



The influence of diabetes on postoperative complications following colorectal surgery

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Abstract

Background Diabetes mellitus has been commonly associated with poor surgical outcomes. The aim of this meta-analysis was to assess the impact of diabetes on postoperative complications following colorectal surgery.

Methods Medline, Embase and China National Knowledge Infrastructure electronic databases were reviewed from inception until May 9th 2020. Meta-analysis of proportions and comparative meta-analysis were conducted. Studies that involved patients with diabetes mellitus having colorectal surgery, with the inclusion of patients without a history of diabetes as a control, were selected. The outcomes measured were postoperative complications.

Results Fifty-five studies with a total of 666,886 patients comprising 93,173 patients with diabetes and 573,713 patients without diabetes were included. Anastomotic leak (OR 2.407; 95% CI 1.837–3.155; $p < 0.001$), surgical site infections (OR 1.979; 95% CI 1.636–2.394; $p < 0.001$), urinary complications (OR 1.687; 95% CI 1.210–2.353; $p = 0.002$), and hospital readmissions (OR 1.406; 95% CI 1.349–1.466; $p < 0.001$) were found to be significantly higher amongst patients with diabetes following colorectal surgery. The incidence of septicemia, intra-abdominal infections, mechanical failure of wound healing comprising wound dehiscence and disruption, pulmonary complications, reoperation, and 30-day mortality were not significantly increased.

Conclusions This meta-analysis and systematic review found a higher incidence of postoperative complications including anastomotic leaks and a higher re-admission rate. Risk profiling for diabetes prior to surgery and perioperative optimization for patients with diabetes is critical to improve surgical outcomes.

Keywords Colorectal surgery · Diabetes mellitus · Hyperglycemia · Postoperative care · Complications

Introduction

Twenty percent of surgical patients have diabetes mellitus [1]. As global diabetic prevalence is projected to increase from 9.3% in 2019 to 10.2% by 2030 [2], diabetes continues

to be a significant comorbidity that needs to be accounted for during surgical planning. Furthermore, undiagnosed diabetes or ‘pre-diabetes’ results in an underestimation of the true number of patients with diabetes having colorectal surgery, with studies reporting that the true prevalence of diabetes in hospitalised patients has been understated by up to 40% [3, 4]. In the existing literature, poor glycemic control and hyperglycemia has been associated with impaired wound healing and increased susceptibility to infections, leading to an elevated risk of postoperative complications [5]. Furthermore, hyperglycemia results in impairment of the inflammatory mediated response, leading to the failure of local vasodilation, bacteria opsonisation, neutrophil adherence, chemotaxis and phagocytosis. These effects result in decreased peripheral blood flow and angiogenesis which ultimately delay wound healing [6–9]. Such immunological and physiological changes negatively affect anastomoses and

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increases the occurrence of infectious complications, leading to poorer surgical outcomes.

Currently, evidence from both multicenter and cohort studies suggest that patients with diabetes having colorectal surgery experience a significantly higher risk of surgical site infection (SSI) [10–12] and anastomotic leakage (AL) [13, 14] postoperatively. However, studies exploring the impact of diabetes on other postoperative complications aside from SSI and AL are scarce. As a result, the effect of diabetes on postoperative outcomes, including pulmonary, urinary, and cardiac complications, following colorectal surgery requires further analysis so as to better evaluate the clinical impact of diabetes on surgical outcomes.

Materials and methods

Search strategy

This systematic review and meta-analysis utilize the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines methodology [15]. Relevant articles were identified by conducting a complete search on three electronic databases including Medline, Embase and China National Knowledge Infrastructure (CNKI) from inception through May 9th 2020. Search terms composed of MeSH terms and keywords relating to “Diabetes” or “Hyperglycemia”, and “Colorectal Surgery” were used. The detailed search strategy used for Medline is presented in Supplementary Material 1. All appropriate abstracts were imported into EndNote X9 to have duplicates removed. Similar methods were employed as with our previous reviews [16, 17].

Criteria for the selection of studies

Articles written in English and Chinese were included in this review paper. Studies were eligible for inclusion if they fulfilled the following criteria: (1) involvement of patients having colorectal surgery for malignant or benign causes; (2) analysis of the association between diabetes and postoperative complications after colorectal surgery; and (3) inclusion of patients without diabetes as control subjects. Studies were excluded if they: (1) were review articles, conference abstracts, non-human cohort studies or case reports; (2) did not involve control subjects; or (3) did not analyse data regarding postoperative complications.

Randomized controlled trials (RCTs) and observational studies including cohort, case–control, or cross-sectional studies were considered for this review. Patients with type 1 and type 2 diabetes were included in our analysis, while those with gestational diabetes were excluded. The primary outcome measured was the postoperative complications after

colorectal surgery. Short-term complications were defined as complications occurring within 30 days after the surgery was performed, and consisted of AL, septicemia, SSI, intra-abdominal abscess, acute renal failure, mechanical wounds, cardiac, urinary, and pulmonary complications, ileus, clostridium difficile colitis, and 30-day mortality. Long-term complications were defined as complications occurring more than 30 days after the surgery was performed and consisted of 1-year mortality, reoperation and hospital readmission.

Data extraction and assessment of quality

Predefined data were extracted from the selected articles into a structured proforma by two independent authors, (DT and HTM). Data extracted from each paper included the general information of the study (author’s name, article title, publication year, geographical region of the study, study design and indication for surgery), characteristics of the participants with and without diabetes, and statistical results of postoperative complications. For quality assessment of the included studies, the Newcastle–Ottawa Quality Assessment Form for Cohort Studies [18] and Jadad Scale [19] were utilized. The Newcastle–Ottawa Quality Assessment Form for Cohort Studies [18] is designed to assess the quality of nonrandomised studies in meta-analyses and evaluates studies on three domains: the selection of the study groups; the comparability of the groups; and the outcome of interest for cohort studies. The Jadad scale [19] for RCTs is created to assess the methodological quality of a clinical trial, by assessing the effectiveness of blinding.

Statistical analysis

All analysis was conducted in STATA 16.1 (StataCorp LLC). A meta-analysis of proportions was conducted using the *metaprop* function and effect sizes were pooled in random effects [20]. For the meta-analysis of dichotomous variables, odds ratio (OR) estimates with their corresponding 95% confidence intervals (CI) were combined and weighted to calculate a pooled OR using the DerSimonian–Laird random-effects method [21]. Significance was considered when $p < 0.05$. Regardless of inter-study heterogeneity assessed using Cochran Q statistics and I^2 statistics, random effects were applied in the analysis of all dichotomous data.

Results

Of the 1734 records identified through the combined search results with duplicates removed, 258 manuscripts were reviewed in full text, and 55 articles [10, 12, 13, 22–56, 58–73] met our inclusion and exclusion criteria (Fig. 1). These included studies consisted of 51 retrospective cohort

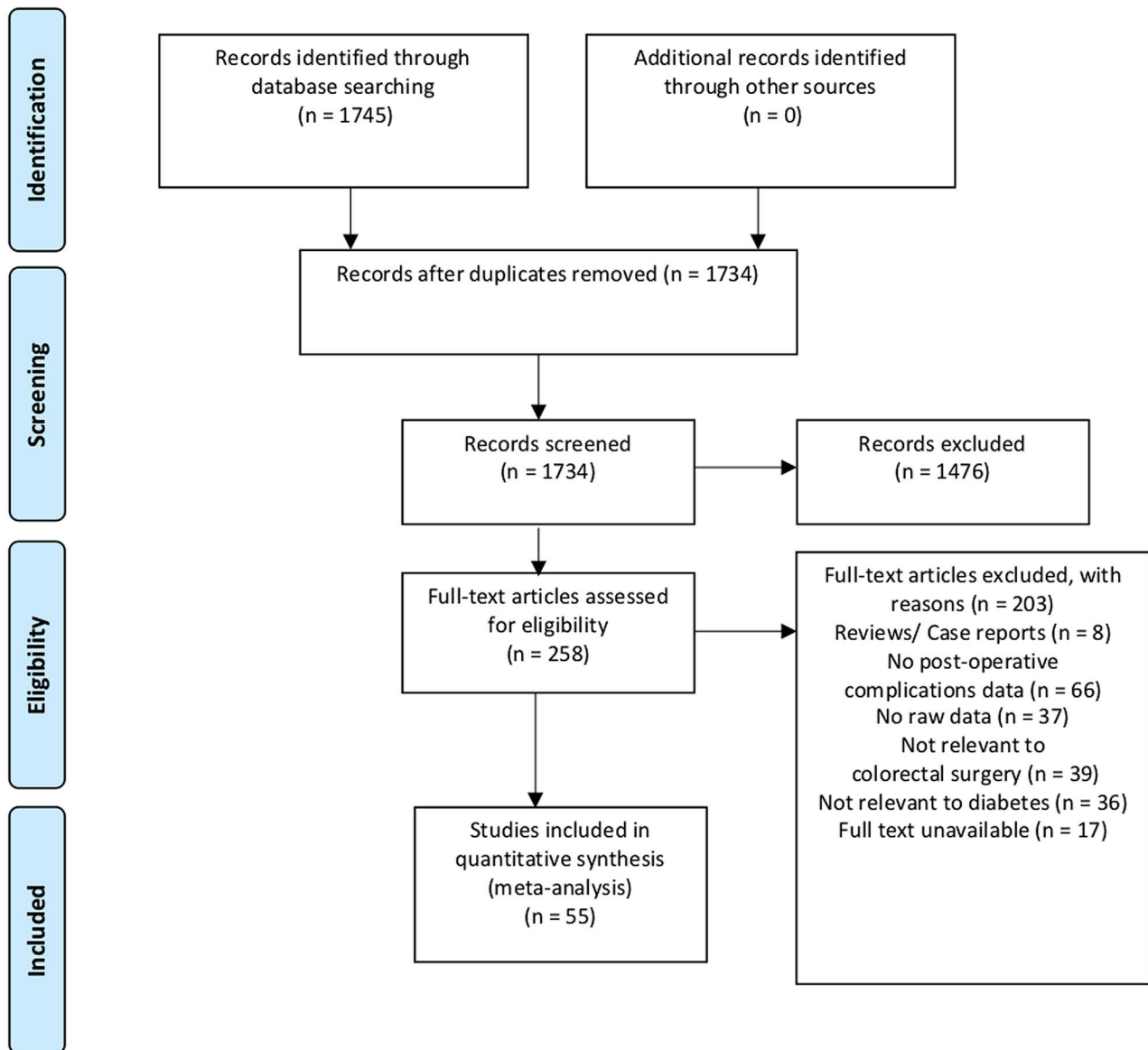


Fig. 1 PRISMA flow chart

studies, three prospective cohort studies and one randomized controlled trial. A total of 666,886 patients were included for analysis, comprising 93,173 patients with diabetes and 573,713 patients without diabetes as a control. A summary of the key characteristics and quality assessment of included studies is presented in Supplementary Material 2.

Prevalence of postoperative complications

The prevalence rates of the postoperative complications that were reported in the included studies are summarized in Table 1. Among patients with diabetes, the prevalence rates of SSI after colorectal surgery was 20% (CI

0.16–0.24). The prevalence of intra-abdominal abscess was 6% (CI 0.04–0.09). Septicemia had a prevalence of 6% (CI 0.05–0.06), while mechanical wound complications comprising of wound dehiscence and disruption occurred in 2% (CI 0.01–0.02). Additionally, pooled proportions found a prevalence rate of 8% for urinary complications (CI 0.05–0.11) and pulmonary complications were reported at 5% (CI: 0.03–0.07). AL occurred at a rate of 11% (CI 0.08–0.13) in patients with diabetes (Fig. 2). Thirty-day mortality was 5% (CI 0.00–0.14), hospital readmission 13% (CI 0.12–0.13) and reoperation rate was 6% (CI 0.06–0.07).

Table 1 Summary of key results for postoperative complications in patients with diabetes vs without diabetes

Outcomes	No. of papers	Total sample size	Pooled prevalence in patients with diabetes (CI)	OR (95% CI)	<i>p</i> value
Anastomotic leakage	29	66,457	11% (0.08–0.13)	2.41 (1.84–3.16)	<0.001*
Infectious complications					
Surgical site infection	21	564,889	20% (0.16–0.24)	1.98 (1.64–2.39)	<0.001*
Intra-abdominal abscess	5	171,414	6% (0.04–0.09)	1.88 (0.99–3.57)	0.053
Septicemia	2	170,334	6% (0.05–0.06)	2.93 (0.35–24.27)	0.320
Systemic complications					
Urinary complications	5	391,776	8% (0.05–0.11)	1.69 (1.21–2.35)	0.002*
Pulmonary complications	3	388,878	5% (0.03–0.07)	1.29 (0.77–2.16)	0.335
Cardiac complications	1	218,534	5% (0.05–0.05)	1.00 (0.95–1.05)	0.997
Acute renal failure	1	1019	5% (0.03–0.10)	8.22 (2.88–23.41)	<0.001*
Mechanical failure of wound healing	3	418,364	2% (0.01–0.02)	0.98 (0.71–1.35)	0.880
Ileus	1	169,325	19% (0.19–0.20)	1.19 (1.15–1.24)	<0.001*
Cd colitis	1	1019	4% (0.02–0.09)	7.58 (2.38–24.18)	0.001*
30-day mortality	3	31,118	5% (0.00–0.14)	2.65 (0.80–8.70)	0.109
1-year mortality	1	320	11% (0.05–0.21)	0.98 (0.41–2.36)	0.969
Readmission	2	181,867	13% (0.12–0.13)	1.41 (1.35–1.47)	<0.001*
Reoperation	2	171,050	6% (0.06–0.07)	1.18 (0.99–1.41)	0.068

*Statistically significant at $p < 0.05$

Complications in patients with diabetes vs without diabetes

A summary of key outcomes comparing postoperative complications between patients with and without diabetes is presented in Table 1.

Anastomotic leak

In a pooled analysis of 66,457 patients (7936 with diabetes and 58,521 without), it was found that patients with diabetes experienced a significantly higher risk of developing AL (OR 2.40; 95% CI 1.84–3.16, $p < 0.001$) (Fig. 3).

Infectious complications

From the pooled analysis of 564,889 patients (83,785 with diabetes), patients with diabetes experienced a significantly enhanced risk of SSI (OR = 1.98; 95% CI 1.64–2.39, $p < 0.001$) (Fig. 4). These complications were of varying severity, with analysis revealing a non-significant difference in rates of intra-abdominal abscess formation (OR = 1.88; 95% CI 0.99–3.57; $p = 0.053$) in 171,414 patients (24,469 with diabetes). Pooled analysis involving 170,334 patients (24,293 with diabetes) showed that patients with diabetes experienced an increased risk of developing septicemia postoperatively, although without

statistical significance (OR = 2.93; 95% CI 0.35–24.27, $p = 0.320$).

Systemic postoperative complications

Analysis of 391,776 patients (58,033 with diabetes) indicated a significant difference (OR = 1.69; 95% CI 1.21–2.35, $p = 0.002$) in the urinary complication rates between patients with and without diabetes. Pooled analysis of 388,878 patients (57,876 with diabetes) showed a non-significant difference in pulmonary complications between patients with and without diabetes (OR = 1.29; 95% CI 0.77–2.16; $p = 0.335$).

Readmissions and reoperations

In a pooled analysis of 181,867 patients (24,396 with diabetes), diabetes significantly increased the likelihood of hospital readmission following colorectal surgery (OR 1.41; 95% CI 1.35–1.47, $p < 0.001$). Analysis of 171,050 patients (24,396 with diabetes) yielded non-significant influence (OR = 1.18; CI = 0.99–1.41, $p = 0.068$) on the rate of reoperation within 30 days of surgery.

30-Day mortality

In a pooled analysis of 31,118 patients (3526 with diabetes), diabetes contributed to an increase in the risk of 30-day

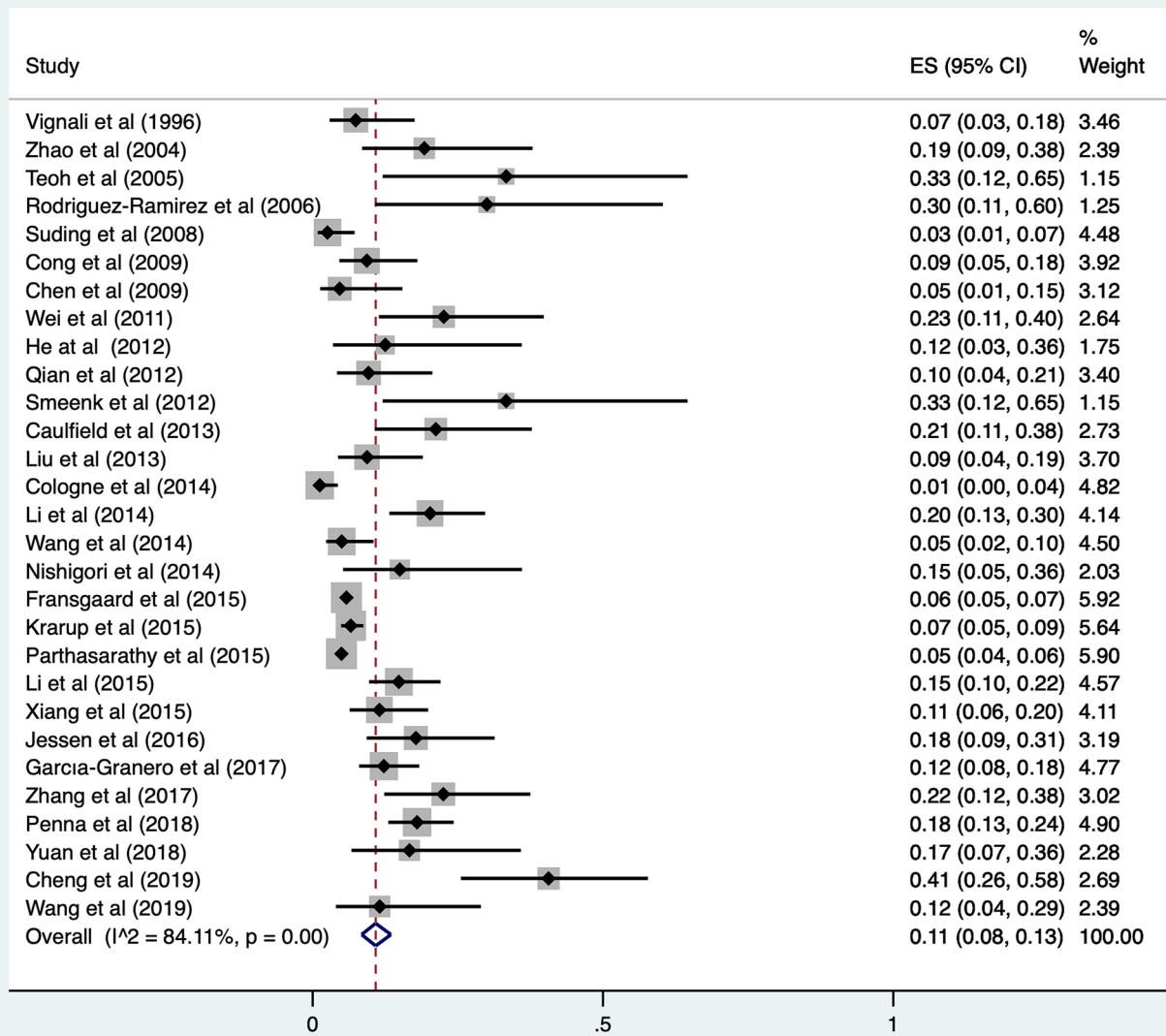


Fig. 2 Prevalence of anastomotic leak

mortality (OR 2.65; 95% CI 0.80–8.70, $p=0.109$). However, the results were not statistically significant.

Discussion

Diabetes is a well-known risk factor for a range of post-operative complications following colorectal surgery, with its effects on postoperative mortality [74], AL [14], and SSI [75] being well-established. In line with existing literature, this meta-analysis found AL and SSI to be the most commonly reported postoperative complications amongst patients with diabetes. Additionally, several lesser-known complications affecting the respiratory, urinary, and

gastrointestinal systems were also identified. Results from this analysis identified diabetes as a significant risk factor for AL and SSI after colorectal surgery. While previous studies [14, 75] have also found significant associations between diabetes and AL and SSI, this study expanded on the existing literature by conducting an analysis of proportions and providing prevalence rates for these complications.

Pooled analysis also found that diabetes increased the occurrence of pulmonary complications following colorectal surgery. Despite this being without overall statistical significance, individual studies reported significant associations between diabetes and pulmonary complications, especially for infectious complications such as pneumonia. Cologne et al. [32] and Ramsey et al. [64] concluded that diabetes

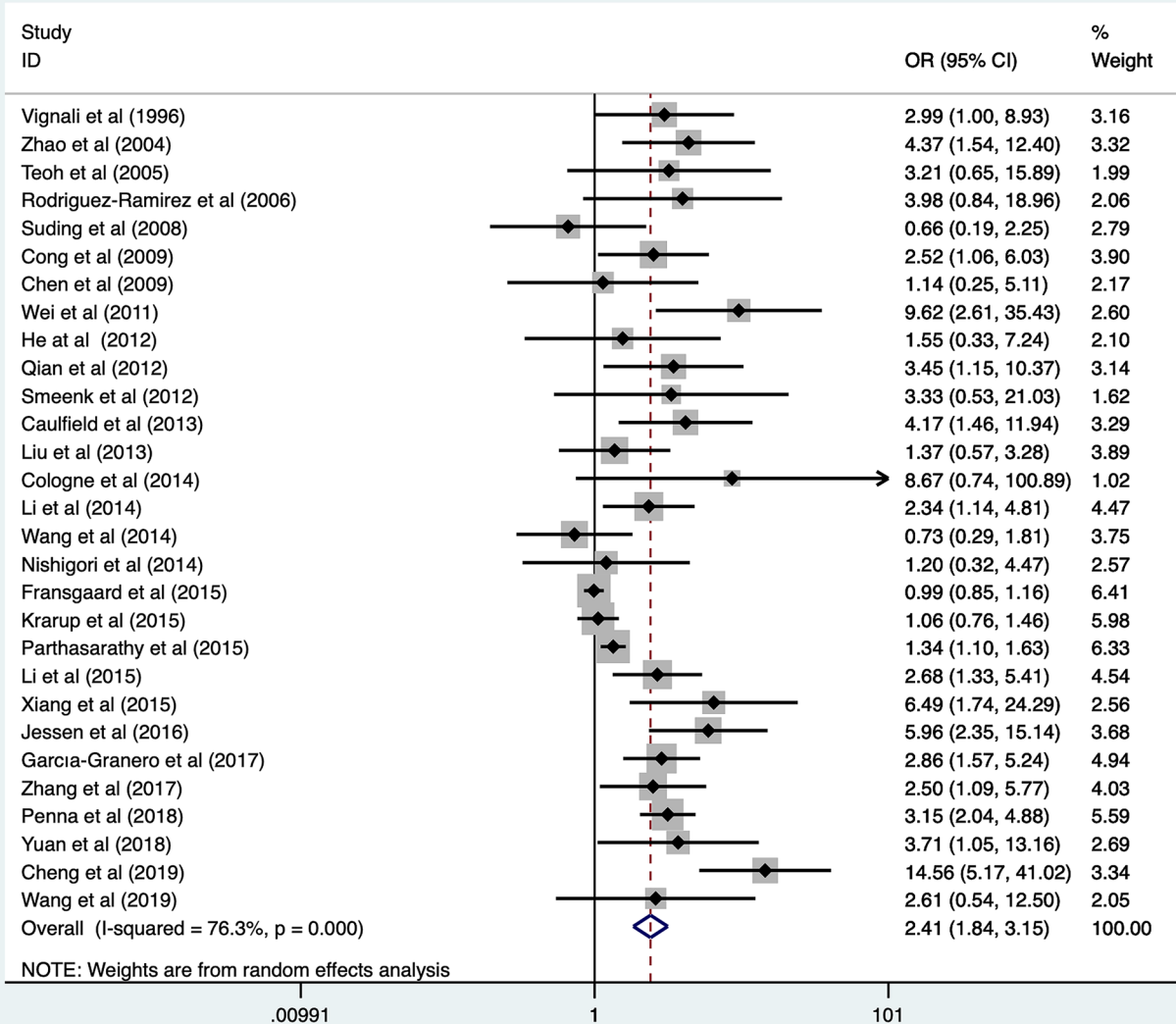


Fig. 3 Forest plot for anastomotic leakage

was a significant risk factor for pneumonia following surgery for colonic diverticulitis and colectomy. However, this was offset by a large cohort study by Anand et al. [73] which concluded that diabetes was not significantly associated with pulmonary complications after colorectal surgery. While there is a paucity of previous literature reviewing the effects of diabetes on pulmonary complications after colorectal surgery, it has been shown that patients with diabetes are predisposed to lower respiratory tract infections including pneumonia [76] due to compromised immune function. The occurrence of postoperative pneumonia is of considerable clinical interest as it is significantly associated with prolonged length of hospital stay ranging from 7–9 days, as well as increased treatment costs [43, 77]. Further investigation

is, therefore, required to strengthen the association between diabetes and pulmonary complications after colorectal surgery.

Furthermore, pooled analysis identified diabetes as a significant risk factor for urinary complications including urinary retention, urinary dysfunction, and urinary tract infection. In particular, Toyonaga et al. [43] found diabetes to be significantly associated with urinary retention after anorectal surgery for benign causes, attributing it to the impairment of autonomic nerves supplying the detrusor muscles within the bladder. Toritani et al. [78] also suggested that diabetes was a risk factor for urinary dysfunction following surgery for rectal cancer due to autonomic nerve impairment which decreases bladder sensation and results in an increased

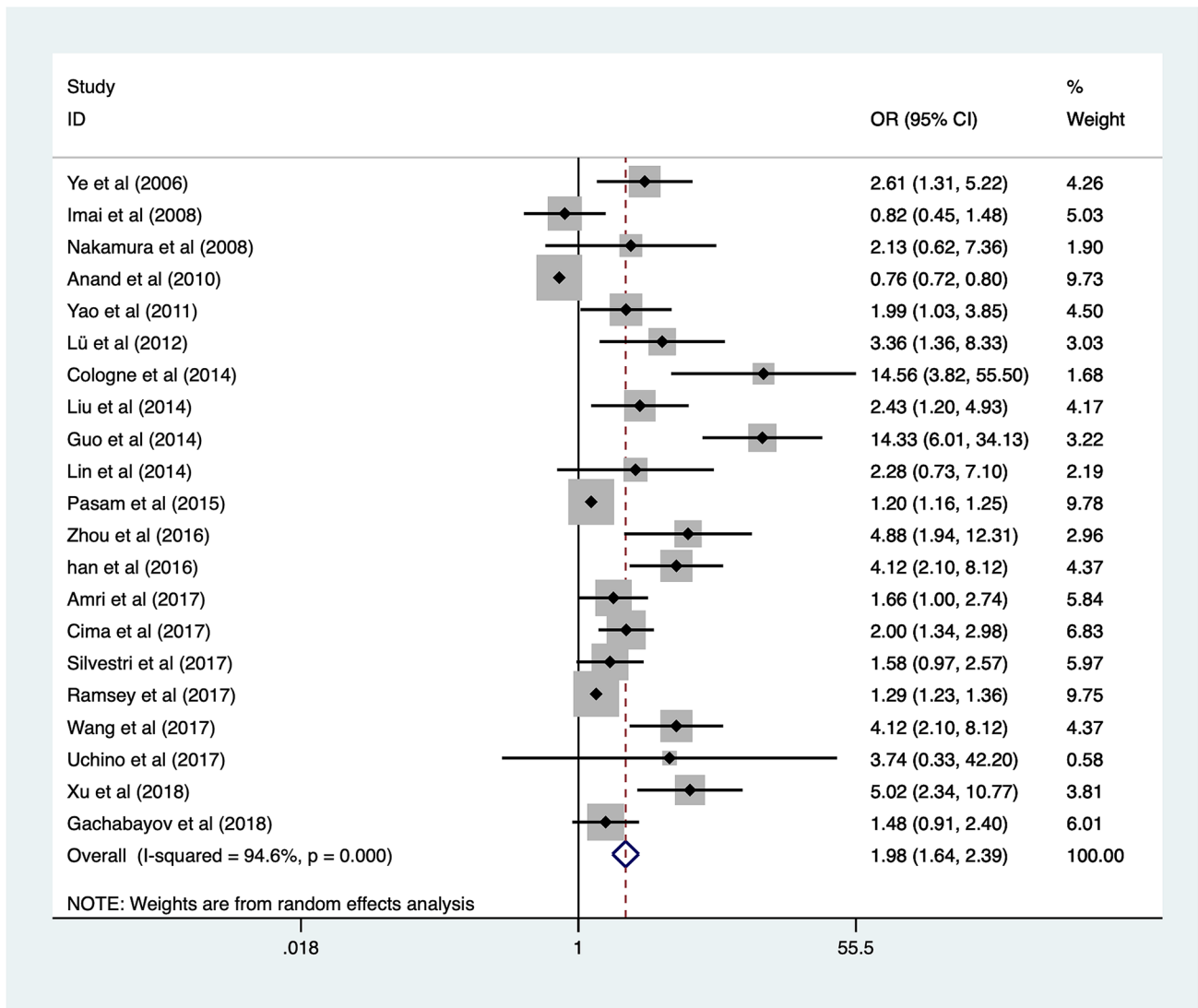


Fig. 4 Forest plot for surgical site infections

bladder capacity. The significant association between diabetes and postoperative urinary complications has several clinical implications. Given that the prevalence of diabetic bladder dysfunction is already often underestimated in postoperative patients [79], there is a need for closer monitoring of patients with diabetes to prevent re-catheterisation and to allow for earlier detection of urine retention. Akin to patients who have had pelvic surgery with rates of urinary retention of 15–25% [80], patients with underlying diabetic urinary dysfunction may benefit from preoperative bladder training [81] and regular monitoring for urine retention after trial without catheter to mitigate the increased rate of urinary complications associated with diabetes. Preoperative urodynamic factors such as peak flow rate, detrusor straining pressure during voiding, and the presence of straining to the void have also been suggested to be predictive of postoperative

urinary retention [82, 83] and could be helpful during surgical planning to manage the occurrence of such complications, especially in high risk groups such as patients with diabetes.

In addition to results from our meta-analysis, several studies included in our review reported less common postoperative complications associated with diabetes. Cologne et al. [32] concluded that diabetes was a significant risk factor for acute renal failure postoperatively after multivariate analysis adjusting for age, sex, and other existing comorbidities (adjusted OR 3.40, 95% CI 2.00–5.60, $p < 0.001$). This was attributed to the pro-inflammatory effects of diabetes and the resultant micro- and macrovascular pathologies that negatively affect the renal system [84, 85]. The study also emphasized the elevated HbA1c levels in the study population (8.2%), which was suggestive of poorly controlled diabetes

and could have been a contributing factor for the occurrence of acute renal failure following colorectal surgery. However, this remains debateable as large cohort studies [86, 87] have shown that preoperative HbA1c levels do not predict many postoperative outcomes such as wound infection and postoperative ileus.

Ramsey et al. [64] found insulin-dependent diabetes to be a significant risk factor for the occurrence of ileus following colectomy (OR 1.40, 95% CI 1.30–1.49, $p < 0.001$). The increased occurrence of ileus after colectomy was attributed to damage to myenteric neurons from chronic diabetes [88], which is a common cause of diabetes-associated gastrointestinal complications. This is corroborated by previous studies which have suggested diabetes as a significant risk factor for postoperative ileus in abdominal surgery [89]. In the existing literature, there is limited support for the role of prokinetics such as erythromycin, metoclopramide, and cisapride in treating postoperative ileus [90, 91]. Current guidelines for the management of ileus are instead centred around a multi-modal approach including the use of thoracic epidural anaesthesia and analgesia intraoperatively, which allows for a reduction in postoperative administration of narcotic analgesics [92]. Furthermore, minimally invasive surgery is in itself a predictor of good outcomes as it is associated with reduced pain, and reduced opiate requirements, along with early mobilization, which contributes to a reduced occurrence of ileus [93], and should, therefore, be considered in patients with diabetes.

Finally, Anand et al. [73] concluded that diabetes was not associated with an increased occurrence of cardiac complications following colorectal surgery. However, the existing literature has demonstrated significant associations between diabetes and postoperative myocardial infarction in general surgery [94, 95]. Appropriate consideration should still be given to these complications due to their severity, with the occurrence of myocardial infarction following colorectal surgery being associated with a sixfold increase in patient mortality [96]. Hollenberg et al. [94] recommend the use of intensive Holter monitoring in high-risk patients. Similarly, careful perioperative monitoring should be considered for patients with additional risk factors in conjunction with diabetes that predispose them to postoperative myocardial infarction, including age 70 years and above, compromised renal function, and a history of congestive heart failure [96]. Additionally, in previous meta-analyses, the use of epidural analgesia has been suggested to decrease the incidence of postoperative myocardial infarction [97, 98].

Tighter glycemic control should be implemented to mitigate the negative impact of diabetes on postoperative complications after colorectal surgery. Studies concluded that the elevated risk of infectious complications in patients with hyperglycemia improves with the administration of insulin with a dose–effect relationship between insulin and the

occurrence of postoperative infections [99]. Van den Berghe et al. [98] also found that intensive insulin therapy targeted at maintaining blood glucose levels between 80 and 110 mg/dL was effective in decreasing mortality in patients admitted to surgical intensive care. Furthermore, patients receiving intensive insulin therapy were less likely to require prolonged mechanical ventilation and intensive care. This has a positive impact on the incidence of ventilator-associated pneumonia [99] and should be considered in the postoperative management of patients with diabetes who could be at a higher risk of pulmonary related complications.

Limitations

There are several limitations to this review. First, there was a shortage of literature that evaluated the impact of diabetes on less commonly reported complications such as ileus, and urinary retention. Relevant included studies also did not provide clear definitions for urinary, pulmonary, and cardiac complications. However, we expect that these definitions are largely similar and would not have a significant influence on our results. Additionally, due to the limited baseline characteristics reported such as HbA1c levels, it was not possible to conduct meta-analysis and meta-regression for some of these complications, which could have potentially yielded useful information such as the impact of well-managed versus poorly managed diabetes on clinical outcomes. Finally, demographics and baseline characteristics of the diabetes subgroup were not disclosed in a majority of the included articles, which contributed to the heterogeneity of the data. Regardless of these limitations, this study provides a comprehensive review of the effects of diabetes on a range of postoperative complications following colorectal surgery beyond well-understood outcomes such as AL and SSI.

Conclusions

While complications such as AL and SSI are well reported on and accounted for during surgical planning [100], less commonly reported complications such as urinary retention and ileus also significantly impact surgical outcomes and should not be neglected. Not only is the prevalence of such complications higher in at-risk groups such as patients with diabetes, but the clinical impact including the length of hospital stay and treatment costs is also greater for these patients. The perioperative management plan for high-risk patients, encompassing anesthesia techniques, administration of intravenous fluids, and postoperative analgesia, should take into account a wider range of postoperative complications beyond AL and SSI to ensure desirable surgical outcomes.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by DJHT, HTM, CYLY and CHN. The first draft of the manuscript was written by all authors and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals by any of the authors.

Informed consent For this type of study formal consent is not required.

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