with postoperative complications
St-Amour <i>et al</i> ^[19]	NA	NA	NA	NA	NA	No significant effect of ERAS® compliance on time to receipt of adjuvant chemotherapy from surgery, or disease-free survival

¹Expressed either as median (range) or mean (± SD).²90-d readmissions (as opposed to others reporting 30-d readmissions). CD: Clavien-dindo; CAD: Canadian dollars; CR-POPF: Clinically-relevant post-pancreatectomy pancreatic fistula; DGE: Delayed gastric emptying; ERAS: Enhanced recovery after surgery; ERP: Enhanced recovery pathway; NA: Not available; POD: Post-operative day.

DISCUSSION

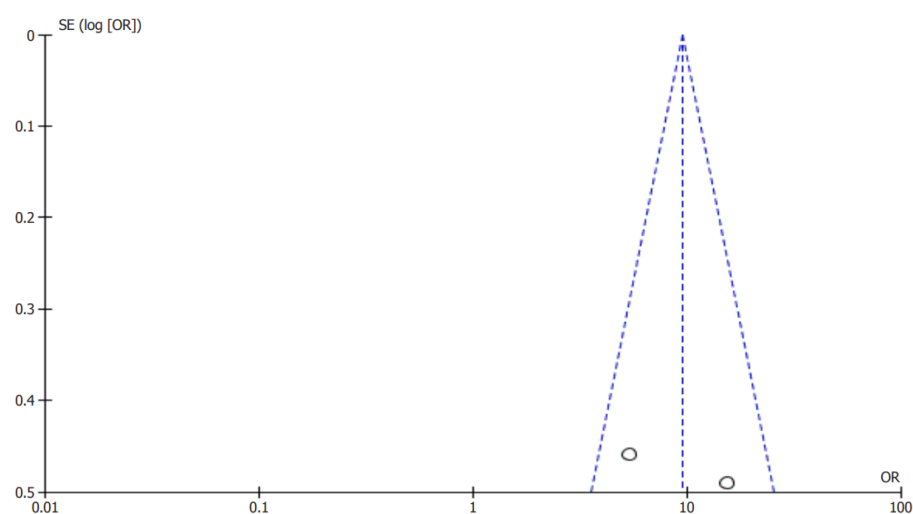
These data highlight the importance of deviations from clinical pathways in PD on post-operative outcomes especially development of all complications (pancreas-specific, as well as, medical) and duration of length of stay. Individual studies also highlighted that reduced compliance with parameters assessed within the pathways was associated with a higher likelihood of needing re-exploration^[23], higher

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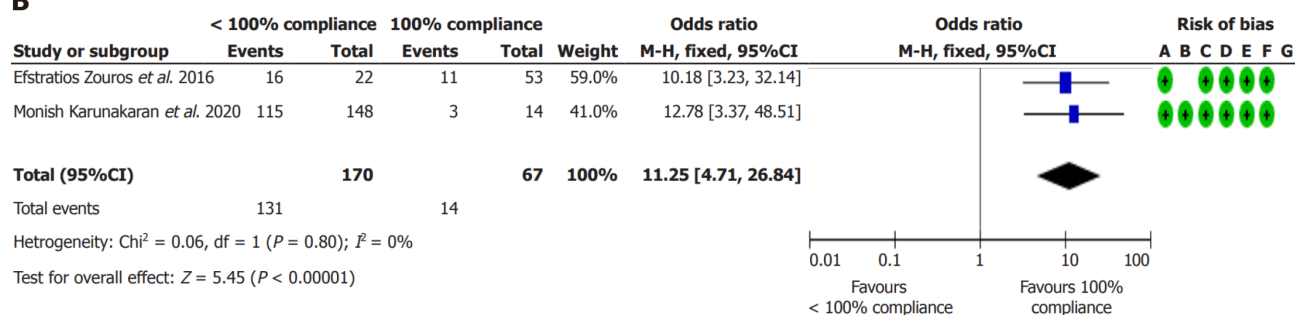


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Binding of participants and personnel (performance bias)
- (D) Binding of outcome assessment (direction bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias



B



Risk of bias legend

- (A) Random sequence generation (selection bias)
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- (G) Other bias

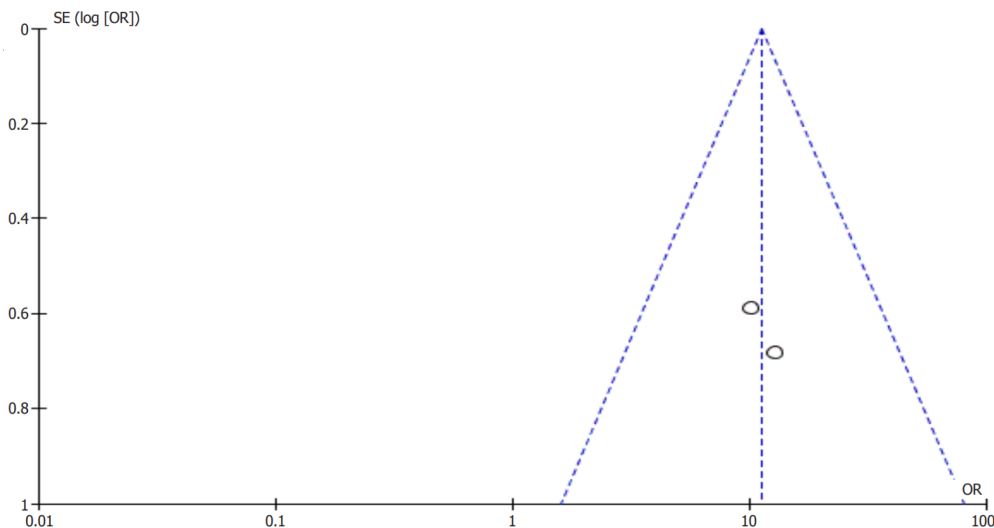


Figure 2 There was minimal publication bias in the included studies as assessed by funnel plots. A: Forest plot comparing $\geq 50\%$ and $< 50\%$ compliance to the clinical pathway on overall post-pancreatoduodenectomy complications. Funnel plot shows moderate heterogeneity; B: Forest plot comparing 100% and $< 100\%$ compliance to the clinical pathway on overall post-pancreatoduodenectomy complications. Funnel plot shows no heterogeneity. CI: Confidence interval.

mortality^[6,23], 90-d readmission rates^[6] and overall hospitalization-related costs^[18].

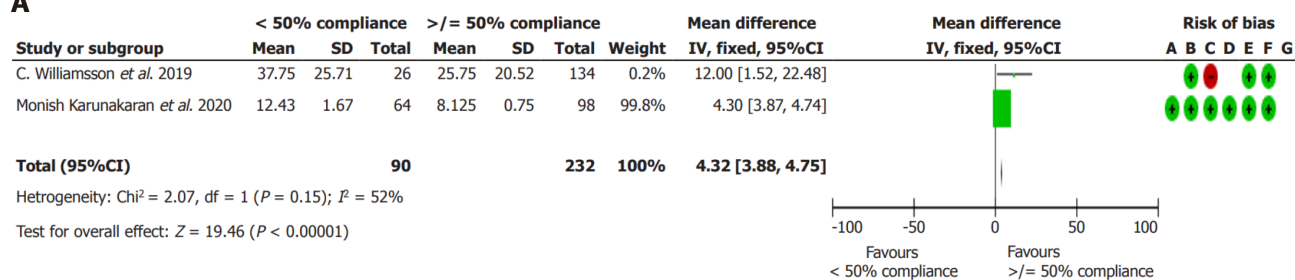
The addition of ERAS® to the pancreatic surgeons armamentarium has certainly helped improve outcomes^[26,27], especially reductions in overall and minor morbidity, incidences of delayed gastric emptying, incisional and intra-abdominal infections, and shortened length of stay, without increasing 30-d readmission and mortality^[9]. It has been reported that up to 30% of patients are unable to receive adjuvant chemotherapy for pancreatic cancer for a variety of reasons^[28]. All of the benefits achieved from pursuing an enhanced recovery are, thus, of major relevance when specifically considering PD for pancreatic cancer and the importance of an enhanced recovery of the patient, sufficient to enable them to be fit to receive, and complete^[29], adjuvant therapy that offers the best chance for cure^[30,31].

Focusing on the enhanced recovery of our patients, the present analysis incorporating 11 studies^[6,10,16-24] has highlighted varying patterns of application of clinical pathways to PD. In four^[10,16,22,23] of the included studies, the teams employed a pre-, intra- and post-operative pathway, while in 6 other studies^[6,17,18,20,21,24] the teams focused on a post-operative clinical pathway alone. One study did not specify their protocol details^[19]. Not surprisingly, overall compliance to the pathways remained relatively high 65.7% (IQR: 62.7%-72.3%). Compliance to post-PD pathways is challenging given the major anatomical changes introduced by the surgery, itself. Hence, most studies reported compliance to this component varying between 34.5% and 52.25%. Comparison between studies show that the difference (between overall and post-operative compliance) widens as the number of post-operative parameters decrease. However, despite the apparently low compliance, the surgical teams were able to help their patients achieve the desired outcomes^[11]. This is likely a reflection of the culture (targeting enhanced recovery) of the team adopting these protocols by providing themselves, and their patients, with measurable and achievable goals.

Postoperative components of a clinical pathway display maximal variance and such deviations are known to correlate with the final outcomes^[32]. Lessons learnt from colorectal surgery suggest that postoperative compliance is the most difficult to achieve but is most strongly associated with optimal recovery^[33]. We, thus, focused on this aspect of enhanced recovery in patients undergoing PD. An important consideration at the present time then is “what would be the minimum acceptable level of compliance following PD to improve outcomes”. Once again, borrowing wisdom from colorectal surgery, Pędziwiatr *et al*^[34] demonstrated that a compliance of $> 80\%$ is required to decrease length of hospitalization. This is similar to the findings of Ahmed *et al*^[35] who noted that an overall protocol compliance of 77% resulted in no significant difference in outcomes following colorectal surgery compared with a compliance rate of 88%.

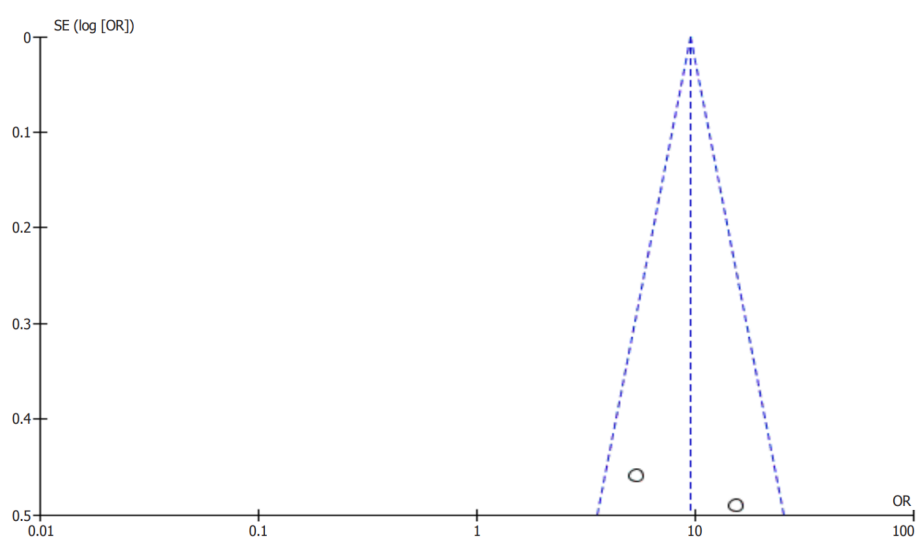
However, we must not lose focus of the aim of this study which is, namely, to enhance the value of information gleaned from this audit/analysis of deviations from clinical pathways post-PD to improve the care of pancreatic cancer patients undergoing surgery. Quite clearly, clinical pathways targeting early and meaningful

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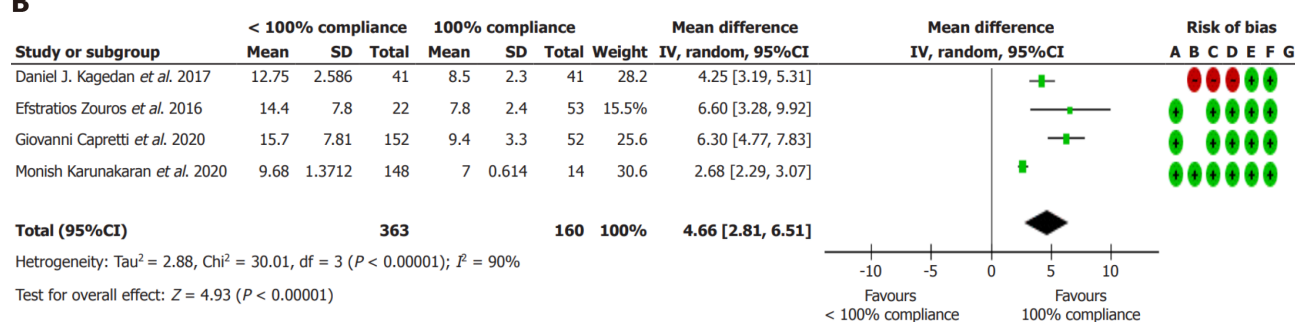


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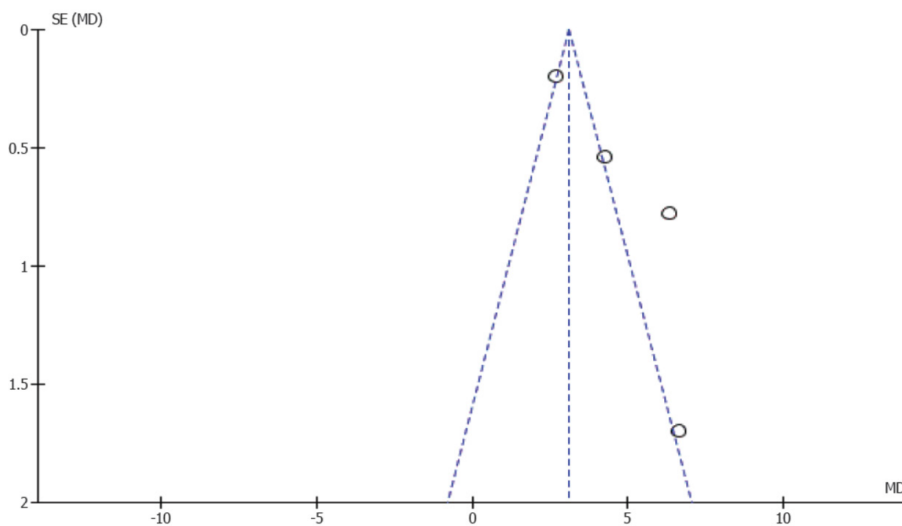


Figure 3 There was minimal publication bias in the included studies as assessed by funnel plots. A: Forest plot comparing $\geq 50\%$ and $< 50\%$ compliance to the clinical pathway on post-pancreatoduodenectomy length of hospital stay. Funnel plot shows moderate heterogeneity; B: Forest plot comparing 100% and $< 100\%$ compliance to the clinical pathway on post-pancreatoduodenectomy length of hospital stay. Funnel plot shows significant heterogeneity. CI: Confidence interval.

recovery can reduce post-PD complications and length of stay in hospital after surgery. Being able to identify deviations from a clinical pathway presents an opportunity to identify patients who are likely to develop complications thereby triggering the need for closer monitoring. Such an approach is important, not because the deviations per se result in complications, but they are indicative of an impending complication. Early identification of such a patient provides the clinician with the benefit of “lead time”, wherein a timely intervention might avert a major complication and even the risk of mortality^[6], thereby improving failure-to-rescue^[36,37] metrics and overall outcomes. The study by Karunakaran *et al*^[6] revealed that on multivariate analysis, the need to reinsert the nasogastric/Ryle’s tube [hazard ratio (HR): 3.7, 95%CI: 1.9-7.2; $P < 0.0001$], the inability to commence a soft diet on post-operative day 5 (HR: 2.7, 95%CI: 1.6-4.5; $P < 0.0001$), the failure to remove the indwelling urinary catheter on postoperative day 2 (HR: 1.9, 95%CI: 1.2-3.0; $P < 0.01$), and failure to cease perioperatively planned antibiotics on postoperative day 2 (HR: 3.1, 95%CI: 1.7-5.4; $P < 0.0001$) were the 4 deviations that were significantly associated with likelihood of re-admission within 90 d of discharge. Such exploratory analysis present data to alert pancreatic cancer surgeons with specific deviations that are linked to sinister outcomes, prompting directed action.

Identifying factors predictive of patient- and surgery-related factors associated with deviations is helpful. Advancing age^[22,38], higher body mass index^[6,22], hypoalbuminemia^[6,38], cardiac co-morbidities^[6], and the finding of a soft pancreas^[22] have been associated with an increased risk of deviations. Early characterization of patients who are less likely to comply can prompt prehabilitation measures and/or customized care pathways to avoid non-compliance and increase the efficacy of pathways. There is already evidence, though anecdotal, that intensive preoperative prehabilitation in the form of cardiorespiratory functional capacity strengthening training, muscular strength training and respiratory physiotherapy reduces postoperative pulmonary complications and shorten postoperative hospital stay after PD^[39]. Prehabilitation prior to pancreatic cancer surgery is still in its infancy. However, the emerging evidence is encouraging^[40] prompting the need for a concerted approach towards its implementation on a larger scale.

In the current meta-analysis, interestingly, the comparison of a 100% compliance *vs* any level of non-compliance revealed no heterogeneity ($I^2 = 0\%$, $P = 0.80$) when predicting complications. However, there was significant heterogeneity ($I^2 = 90\%$, $P = 0.00001$) when analyzing length of hospital stay. This reiterates the variability in practices that guide or determine length of stay and timing of discharge^[41].

There are certain limitations of this study. This is a study data meta-analysis and not a patient-data meta-analysis, with their attendant risk of heterogeneity. Moreover, this approach prevented us from segregating patients who underwent PD for pancreatic cancer, from other indications. However, we do not think this should grossly interfere with the inferences of this study. Secondly, it is based on a limited number of studies.

Thirdly, there has been a significant difference in the clinical pathway components between studies, though this is largely unavoidable and attributable to the practice of devising clinical pathways in accordance with the local protocols and socio-cultural needs. Finally, there is no universally accepted compliance cut-off to guide prediction of adverse events which precludes a head-to-head comparison between patient cohorts.

Nonetheless, this is the first systematic review addressing the impact of clinical pathway compliance on outcomes following PD and highlights that measures to improve compliance to clinical pathway components can potentially increase its success rates and improve quality. Further research on outcomes with respect to compliance is warranted to determine the minimum level of compliance to achieve these goals.

CONCLUSION

From a surgeon's perspective, a margin-negative (R0) resection accomplished with minimal postoperative complications is certainly our best contribution to long-term survival in pancreatic cancer^[42]. However, it remains our responsibility to ensure that we contribute to the enhanced recovery of our patients to enable them to take the next step towards fighting their cancer. Understanding the relevance of deviations to clinical pathways post-PD presents us with opportunities to actively pursue an enhanced-recovery of our patients.

ARTICLE HIGHLIGHTS

Research background

Enhanced recovery after surgery is steadily gaining importance in patients undergoing pancreatic surgery, including pancreatoduodenectomy (PD). While clinical pathways targeting enhanced-recovery can achieve their intended outcome in reducing length of stay, compliance to these pathways, and their relevance is poorly understood.

Research motivation

Appreciating the importance of deviations from a clinical pathway for pancreatic surgery will empower surgeons not only to identify patients at risk of complications but also to develop strategies to improve the pathway and, in turn, patient outcomes.

Research objectives

The objective of this systematic review was to assess the impact of deviations from/non-compliance to a clinical pathway on post-PD outcomes.

Research methods

A systematic review and meta-analysis of the literature gleaned from a search performed on MEDLINE, SCOPUS, EMBASE, and Google Scholar databases for the articles published between January 2000 and November 2020 relating to compliance with clinical pathways and its impact on outcomes in patients undergoing PD, was performed.

Research results

Eleven studies including 1852 patients were identified. Median overall compliance to all components of the clinical pathway was 65.7% [interquartile range (IQR): 62.7%-72.3%] with median compliance to post-operative parameters of the clinical pathway being 44% (IQR: 34.5%-52.25%). Meta-analysis using a fixed-effects model showed that $\geq 50\%$ compliance to a clinical pathway predicted significantly fewer post-operative complications [pooled odds ratio (OR): 9.46, 95% confidence interval (CI): 5.00-17.90; $P < 0.00001$] and a significantly shorter length of hospital stay (pooled mean difference 4.32, 95%CI: -3.88 to -4.75; $P < 0.0001$). A 100% compliance was associated with significantly fewer post-operative complications (pooled OR 11.25, 95%CI: 4.71-26.84; $P < 0.00001$) and shorter hospital stay (pooled mean difference of 4.66, 95%CI: 2.81-6.51; $P < 0.00001$).

Research conclusions

Compliance to post-PD clinical pathways remains low. Deviations are associated with an increased risk of complications and length of hospital stay.

Research perspectives

Understanding the relevance of deviations to clinical pathways post-PD presents pancreatic surgeons with opportunities to scrutinize (and amend) their existing pathways with the ultimate goal of enhancing the recovery of their patients.

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