Association of Diabetes Mellitus With Postoperative Complications and Mortality After Non-Cardiac Surgery: A Meta-Analysis and Systematic Review

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Background: Although a variety of data showing that diabetes mellitus (DM) (Type 1 or Type 2) is associated with postoperative complication, there is still a lack of detailed studies that go through the specific diabetic subgroups. The goal of this meta-analysis is to assess the relationship between DM and various complications after non-cardiac surgery.

Methods: We searched articles published in three mainstream electronic databases (PubMed, EMBASE, Web of science) before November, 2020. A random effects model was conducted since heterogeneity always exist when comparing results between different types of surgery.

Results: This paper included 125 studies with a total sample size of 3,208,776 participants. DM was a risk factor for any postoperative complication (Odds ratio (OR)=1.653 [1.487, 1.839]). The risk of insulin-dependent DM (OR=1.895 [1.331, 2.698]) was higher than that of non-insulin-dependent DM (OR=1.554 [1.061, 2.277]) for any postoperative complication. DM had a higher risk of infections (OR=1.537 [1.322, 1.787]), wound healing disorders (OR=2.010 [1.326, 3.046]), hematoma (OR=1.369 [1.120, 1.673]), renal insufficiency (OR=1.987 [1.311, 3.013]), myocardial infarction (OR=1.372 [0.574, 3.278]). Meanwhile, DM was a risk factor for postoperative reoperation (OR=1.568 [1.124, 2.188]), readmission (OR=1.404 [1.274, 1.548]) and death (OR=1.606 [1.178, 2.191]).

Conclusions: DM is a risk factor for any postoperative complications, hospitalization and death after non-cardiac surgery. These findings underscore the importance of preoperative risk factor assessment of DM for the safe outcome of surgical patients.

Keywords: diabetes mellitus, non-cardiac surgery, risk factor, postoperative complication, meta-analysis

Abbreviations: CI, Confidence Intervals; DM, Diabetes mellitus; IDDM, Insulin-Dependent Diabetes Mellitus; LOS, length of stay; MI, Myocardial infarction; NIDDM, Non-Insulin-Dependent Diabetes Mellitus; NOS, Newcastle-Ottawa scale; OR, Odds Ratio; RR, Relative Risk; WHD, Wound Healing Disorders; VTE, Venous Thromboembolism.
1 INTRODUCTION

Each year more than 300 million surgeries are performed in the world (1). The baseline 30-day mortality of hospitalized patients undergoing non-cardiac surgery is 1.5% worldwide, primarily depending on surgical method, surgical decision-making or technique, and comorbidities (2). It is important to identify factors that increase the risk of surgery before making clinical decisions (3). The preoperative identification of risk factors has important clinical implications. First, it helps surgeons correct those risk factors that can be optimized prior to surgery to reduce surgical risk. Second, it directs patients to undergo low-risk surgery or transfer to appropriate medical institutions with stronger technical ability. Third, it is beneficial to make correct decisions based on risk-benefit evaluation. To date, it is still a very tough task to preoperatively identify high-risk patients or the subgroup population who would benefit most from surgery.

Diabetes mellitus (DM) (Type 1 or Type 2) is a multifaceted metabolic disease that affects more than 340 million people worldwide (4). They are at high risk for microvascular (neuropathy, nephropathy or retinopathy) or macrovascular (peripheral vascular, cardiovascular disease) complications, both of which increase perioperative morbidity and mortality (5). Surgical patients with DM are more likely to have prolonged hospital stays, admission to intensive care units, myocardial infarction, respiratory infections, poor wound healing, and increased risk of general morbidity and mortality (6–9). It is important for surgeons to be aware of possible complications and associated contributing factors so that they can be appropriately counseled preoperatively. Clinicians should develop direct strategies in the perioperative period to minimize surgical risks based on existing DM screening programs (10).

To date, there seems to lack detailed studies that go through this specific diabetic subgroup, although there are very convincing data showing that DM is associated with a variety of postoperative complications (5). After all, exactly which complications are associated with DM remains controversial. In order to provide clinicians with a reference to assess the surgical risk, we performed meta-analysis and systematic review of various complications after noncardiac surgery in patients with DM.

2 METHODS

2.1 Protocol and Guidance

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) guidelines (11). No registration details are available.

2.2 Eligibility Criteria

In this manuscript were included studies, which described DM as a preoperative risk factor. These studies that presented postoperative complications, mortality, morbidity, length of ICU stay and prolonged hospital stay, providing adjusted or unadjusted relative risk (RR) or odds ratio (OR) with 95% confidence interval (CI); or providing relevant information that can be used to figure out RR or OR. The studies’ design relied on retrospective data.

2.3 Information Sources and Search Strategy

We searched for articles published before November 30, 2020 regardless of language in a total of three electronic databases (PubMed, EMBASE, Web of science). We restricted our search to human studies. In the search we used the following terms: “diabetes”, “postoperative complications”, “surgical procedures”, “operative,” “hospitalization”, “risk factors”, “treatment outcome”, “perioperative care”, “perioperative period”, “reoperation” and “wound healing”. References of identified studies, recent guidelines and reviews on this topic were also selected by manual screening. Studies on cardiac surgery were excluded.

2.4 Study Selection and Data Collection

Two authors independently selected studies by screening titles and abstracts, and any disagreements were resolved by the senior author. Data extraction was performed independently by two authors. Study characteristics including author, publication year, country, sample size, mean or median age, number of patients with DM, type of DM, and type of surgery were extracted. Data were extracted for pooling, including total number of subjects, number of events of various complications, RR or OR. If the data were only available as graphs, the free software Plot Digitizer was used to estimate from the graphs. Quality assessment was using the Newcastle-Ottawa scale (NOS) for assessing quality of observational studies.

2.5 Definition of Outcomes

Our outcome measure is the OR of the incidence of complications in diabetic versus nondiabetic patients after surgery. It also shows the OR of mortality, readmission, reoperation, and prolonged length of stay (LOS). We have pooled OR for 7 postoperative complications, including any complication, infections, wound healing disorders (WHD), venous thromboembolism (VTE), hematoma, renal insufficiency, and myocardial infarction (MI).

2.6 Statistical Analysis

Homogeneity of effect estimates was tested using the Cochran Q and I² statistics (12, 13). A random effects model was conducted because of heterogeneity always exist when comparing results between different types of surgery, and subgroup analyses were performed. All outcomes were presented as OR with 95% CI. All analyses were performed using Stata/SE version 15.0 (StataCorp, College Station, TX, USA). Publication bias was assessed by evaluating small-study effects with comparison adjusted funnel plot symmetry if 10 or more studies were available.
3 RESULTS

3.1 Study Selection and Study Characteristics

Our literature search yielded a total of 2,737 retrievals, 125 studies were used for meta-analysis. Figure 1. A total of 72 studies were from the United States, accounting for more than half of the 125 studies included. The number of patients with DM was 356,300, accounting for 11.1% of the huge sample size of 3,208,776. The vast majority of studies focused on all types of DM, and only eight studies distinguished between IDDM and NIDDM. The types of surgery mainly covered orthopedic surgery, oncological surgery, transplantation surgery, plastic surgery, weight loss surgery, oral surgery, neurological surgery, ophthalmological surgery, etc., with the exception of cardiac surgery. The quality of the included studies was assessed using the NOS criteria. The NOS quality scores of the included studies ranged from 6 to 9 points (Table 1).

3.2 Synthesis of Results

3.2.1 Any Complication

A total of 61 studies reported any complication. The pooled OR of any complication in patients with DM vs those without DM was 1.653 [1.487, 1.839], suggesting that DM was a risk factor for any postoperative complication (Table 2 and Figure 2). The results of subgroup analyses showed that OR of any complication in patients with IDDM and NIDDM vs those without DM were 1.895 [1.331, 2.698] and 1.554 [1.061, 2.277], respectively, suggesting that IDDM and NIDDM were risk factors for any postoperative complication, and the risk of IDDM was higher than that of NIDDM (Table 2 and Supplementary Figures S1, S2).

3.2.2 Organ or System Complications

3.2.2.1 Infections

A total of 40 studies reported infections. The pooled OR of infections in patients with DM vs those without DM was 1.537 [1.322, 1.787], suggesting that DM was a risk factor for postoperative infections (Table 2 and Supplementary Figure S3).

3.2.2.2 Venous Thromboembolism

A total of 11 studies reported VTE. The pooled OR of VTE in patients with DM vs those without DM was 1.189 [0.759, 1.864], which was statistically insignificant. This result suggested that DM was not a risk factor for postoperative VTE (Table 2 and Supplementary Figure S4).
### TABLE 1 | Characteristics of included studies.

| Study                        | Year | Age | Sample size | Number of DM | Country | Surgery                                                                 | Selection | Comparability | Outcome |
|------------------------------|------|-----|-------------|--------------|---------|--------------------------------------------------------------------------|-----------|---------------|---------|
| Afshari et al. (14)          | 2016 | –   | 1493        | 166          | USA     | thighplasty                                                              | ☆☆☆☆      | ☆☆☆          | ☆☆☆☆   |
| Aigner et al. (15)           | 2017 | 72.5| (6.1)       | 237          | Germany | open reduction and internal fixation of geriatric ankle fractures        | ☆☆☆☆      | ☆☆☆          | ☆☆☆☆   |
| Akhter et al. (16)           | 2016 | –   | 1196        | 133          | India   | surgery                                                                   | ☆☆☆☆      | ☆☆☆          | ☆☆☆☆   |
| Ammor et al. (17)            | 2018 | 69  | 6985        | 1389         | USA     | gastrectomy for malignancy                                              | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Arnold et al. (18)           | 2014 | 60.1| (10.7)      | 278          | USA     | surgical decompression, in cervical spondylotic myelopathy              | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bailey et al. (19)           | 2003 | 63.4| (9.9)       | 1777         | USA     | esophagectomy                                                             | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bailón-Cuadrado et al. (20)  | 2019 | 68.6| (11.1)      | 180          | Spain   | curative surgery for colorectal cancer                                   | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bamba et al. (21)            | 2016 | 40.9| (13.9)      | 129007       | USA     | aesthetic surgery                                                         | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bascom et al. (22)           | 2016 | 43.9| 829         | 43           | Canada  | bulbar urethroplasty                                                     | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Belmont et al. (23)          | 2015 | 67.3| (10.2)      | 15321        | USA     | total knee arthroplasty                                                  | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Belmont et al. (24)          | 2014 | 50.3| (18.2)      | 3328         | USA     | ankle fracture fixation                                                  | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bennahid et al. (25)         | 2020 | 64.7| 504         | 152          | USA     | vascular procedures requiring infrainguinal incisions                    | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bohli et al. (2)             | 2019 | –   | 7582        | 842          | USA     | open reduction and internal fixation of closed ankle fractures          | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bolognesi et al. (26)         | 2008 | 61.0| 76.0        | 751340       | USA     | total hip and total knee arthroplasty                                    | ☆☆☆☆      | ☆☆☆          | ☆☆☆☆   |
| Bower et al. (27)            | 2010 | 61.6| (14.1)      | 1343         | USA     | surgical outcomes of noncardiovascular patients                          | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Browne et al. (28)           | 2007 | 48.9| (18.16)     | 197461       | USA     | lumbar fusion                                                            | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Buchanan et al. (29)         | 2004 | 43  | 167         | 19           | USA     | open achilles tendon repair                                              | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Bur et al. (31)              | 2016 | 64.2| 7605        | 844          | USA     | head and neck cancer surgery                                             | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Cammarata et al. (32)        | 2019 | –   | 7030        | 770          | USA     | abdominal panniculectomy                                                 | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Chen et al. (33)             | 2009 | –   | 195         | 30           | USA     | spinal arthrodesis                                                       | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Chen et al. (34)             | 2019 | 53.9| (12.4)      | 207          | USA     | open hapectomy                                                           | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Chiu et al. (35)             | 2020 | 54.6| (11.5)      | 40           | Taiwan  | sequential free flap reconstruction                                      | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Ciuflo et al. (36)           | 2019 | 64.5| (13.3)      | 4631         | USA     | below knee amputation                                                    | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Cook et al. (37)             | 2008 | 53  | (13.20)     | 37732        | USA     | cervical fusion                                                          | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Cote et al. (38)             | 2019 | –   | 1005        | 112          | USA     | microvascular decompression                                              | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Courtney et al. (39)         | 2017 | 65.9| 169406      | 25913        | USA     | total joint arthroplasty                                                 | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Cutler et al. (40)           | 2020 | 54.8| 414         | 29           | USA     | total elbow arthroplasty                                                 | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Dodd et al. (41)             | 2016 | 53.4| 6800        | 836          | USA     | ankle fractures                                                          | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Duque et al. (42)            | 1997 | –   | 605         | 46           | Spain   | thoracotomy for bronchogenic carcinoma                                    | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Farivar et al. (43)          | 2017 | 73  | (9)         | 5881         | USA     | endovascular aneurysm repair of infrarenal abdominal aortic aneurysms    | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Fischer et al. (44)          | 2014 | 58  | 47443       | 7288         | USA     | mastectomy alone compared to immediate breast reconstruction           | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |
| Franck et al. (45)           | 2018 | 55.2| 60          | 7            | USA     | local muscle flap closure following spinal tumor extirpation             | ☆☆☆       | ☆☆☆          | ☆☆☆☆   |

(Continued)
| Study                      | Year  | Age   | Sample size | Number of DM | Country | Surgery                                                                 | Selection | Comparability | Outcome |
|---------------------------|-------|-------|-------------|--------------|---------|--------------------------------------------------------------------------|-----------|---------------|---------|
| Freire et al. (46)        | 2015  | 47    | 819         | 150          | Brazil  | kidney transplantation                                                   ☆☆☆☆      | ☆☆         | ☆☆☆☆         |
| Fu et al. (47)            | 2016  | –     | 3671        | 455          | USA     | anterior cervical discectomy and fusion                                  ☆☆☆☆☆     | ☆☆         | ☆☆☆☆         |
| Ganesh et al. (48)        | 2005  | 62.9  | 160598      | 9174         | USA     | ankle fracture                                                           ☆☆☆         | ☆           | ☆☆☆☆         |
| Golimaux et al. (49)      | 2014  | –     | 15480       | 2437         | USA     | elective lumbar fusion                                                   ☆☆☆        | ☆☆☆☆       | ☆☆☆☆         |
| Gupta et al. (50)         | 2017  | 40.2  | 183914      | 20414        | USA     | aesthetic surgical                                                       ☆☆☆        | ☆           | ☆☆☆☆         |
| Gupta et al. (51)         | 2016  | 40.9  | 127961      | 2346         | USA     | aesthetic surgery                                                       ☆☆☆        | ☆           | ☆☆☆☆         |
| Gupta et al. (52)         | 2016  | 40.9  | 11300       | 303          | USA     | facelift                                                                 ☆☆☆☆☆     | ☆☆         | ☆☆☆☆         |
| Gupta et al. (53)         | 2017  | 40.9  | 129007      | 2368         | USA     | aesthetic breast surgery                                                 ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Hadaya et al. (54)        | 2020  | 60.8  | 22739       | 2524         | USA     | elective pneumonectomy                                                   ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Harritt et al. (55)       | 2017  | 64.4  | 370         | 37           | Germany | elective rectal cancer resection                                         ☆☆☆        | ☆☆☆☆       | ☆☆☆☆         |
| Hunecke et al. (56)       | 2019  | 43.7  | 121         | 18           | Germany | abdominoplasty after massive weight loss                                  ☆☆☆        | ☆           | ☆☆☆☆         |
| Inabnet et al. (57)       | 2010  | 44.2  | 3802        | 1323         | USA     | non-lap band primary and revisional bariatric surgical procedures        ☆☆☆        | ☆           | ☆☆☆☆         |
| Janczak et al. (58)       | 2019  | 67.9  | 205         | 46           | Poland  | elective open surgery for infrarenal aortic aneurysms                    ☆☆☆        | ☆           | ☆☆☆☆         |
| John and Thuluvath (59)   | 2001  | 53.6  | 171         | 57           | USA     | liver transplantation                                                    ☆☆☆☆☆     | ☆☆         | ☆☆☆☆         |
| Kantar et al. (60)        | 2018  | 54.4  | 7035        | 770          | USA     | abdominal panniculectomy                                                  ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Karthikesalingam et al. (61)| 2011 | 40    | 123         | 14           | UK      | abdominoplasty                                                           ☆☆☆        | ☆☆☆☆       | ☆☆☆☆         |
| Kauvar et al. (62)        | 2017  | 77    | 3344        | 648          | USA     | elective endovascular aortic aneurysm repair                             ☆☆☆        | ☆☆☆         | ☆☆☆☆         |
| Koch et al. (63)          | 2015  | 53    | 405         | 79           | Germany | kidney transplantation                                                   ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Lange et al. (64)         | 2009  | 72    | 121         | 27           | Netherlands | peripheral vascular surgery                     ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Lee et al. (65)           | 2018  | –     | 2301        | 421          | Korea   | elective posterior lumbar fusion                                         ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Lewin et al. (66)         | 2014  | 39.6  | 512         | 14           | Sweden  | breast reduction surgery                                                 ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Li et al. (67)            | 2017  | –     | 3024        | 223          | China   | gastric cancer                                                            ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Lindqvist et al. (68)     | 2019  | 57.4  | 886         | 22           | Sweden  | sentinel lymph node biopsy for cutaneous melanoma                        ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Lopez Ramos et al. (69)   | 2018  | 61    | 40802       | 4880         | USA     | cranial neurosurgery                                                     ☆☆☆        | ☆☆          | ☆☆☆☆         |
| Louie et al. (70)         | 2017  | 51.3  | 3251        | 387          | USA     | open reduction internal fixation of ankle fractures                      ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Lv et al. (71)            | 2015  | 49.7  | 438         | 140          | China   | liver transplantation                                                    ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Ma et al. (72)            | 2019  | 62.6  | 545         | 61           | China   | radical gastrectomy                                                      ☆☆☆        | ☆☆☆☆       | ☆☆☆☆         |
| Maradit Kremers et al. (73)| 2015 | 66.2  | 20171       | 3507         | USA     | total hip and knee arthroplasty                                           ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Matsuda et al. (74)       | 2009  | 66.2  | 80          | 9            | Japan   | abdominoperineal resection                                               ☆☆☆        | ☆☆          | ☆☆☆☆         |
| McEvany et al. (75)       | 2019  | 69.5  | 8819        | 1874         | USA     | shoulder arthroplasty                                                    ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Meding et al. (76)        | 2003  | –     | 5220        | 329          | USA     | total knee replacement                                                   ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Memenkos et al. (77)      | 2010  | 37    | 261         | 36           | Greece  | laparoscopic sleeve gastrectomy                                           ☆☆☆☆☆     | ☆           | ☆☆☆☆         |
| Michalak et al. (78)      | 2016  | 53.3  | 1141        | 115          | USA     | cerebrovascular surgery                                                  ☆☆☆        | ☆☆☆☆       | ☆☆☆☆         |

(Continued)
| Study                  | Year | Age     | Sample Size | Number of DM | Country       | Surgery                                                                 | Selection | Comparability | Outcome |
|-----------------------|------|---------|-------------|--------------|---------------|--------------------------------------------------------------------------|-----------|---------------|---------|
| Moon et al. (79)      | 2008 | 67.6    | 342         | 171          | Korea         | total knee arthroplasty                                                   | ☆☆☆☆☆    | ☆☆☆☆☆         |         |
| Moon et al. (80)      | 2018 | 49.9    | 5538        | 615          | USA           | sleeve gastrectomy                                                       | ☆☆☆☆☆    | ☆☆☆☆☆         |         |
| Morgan et al. (81)    | 2015 | 48      | 12062       | 1339         | Australia     | bariatric surgery                                                        | ☆☆☆☆☆    | ☆☆☆☆☆         |         |
| Nair et al. (82)      | 2009 | 52 (19) | 221         | 55           | USA           | liver transplantation                                                    | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Newman et al. (83)    | 2014 | 60.4    | 3352        | 406          | USA           | total knee and total hip arthroplasty                                     | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Nguyen et al. (84)    | 2019 | 62      | 563         | 69           | Canada        | gynecologic oncology                                                     | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Nguyen et al. (85)    | 2016 | 48.65   | 2294        | 126          | USA           | brachioplasty                                                            | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Okamura et al. (86)   | 2017 | 63 (8)  | 300         | 35           | Japan         | esophagectomy                                                            | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Palmerola et al. (87) | 2016 | 64 (54-94) | 191    | 21           | USA           | urologic surgery                                                         | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Park et al. (88)      | 2016 | 51.44   | 7948        | 1284         | Korea         | anterior cervical disectomy and fusion for cervical spondylotic, radiculopathy, myelopathy | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Patton et al. (89)    | 2015 | 55.4    | 87          | 6            | USA           | total ankle arthroplast                                                   | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Pearse et al. (90)    | 2012 | 56.7    | 46539       | 5576         | UK            | non-cardiac surgery                                                      | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Pino et al. (91)      | 2019 | 57.7    | 303         | 34           | Spain         | unplanned surgery in cervical spondylotic myelopathy surgically treated | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Ponce et al. (92)     | 2014 | 69 (13) | 66485       | 13730        | USA           | shoulder arthroplasty                                                    | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Pugely et al. (93)    | 2013 | 52.6    | 4310        | 455          | USA           | lumbar disectomy                                                         | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Qin et al. (94)       | 2014 | 55.9    | 29736       | 1478         | USA           | breast reconstruction                                                    | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Raikin et al. (95)    | 2010 | –       | 106         | 11           | USA           | total ankle arthroplasty                                                 | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Rao et al. (96)       | 2020 | 69.9    | 1074        | 433          | USA           | shoulder arthroplasty                                                    | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Rensing et al. (97)   | 2017 | 44      | 1626        | 79           | USA           | primary repair of achilles tendon ruptures                                | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Roche et al. (98)     | 2018 | 61.24   | 9439        | 1402         | USA           | parathyroidectomy for primary hyperparathyroidism                       | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Rubel et al. (99)     | 2019 | 57.5    | 169788      | 31289        | USA           | elective primary lumbar spine surgery                                    | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Sakai et al. (100)    | 2014 | 44.0    | 107         | 12           | Japan         | surgery for laryngeal and hypopharyngeal cancers bariatic surgery        | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Sanni et al. (101)    | 2014 | 12     | 20308       | 5268         | USA           | bariatric surgery                                                        | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Schermitzsch et al.   | 2015 | 34.9    | 153         | 6            | Canada        | plate fixation of the midshaft clavicle                                  | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Schirrmel et al. (102)| 2010 | 51      | 171         | 8            | Netherlands   | spinal fusion                                                            | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Schipper et al. (104) | 2015 | 65.7    | 12122       | 2394         | USA           | ankle arthrodesis and total ankle arthroplasty                           | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Schlottmann et al. (105)| 2017 | 63    | 4053        | 229          | USA           | esophagectomy                                                            | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Schürner et al. (106) | 2018 | 40      | 711         | 200          | Switzerland    | primary roux-en-y gastric bypass surgery                                  | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Shah et al. (107)     | 2019 | 65 (11) | 3344        | 346          | USA           | thumb cmc joint arthroplasty                                              | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Shigeishi et al. (108)| 2015 | 41(5)-84| 324         | 12           | Japan         | oral surgery                                                             | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Shimada et al. (109)  | 1994 | 57.5    | 209         | 23           | Japan.         | hepatic resection                                                        | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Smith et al. (110)    | 2017 | 45.78   | 272         | 30           | USA           | tibia fractures treated with intramedullary fixation                     | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |
| Söderbäck et al. (111)| 2019 | 71.1    | 30050       | 952          | Sweden        | colorectal cancer surgery                                                | ☆☆☆☆☆☆   | ☆☆☆☆☆☆       |         |

(Continued)
3.2.2.3 Wound Healing Disorders
A total of nine studies reported WHD. The pooled OR of WHD in patients with DM vs those without DM was 2.010 [1.326, 3.046], suggesting that DM was a risk factor for postoperative WHD (Table 2 and Supplementary Figure S5).

3.2.2.4 Hematoma
A total of eight studies reported hematoma. The pooled OR of hematoma in patients with DM vs those without DM was 1.369 [1.120, 1.673], suggesting that DM was a risk factor for postoperative hematoma (Table 2 and Supplementary Figure S6).

3.2.2.5 Renal Insufficiency
A total of five studies reported renal insufficiency. The pooled OR of renal insufficiency in patients with DM vs those without DM was 1.987 [1.311, 3.013], suggesting that DM was a risk factor for

| Study                  | Year | Age          | Sample size | Number of DM | Country | Surgery                                      | Selection | Comparability | Outcome |
|------------------------|------|--------------|-------------|--------------|---------|----------------------------------------------|-----------|---------------|---------|
| Sood et al. (112)      | 2015 | 62           | 3820        | 755          | USA     | nephrectomy                                  | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Sood et al. (113)      | 2017 | 69 (61-76)   | 1118        | 214          | USA     | radical cystectomy                           | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Sørensen et al. (114)  | 2002 | 64           | 425         | 47           | Denmark | breast cancer surgery                        | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Souza et al. (115)     | 2007 | 45.6 (10.4)  | 55          | 4            | Brazil  | liver transplantations                       | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Spinazzi et al. (116)  | 2015 | 55.9 (15.2)  | 15317       | 2493         | USA     | pituitary surgery                            | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Stein et al. (117)     | 2011 | –            | 221594      | 64569        | USA     | cataract surgery                             | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Suda et al. (118)      | 2016 | 57.2         | 108         | 25           | Germany | arthrodesis                                  | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Takao et al. (119)     | 2008 | > 80         | 255         | 68           | Japan   | urological surgery                           | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Tang et al. (120)      | 2014 | 68.8         | 236         | 74           | China   | spinal fusion and instrumentation            | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Terho et al. (121)     | 2016 | 63           | 373         | 68           | Finland | laparoscopic cholecystectomy                  | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Tetreault et al. (122) | 2016 | 56.4 (11.9)  | 479         | 59           | Canada  | surgery for the treatment of cervical spondylotic myelopathy | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Timmermans et al. (123)| 2018 | 49.1 (9.2)   | 97          | 5            | Netherlands | free deep flap breast reconstructions      | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Toboni et al. (124)    | 2018 | 60.4         | 4260        | 540          | USA     | ovarian cancer                               | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Tokgöz et al. (125)    | 2011 | 61.6 (12.1)  | 47          | 8            | Turkey  | radical nephrectomy                          | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Venara et al. (126)    | 2014 | 74 (18-109)  | 166         | 25           | France  | treatment of incarcerated hernias, especially in case of bowel resection | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Wadhwa et al. (127)    | 2017 | 54.2 (16.7)  | 9853        | 1690         | USA     | surgery for lumbar degenerative disease     | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Wang et al. (128)      | 2020 | 72 (65-86)   | 118         | 7            | China   | radial forearm-free flap                     | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Wang et al. (129)      | 2017 | –            | 1657        | 184          | China   | laparoscopy-assisted total gastrectomy       | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Webb et al. (130)      | 2017 | –            | 114102      | 20248        | USA     | total knee arthroplasty                      | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Weir et al. (131)      | 2019 | 52.2 (14.7)  | 5222        | 580          | UK      | lumbar spinal surgery                        | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Winocour et al. (132)  | 2017 | 45.5 (10.3)  | 129007      | 2368         | USA     | cosmetic surgery                             | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Wukich et al. (133)    | 2010 | 46.7         | 1000        | 190          | USA     | foot and ankle surgery                       | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Yamauchi et al. (134)  | 2013 | –            | 1438        | 148          | Japan   | lung cancer operations                       | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Zanaty et al. (135)    | 2015 | 46.5 (12.7)  | 348         | 52           | USA     | cranioplasty                                 | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Zhang et al. (136)     | 2015 | 65.8 (11.3)  | 119         | 39           | China   | pancreatoduodenectomy                        | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Zhou et al. (137)      | 2016 | 65.9 (12.0)  | 2795        | 228          | China   | gastrectomy for gastric cancer               | ☆☆☆       | ☆☆☆          | ☆☆☆    |
| Total studies          |      |              | 3208776     | 356300       |         |                                              |           |               |         |

DM, Diabetes mellitus; NOS, Newcastle-Ottawa scale.
TABLE 2 | Outcomes.

| Complications                          | Odds ratio (95%CI) | Studies included |
|----------------------------------------|-------------------|------------------|
| Any complications                      | 1.653 (1.487, 1.839) | 61               |
| Any complications-IDDM                 | 1.895 (1.331, 2.698) | 8                |
| Any complications-NIDDM                | 1.554 (1.061, 2.277) | 7                |
| Infections                             | 1.537 (1.322, 1.787) | 40               |
| VTE                                    | 1.189 (0.795, 1.864) | 1                |
| Wound healing disorders                | 2.010 (1.326, 3.048) | 9                |
| Hematoma                               | 1.369 (1.120, 1.673) | 8                |
| Renal insufficiency/failure            | 1.987 (1.311, 3.013) | 5                |
| MI                                     | 1.372 (0.574, 3.278) | 4                |
| Length of stay                         | 1.581 (1.271, 1.968) | 7                |
| Readmission                           | 1.404 (1.274, 1.548) | 15               |
| Reoperation                            | 1.568 (1.124, 2.188) | 11               |
| Mortality                              | 1.606 (1.178, 2.191) | 18               |
| Mortality-Cancer surgery               | 1.052 (0.419, 2.643) | 3                |
| Mortality-Orthopedic surgery           | 1.817 (1.136, 2.908) | 8                |
| Mortality-Hemangioma resection         | 1.509 (0.889, 2.561) | 3                |
| Mortality-transplant                   | 1.214 (0.410, 3.829) | 2                |

IDDM, Insulin-Dependent Diabetes Mellitus; MI, Myocardial infarction; NIDDM, Non-Insulin-Dependent Diabetes Mellitus; VTE, Venous Thromboembolism.

FIGURE 2 | Forest plot of odds ratio of any postoperative complication in patients with DM vs those without DM.
postoperative renal insufficiency (Table 2 and Supplementary Figure S7).

### 3.2.2.6 Myocardial Infarction
A total of four studies reported MI. The pooled OR of MI in patients with DM vs those without DM was 1.372 [0.574, 3.278], which was statistically insignificant. This result suggested that DM was not a risk factor for postoperative MI (Table 2 and Supplementary Figure S8).

### 3.2.3 Hospitalization
A total of seven studies reported LOS. The pooled OR of LOS in patients with DM vs those without DM was 1.987 [1.311, 3.013], suggesting that DM was a risk factor for extended LOS after surgery. A total of eleven and fifteen studies reported reoperation and readmission with the pooled OR 1.568 [1.124, 2.188] and 1.404 [1.274, 1.548], respectively. The results suggested that DM was a risk factor for postoperative reoperation and readmission (Table 2 and Supplementary Figures S9–S11).

### 3.2.4 Survival
A total of 18 studies reported mortality. The pooled OR of mortality in patients with DM vs those without DM was 1.606 [1.178, 2.191], suggesting that DM was a risk factor for postoperative death (Figure 3). The results of subgroup analyses revealed that the pooled OR of mortality in patients with DM vs those without DM was 1.817 [1.136, 2.906] after orthopedic surgery, while the pooled OR of mortality were 1.052 [0.419, 2.643], 1.509 [0.889, 2.561] and 1.214 [0.410, 3.592] after cancer surgery, hemangioma resection and transplant, respectively. The results suggested that DM was a risk factor for death after orthopedic surgery, not for death after cancer surgery, hemangioma resection and transplant (Table 2 and Supplementary Figures S12–S15).

### 3.3 Subgroup Analysis
According to the type of surgery, we had three subgroups: general surgery, orthopedics and aesthetic surgery. Only the results of general surgery are slightly different from the overall results, the pooled OR of VTE in patients with DM vs those without DM was 3.627 [2.405, 5.469], suggesting that DM was a risk factor for postoperative VTE. The analysis results of the other two subgroups were consistent with the overall results. (Table 3 and Supplementary Figures S16–S22).

### 3.4 Publication Bias
We performed Egger’s test based on six comparisons (any complication, infection, VTE, readmission, reoperation, and mortality) with more than ten included studies. P-value of Egger’s test for VTE was 0.688, suggesting no publication bias, while P-values for the other five comparisons were less than 0.1, standing for different degrees of the publication bias. The trim-and-fill procedure was adopted for these 5 comparisons. After four additional studies were filled to “reoperation”, the result of the meta-analysis changed, and the OR changed from statistically to non-statistically significant, suggesting that DM as a risk factor for reoperation are not necessarily reliable and should be interpreted carefully. The other four comparisons (any complication, infection, readmission, and mortality) showed varying degree of changes in the pooled effect values after the adoption of trim-fill method, but without any change in the statistical significance (Supplementary Figures S33–S38).

![Forest plot of odds ratio of postoperative mortality in patients with DM vs those without DM.](image-url)
TABLE 3 | Outcomes of subgroup analysis.

| Aesthetic Surgery Complications | OR (95%CI)     | Studies included |
|---------------------------------|---------------|-----------------|
| Any complications                | 1.582 (1.044, 2.396) | 10              |
| Infections                       | 1.670 (1.344, 2.074) | 7               |
| VTE                              | 0.270 (0.069, 1.059) | 2               |
| Hematoma                         | 1.362 (1.074, 1.727) | 5               |
|                              |                |                 |
| General Surgery Complications    | OR (95%CI)     | Studies included |
| Any complications                | 1.847 (1.595, 2.139) | 32              |
| Infections                       | 1.732 (1.268, 2.364) | 14              |
| VTE                              | 3.627 (2.405, 5.469) | 2               |
| Wound healing disorders          | 2.053 (1.126, 3.740) | 5               |
| Renal insufficiency/failure      | 2.259 (1.234, 4.135) | 4               |
| Mortality                        | 1.400 (0.976, 2.010) | 10              |
|                              |                |                 |
| Orthopedic Surgery Complications | OR (95%CI)     | Studies included |
| Any complications                | 1.409 (1.194, 1.664) | 19              |
| Infections                       | 1.245 (1.136, 1.786) | 19              |
| VTE                              | 0.975 (0.789, 1.206) | 7               |
| Wound healing disorders          | 2.355 (1.380, 4.017) | 3               |
| Renal insufficiency/failure      | 1.607 (0.821, 3.145) | 3               |
| MI                               | 1.372 (0.574, 3.278) | 4               |
| Mortality                        | 1.817 (1.136, 2.906) | 8               |

Mi: Myocardial infarction; VTE: Venous Thromboembolism.

4 DISCUSSION

As the number of people with DM increases, a large number of diabetic patients are facing various health problems that require surgical treatment. DM is generally considered a major risk factor for postoperative complications (138). Although this is intuitive enough for clinicians, it is unclear which postoperative complications are exactly related to DM because there may be other comorbidities in patients with DM. This meta-analysis included 125 studies with a total sample size of 3,208,776.

We started out with a meta-analysis of any complication. The results showed that DM was a risk factor for any postoperative complication, which was consistent with previous studies (99). Our subgroup analyses showed that both IDDM and NIDDM were risk factors for any postoperative complication, and the risk of IDDM was higher than that of NIDDM. These findings suggested that IDDM, not just DM in general sense, should be an important risk factor in clinical evaluation of patients. This might explain why some diabetic patients, while their blood glucose was under control, still experienced various postoperative complications. The results of our meta-analysis are in accord with Nathan et al. study which found a 2.5-fold increase in the readmission rate of IDDM patients after posterior lumbar fusion. Subgroup analysis showed that readmission rate was nearly the same for patients with NIDDM as for those without DM, while it was twice as high in patients with IDDM as those without DM (65). Similar findings were reported in lumbar fusion surgery. Nicholas et al. suggested that compared with patients without DM, IDDM was more significantly associated with an increased risk of postoperative complications, extended length of hospital stay, postoperative adverse events, and readmission than NIDDM. Furthermore, the complications associated with IDDM were more severe than those associated with NIDDM (49). These findings indicated that whether a patient has IDDM is more important than whether a patient has DM (type 1 or type 2) when considering a patient as a surgical candidate.

It is well known that DM is a risk factor for perioperative complications (4, 46). Our analyses revealed that DM is an independent risk factor for wound infections, WHD, hematoma, and renal insufficiency. DM has been identified as a risk factor for postoperative infection and poor healing because of its vascular lesions and immune effects (139). DM present with neutrophil dysfunction which increases the risk of infection by the pathogen and decreases healing capacity (52). DM is associated with tissue hypoxia and increased blood viscosity. This slows the inflammatory response, which in turn alters wound healing and increases the risk of infection, especially in the lower extremities (140–143). In addition, several factors prevent wound healing in patients with DM, including reduced angiogenesis, multiple growth factors, and impaired macrophage function (144). These may be responsible for postoperative complications of DM.

Moreover, we also found that DM can increase the incidence of postoperative renal insufficiency, which deserves our attention. After hip and knee arthroplasty, diabetic patients are 1.5 times more likely to develop acute renal failure than nondiabetic patients (92). After orthotopic liver transplantation, renal insufficiency is significantly higher in patients with preexisting DM than in patients without DM (59.7% vs. 20.2%, P < 0.001) (59). Considering the elevated incidence of postoperative renal insufficiency in diabetic patients, surgeons should pay more attention to postoperative fluid management, intraoperative hypotension anesthesia, and perioperative nephrotoxic medications.

A surprising finding in our study is that DM does not significantly increase the risk of VTE and MI. Diabetic patients are prone to hypercoagulable state due to abnormal regulation of coagulation-related plasma proteins caused by prolonged hyperglycemia. Type 2 DM is associated with an increased risk of thrombosis and cardiovascular disease. Therefore, it is also generally accepted that diabetic patients may be at an increased risk of postoperative thrombosis. For example, Rena et al. retrospectively reviewed 5,538 patients who underwent sleeve gastrectomy between January 1, 2008 and September 30, 2016, at 5 weight loss centers in the United States (80). They found that a personal history of malignancy and type 2 DM increased the risk of mesenteric vein thrombosis. However, many studies have shown different results. Ravinder et al. found that DM was not an independent risk factor for the venous thrombosis in various cosmetic procedures, although it was an independent risk factor for major complications, especially infections. The prevalence of DM did not differ significantly between the VTE and non-VTE groups (21) (0.9% vs 1.8%, P = 0.37). VTE and MI are deadly serious postoperative complications with not only high morbidity and mortality, but also prolonged hospital stay and high charges. Accurate identification of which patients are high risk for thromboembolism helps to take more targeted and appropriate preventive measures. A variety of surgeries were included in our study (cardiac surgery was not within the scope of our study). Eleven studies involved VTE, MI was reported in four studies. Our study suggests that DM is not a risk factor for postoperative VTE...
and MI, and therefore DM should not be considered a priority factor in determining thrombotic risk. Clinicians should pay more attention to age, smoking, and immobility and other factors, which may be associated with thrombosis according to the literature (116).

Our study also found that DM is a risk factor for postoperative reoperation and readmission, and that patients with DM have a higher risk of postoperative death. This is consistent with findings that DM is an independent risk factor for multiple postoperative complications. DM significantly prolongs the hospital stay after ankle fusion and total ankle replacement (104). Ganesh et al. used the NIS database to analyze the effect of DM on the prognosis of patients with ankle fractures and found that DM was associated with a significant increase in hospital stay (4.7 days vs 3.6 days, \( P < 0.001 \)) (48). These are all consistent with our findings. Postoperative infection, hematoma and WHD are causes of reoperation and readmission. It is not surprising, therefore, that diabetic patients are more prone to reoperation and readmission. Although DM is found to be a risk factor for postoperative death, our subgroup analysis suggests that DM is a risk factor for death after orthopedic surgery but not cancer surgery, hemangioma resection and transplant. This is an important finding in our study. This may be related to the specifics of different types of surgery, such as patient population characteristics, length of surgery, and surgical procedures. Based on this finding, orthopedic surgery should be more strictly controlled by surgical standards and should be performed cautiously in patients with DM.

The strengths of this study lie in the large number of studies included the large sample size, and the exploration of the association of DM with multiple postoperative complications. The limitation of this study is that our study of common complications may have heterogeneity due to differences in the type of surgery. In addition, our combined effect size may be overestimated. The reason is that although a small number of included studies have analyzed a large number of complications, they only show significant differences \( P < 0.05 \). Unfortunately, it is that we can only calculate the combined effect size based on studies that provide OR. Finally, what’s noteworthy is that the OR in some studies is not adjusted for confounders because the incidence of some complications may be affected by potential confounders, such as preoperative diseases other than DM, body weight, or age, etc. Therefore, we stratified the pooled values for any complication by crude OR and adjusted OR, respectively, resulting in consistent results. However, we did not stratify the other subdivided complications in the same way.

In summary, our meta-analysis suggested that DM may significantly affect multiple perioperative complications, hospitalization, and survival (cardiac surgery is not within the scope of our study). DM is a risk factor for postoperative infections, WHD, hematoma, renal insufficiency, reoperation, readmission and death after orthopedic surgery. But DM is not the risk of postoperative VTE, MI and not the risk for death after cancer surgery, hemangioma resection and transplant. These findings underscore the importance of preoperative risk factor assessment for the safe outcome of surgical patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XZ, AH, WM, and JL contributed to the conception or design the study; JC, YL, JSL, and HL contributed to acquisition, analysis of data for the study; XZ, AH, YM, and YS contributed to interpretation of data for the study; XZ and AH wrote the first draft of the manuscript. All authors revised it critically for important intellectual content and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.841256/full#supplementary-material

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