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Review

# Metabolic syndrome; associations with adverse outcome after colorectal surgery. A systematic review and meta-analysis

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ABSTRACT

*Background:* Increasing evidence shows that patients with Metabolic Syndrome (MetS) are at risk for adverse outcome after abdominal surgery. The aim of this study was to investigate the impact of MetS and preoperative hyperglycemia, as an individual component of MetS, on adverse outcome after colorectal surgery.
*Methods:* A literature review was systematically performed according to the PRISMA guidelines. Inclusion criteria were observational studies that evaluated the relationship between MetS or preoperative hyperglycemia and outcomes after colorectal surgery (i.e. any complication, severe complication defined as Clavien-Dindo grade ≥ III, anastomotic leakage, surgical site infection, mortality and length of stay).
*Results:* Six studies (246.383 patients) evaluated MetS and eight studies (9.534 patients) reported on hyperglycemia. Incidence rates of MetS varied widely from 7% to 68% across studies. Meta-analysis showed that patients with MetS are more likely to develop severe complications than those without MetS (RR 1.62, 95% CI 1.01–2.59). Moreover, a non-significant trend toward increased risks for any complication (RR 1.35, 95% CI 0.91–2.00), anastomotic leakage (RR 1.67, 95% CI 0.47–5.93) and mortality (RR 1.19, 95% CI 1.00–1.43) was found. Furthermore, preoperative hyperglycemia was associated with an increased risk of surgical site infection (RR 1.35, 95% CI 1.01–1.81).
*Conclusion:* MetS seem to have a negative impact on adverse outcome after colorectal surgery. As a result of few studies meeting inclusion criteria and substantial heterogeneity, evidence is not conclusive. Future prospective observational studies should improve the amount and quality in order to verify current results.

## 1. Introduction

Colorectal surgery challenges the body to withstand major stress. Surgical trauma induces several physiological and metabolic changes, which negatively influences recovery [1–3]. It has been suggested that patients with Metabolic Syndrome (MetS), who are at increased risk of the development of cardiovascular disease [4], are also at high-risk for metabolic distress around surgery [5] and subsequently, for adverse outcome after abdominal surgery [6].

MetS is characterized and defined by a cluster of interrelated metabolic abnormalities that include hyperglycemia, dyslipidemia, abdominal obesity and hypertension [7]. The worldwide prevalence of MetS is high, affecting around 25% of the adult population, and rates are increasing dramatically [8]. The pathophysiology of MetS is highly complex and not clear yet. According to many experts, insulin resistance and visceral obesity stand out as primary causes of MetS [9–11].

Several individual components of MetS are well-established risk factors for adverse outcome after colorectal surgery [12–15]. Literature reporting on the relationship of the clustering of these components and adverse outcome after colorectal surgery is controversial. Moreover, the

*Abbreviations:* AHA/NHLBI, American Heart Association/National heart Lung and Blood Institute Scientific Statement; AMSTAR, A MeaSurement Tool to Assess systematic Reviews; BG, Blood glucose; BMI, Body Mass Index; CAL, Colorectal anastomotic leakage; CI, Confidence interval; CRC, Colorectal cancer; ERAS, Enhanced Recovery After Surgery; FPG, Fasting Plasma Glucose; HbA1c, Hemglobin A1c; IDF, International Diabetes Federation; LoS, Length of stay; MetS, Metabolic Syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHLBI, National Heart, Lung, and Blood Institute; NOS, Newcastle-Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, Risk Ratio; SSI, Surgical site infection; WHO, World Health Organization.

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predictive value of hyperglycemia, as an individual component of MetS, remains insufficiently defined. Hence, the aim of the present systematic review and meta-analysis was to give an overview on the current best evidence on the impact of MetS and preoperative hyperglycemia, as an individual component of MetS, on short-term outcome after colorectal surgery.

## 2. Material and methods

A systematic literature review was performed and reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16] and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines. To define our research question, the CHARMS (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies) was used [17] including the following key points: Population, Index prognostic factors, Comparison, Outcome, Timing and Setting (PICOTS) [18]. A protocol was registered in the international prospective register of systematic reviews (PROSPERO registration number: CRD42020199913). Ethical approval was not required for this review article.

### 2.1. Search strategy

Electronic databases; MEDLINE (from PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library were searched through 02-07-2020 for relevant studies. Key words were: 'metabolic syndrome', 'hyperglycemia', 'colorectal surgery', 'postoperative outcome'. (Supplementary Material for detailed search strategy). Articles published before 1998 were not screened, since MetS was officially defined in 1998 by the World Health Organization [19]. Duplicate studies were removed.

### 2.2. Study selection

Eligible articles were published peer-reviewed retrospective and prospective observational studies (e.g. cohort, cross-sectional and case-control studies) written in English. Inclusion criteria were studies that reported on adult human patients (18 years or older) who had undergone colorectal surgery for malignant or benign disease and evaluated the relationship between MetS (compared with non-MetS) or preoperative hyperglycemia (compared with normoglycemia) and adverse postoperative outcome.

Studies were included if they had used a definition of MetS as stated by one or more of the following expert groups: 1) the World Health Organization (WHO) [19], 2) the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) [10], 3) the International Diabetes Federation (IDF) [11] and 4) the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [20].

One or more of the following measures to define hyperglycemia had to be used: 1) fasting plasma glucose (FPG), 2) oral glucose tolerance test, 3) hemglobin A1c (HbA1c) according to the American Diabetes Association and WHO guidelines or 4) random blood glucose (BG). The cut-off value for hyperglycemia was not predefined; definitions were used as stated by the authors.

Studies assessing one of the following outcomes: any complication, severe complication (defined as Clavien-Dindo grade III or higher), colorectal anastomotic leakage (CAL), surgical site infection (SSI), and mortality within 30–90 days after surgery and/or length of hospital stay (LoS) were included.

Studies were excluded if they were systematic or narrative reviews, meta-analyses, opinions, clinical guidelines, editorials, case reports or congress abstracts. Furthermore, studies evaluating intra- or post-operative hyperglycemia, studies reporting on glucose continuously instead of categorised or studies evaluating the impact of an individual component of MetS rather than the whole syndrome, were excluded. Inclusion and exclusion criteria are summarized in Supplementary Material Table 1.

All retrieved articles were independently screened by two authors (M.R. and C.S.) for titles and abstracts. In case of uncertainty or disagreement, abstracts were discussed for consensus or were re-reviewed by a third reviewer (A.L.) until consensus was reached. The remaining articles were independently read (full-text) by the same authors. Studies that fulfilled the inclusion criteria were hand-searched for additional articles in the final study selection. The study process is summarized in Fig. 1.

### 2.3. Data collection

The following data were extracted from the included studies: name of first author, year of publication, country where the study was performed, study design, sample size, age, gender, number and proportion of cases (MetS or hyperglycemic patients) and controls (non-MetS or normoglycemic patients), definitions, surgery type, setting, outcomes and follow-up time.

### 2.4. Critical appraisal

The Newcastle-Ottawa Scale (NOS), a validated tool for evaluating the quality of non-randomized studies, was used to evaluate the methodological quality of the included studies [21]. The NOS is based on three domains; selection (0–4 points), comparability (0–2), and outcomes of interest (0–3 points). A total score of 8–9 is considered as high, 6–7 as moderate, and ≤5 as low level of quality. Risk of bias was independently rated by two authors (M.R. and C.S.).

### 2.5. Statistical analysis

Outcomes were reported as incidence rates and proportions (for any complication, severe complication, CAL, SSI and mortality) or means/medians with standard deviations/interquartile range (for LoS). A meta-analysis was conducted if there were at least two compatible studies that reported on an outcome of interest. Heterogeneity across studies was assessed visually using forest plots and statistically using the chi-squared test, in which a $P$-value $< 0.10$ was accepted to conclude presence of heterogeneity. Furthermore, the $I^2$ was calculated, which represents the proportion of total variance between studies that is explained by heterogeneity. Heterogeneity was defined as high ($I^2$=75%–100%), moderate ($I^2$=50–75%), low ($I^2$=25–50%) or absent ($I^2$=0–25%). Meta-analyses were performed with the use of the Mantel-Haenszel method to run the random and, fixed-effects model. The random-effects model was used in the presence of heterogeneity (either chi-squared test $P < 0.10$ or $I^2 >$75%). Data was pooled to calculate relative risks with 95% confidence interval (CI) on each outcome. A $P$-value less than 0.05 was considered statistically significant. Sensitivity analyses were performed in order to examine the impact of including or excluding studies in the meta-analyses based on variance in follow-up time. Statistical analyses were performed using Review Manager software 5.4.

## 3. Results

### 3.1. Study selection

A total of 2.278 applicable records were initially identified after removal of duplicates. Based on titles and abstracts, 2.214 studies were excluded, remaining 64 studies to be assessed in full-text. Of those, thirteen studies met the inclusion and exclusion criteria. The reference lists of included studies were checked for additional relevant studies, not providing extra studies (Fig. 1).

#### 3.1.1. Characteristics of studies that assessed MetS

As can be seen in Table 1, six studies reported on MetS [22–27]. The

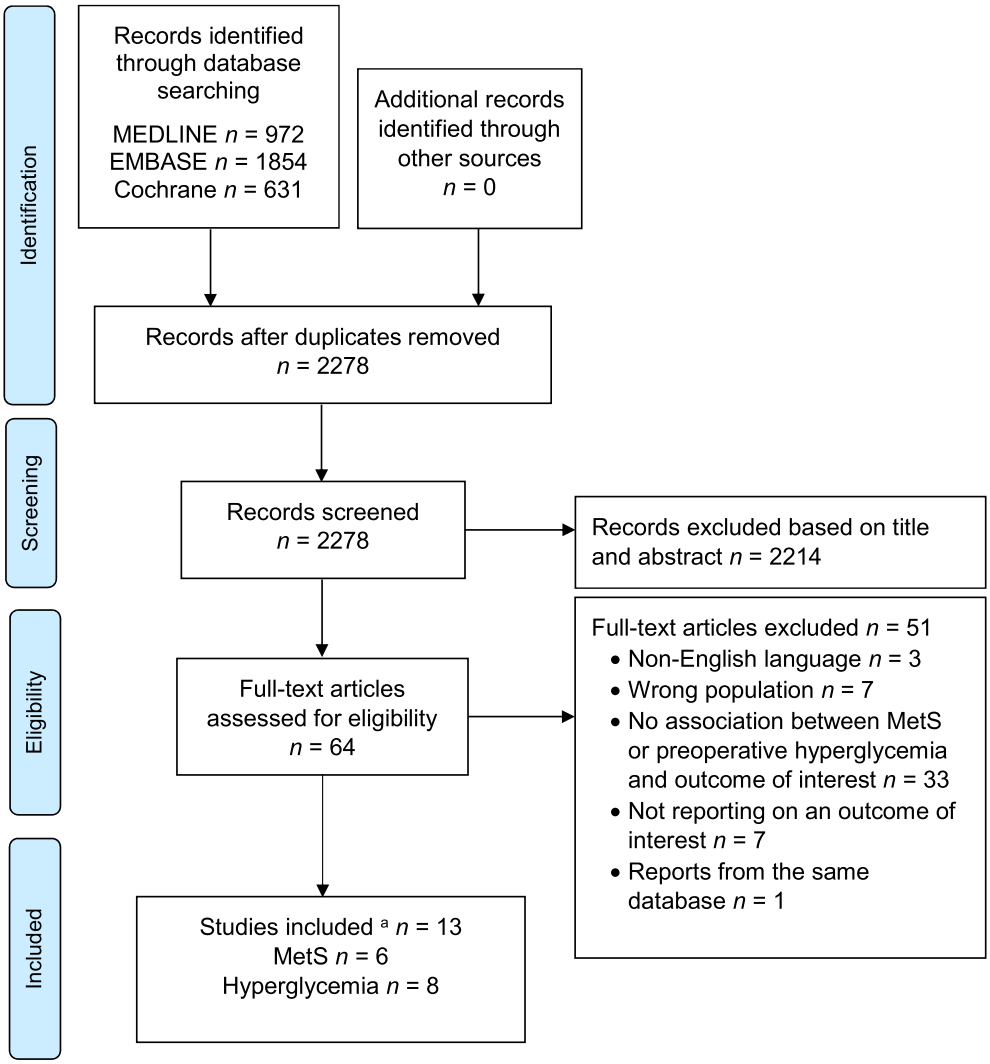



**Fig. 1.** PRISMA Flow diagram
[a] one study reported both on the association of MetS and hyperglycemia. Abbreviations: *n*, number of studies; MetS, metabolic syndrome

majority of the included studies were retrospective observational studies reporting on both colon and rectal surgery. Two out of six studies were classified high-quality level and four studies as moderate level of quality. Risk of bias assessments are presented in Supplementary Table 2. The combined study population was 246.383 patients (range 114–152.952 patients per study). Among the included studies, incidence rates of MetS varied widely from 7% to 68%, and multiple definitions of MetS were used. Three studies [22–24] used the NCEP ATP III criteria and two studies [26,27] used the AHA criteria to define MetS. One study assessed MetS by using the NCEP ATP III, AHA and IDF criteria [25]. The highest prevalence of MetS (40–68%) was reported by studies that used the AHA criteria.

### 3.1.2. *Metabolic syndrome and outcome*

**Any postoperative complication.** All studies assessed any complication after surgery [22–27] (Table 2). A significantly increased complication risk for patients with MetS was seen in three studies [24,26,27]. All but one study could be included in meta-analysis, resulting in a total sample size of 93.431 patients. Pooled analysis demonstrates a higher complication rate for patients with MetS (Fig. 2a), however, this difference was not statistically significant (RR 1.35; 95% CI: 0.91–2.00, $P = 0.13$). Heterogeneity was high ($I^2 = 85\%$, $P < 0.01$). One study, not included in the meta-analysis reported a 7% decreased odds of postoperative complications for patients with MetS (significance not determined) [23].

**Severe complication.** Two studies [22,27] comprising 1.617 patients, reported the incidence of severe complications. Meta-analysis using the fixed-effects model shows that patients with MetS are significantly at higher risk of severe complications compared to patients without MetS (RR 1.62, 95% CI: 1.01–2.59, $P = 0.04$, $I^2 = 59\%$, $P = 0.12$) (Fig. 2b).

**Anastomotic leakage.** Four studies [22,25–27] involving 1.844 patients were included in the analysis regarding the association of MetS and CAL. All four studies did not find a significant association between MetS and CAL. Meta-analysis shows a higher risk of CAL for patients with MetS (RR of 1.67 and 95% CI: 0.47–5.93; Fig. 2c), but this difference was not statistically significant. Heterogeneity was moderate ($I^2 = 65\%$, $P = 0.04$).

**Surgical site infection.** Only, Shariq et al. [24] evaluated SSI and found MetS to be an independent predictor of superficial (OR = 1.46, 95% CI, 1.32–1.60, $P < 0.001$) and deep SSI (OR = 1.40, 95% CI, 1.15–1.70, $P < 0.001$).

**Mortality.** Five studies evaluated mortality [22–24,26,27]. Three studies could be included in the meta-analysis, giving a total sample size of 93.183 patients for evaluation. The pooled analysis shows a higher risk of mortality for patients with MetS (RR of 1.19, 95% CI: 1.00–1.43, $P = 0.06$), however this difference was not statistically significant (Fig. 2d). Heterogeneity was not observed ($I^2 = 0\%$, $P = 0.78$). No

**Table 1**
Characteristics of studies that addressed metabolic syndrome and adverse outcome after colorectal surgery.

| Study, Year | Country | Design | Definition MetS[a] | Sample size | MetS cases, N (%) | Controls, N | Surgery type | Setting | Age[b] | Study quality[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Zarzavadjian et al., 2018[22] | France | RCS | ATP III | 1.236 | 85 (7%) | 1.152 | Colon | ND | 64 (16–93) | 7 |
| Akinyemiju et al., 2018[23] | USA | RCS | ATP III | 152.952 | 10.543 (7%) | 142.409 | Colorectal | ND | ND | 7 |
| Shariq et al., 2019[24] | USA | RCS | modified ATP III[d] | 91.566 | 7.603 (8%) | 83.963 | Colorectal | Elective | 66 (14) | 9 |
| Goulart et al., 2017[25] | Portugal | PCS | ATPIII<br>AHA<br>IDF | 134[e] | 46 (41%)<br>ATPIII<br>79 (68%) AHA<br>71 (67%) IDF | 67<br>38<br>35 | Colorectal | Elective | 68 (13) | 7 |
| Lohsiriwat. et al., 2010[26] | Thailand | PCS | AHA | 114 | 42 (37%) | 72 | Colorectal | Elective | 61 (29–91) | 7 |
| Zhou et al., 2019[27] | China | RCS | AHA | 381 | 153 (40%) | 228 | Rectal | Elective | 65 (16) | 9 |

Abbreviations: MetS, metabolic syndrome, ND, not determined; PCS, prospective cohort study; RCS, retrospective cohort study.
[a] National Cholesterol Education Program Adult Treatment Panel III (ATP III): three of the following conditions: abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, hypertension, diabetes or glucose intolerance (fasting plasma glucose ≥110 mg) American Heart Association/National heart, Lung and Blood Institute Scientific Stagement (AHA): three of the following conditions: abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, diabetes or glucose intolerance (fasting plasma glucose ≥100 mg) International Diabetes Federation (IDF): abdominal obesity plus two of the following conditions: elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, or elevated fasting plasma glucose (≥100 mg/dL or diabetes type 2).
[b] Values are in mean (SD) or median (range).
[c] Scored according to the Newcastle-Ottawa Scale.
[d] Did not include dyslipidemia (i.e. elevated triglycerides, reduced high-density lipoprotein cholesterol) in MetS definition.
[e] MetS could not be defined in all included study patients.

**Table 2**
Summary of outcomes of studies that addressed metabolic syndrome and adverse outcome after colorectal surgery.

| Study | Follow-up | Outcome of interest | Outcome measures |
|---|---|---|---|
| Zarzavadjian et al.[22] | ≤90 days | Any complication | Incidence rate (%) |
| | | Severe complication | Incidence rate (%) |
| | | Anastomotic leakage | Incidence rate (%) |
| | | Mortality | Incidence rate (%) |
| | | Length of stay | Median |
| Akinyemiju et al.[23] | ND | Any complication | Adjusted OR (95% CI) |
| | | Mortality[a] | Adjusted OR (95% CI) |
| Shariq et al.[24] | ≤30 days | Any complication | Incidence rate (%), adjusted OR (95% CI) |
| | | Surgical site infection | Incidence rate (%), adjusted OR (95% CI) |
| | | Mortality | Incidence rate (%), adjusted OR (95% CI) |
| | | Length of stay | Mean (SD), adjusted OR (%)[b] |
| Goulart et al.[25] | ≤30 days | Any complication | Incidence rate (%) |
| | | Anastomotic leakage | Incidence rate (%) |
| Lohsiriwat. et al.[26] | ≤30 days | Any complication | Incidence rate (%), adjusted OR (95% CI) |
| | | Mortality | Incidence rate (%) |
| | | Anastomotic leakage | Incidence rate (%) |
| | | Length of stay | Mean |
| Zhou et al.[27] | ≤30 days | Any complication | Incidence rate (%), adjusted OR (95% CI) |
| | | Severe complication | Incidence rate (%) |
| | | Anastomotic leakage | Incidence rate (%) |
| | | Mortality | Incidence rate (%) |
| | | Length of stay | Median (IQR) |

Abbreviations: CI, confidence interval; IQR, interquartile range; ND, not determined; OR, odds ratio; SD, standard deviation.
Percentile.
[a] In-hospital mortality.
[b] Adjusted OR presented for prolonged length of stay, defined as length of stay above 75[the] percentile.

patients died in the study of Lohsiriwat et al. [26]. Akinyemiju et al. [23] did not report incidence rates, but observed a lower odds of in-hospital mortality for patients with MetS (OR: 0.41, 95% CI: 0.35–0.49).

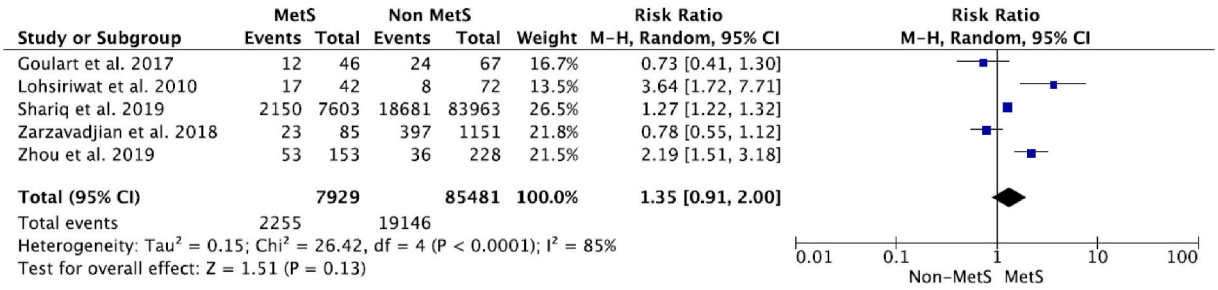
**Length of stay.** Four studies compared LoS for patients with and without MetS [22,24,26,27]. An estimation of an overall pooled effect could not be assessed. A significantly longer LoS for patients with MetS was reported by Lohsiriwat et al. [26] (11.2 versus 8.1 days, $P = 0.006$) and Shariq et al. [24] (for laparoscopic procedures 6.0 versus 5.5 days, $P < 0.001$, for open procedures 9.1 versus 8.5 days, $P < 0.001$). The remaining two studies observed comparable LoS between patients with and without MetS (7 versus 7 days, $P = 0.721$ and 14.4 versus 14.0 days, $P = 0.264$) [22,27].

**Sensitivity analyses.** While the majority of the studies reported on 30-day postoperative outcome, one study had a 90-day follow-up [22]. After exclusion of this study, the pooled risk estimates increased little for any complication (RR from 1.35 to 1.58) and CAL (RR from 1.67 to 2.82) (Supplementary Figs. 1a–c). Risk estimates for any complication and CAL were similar when using incidence rates of MetS according to the AHA or IDF criteria for Goulart et al. [25].

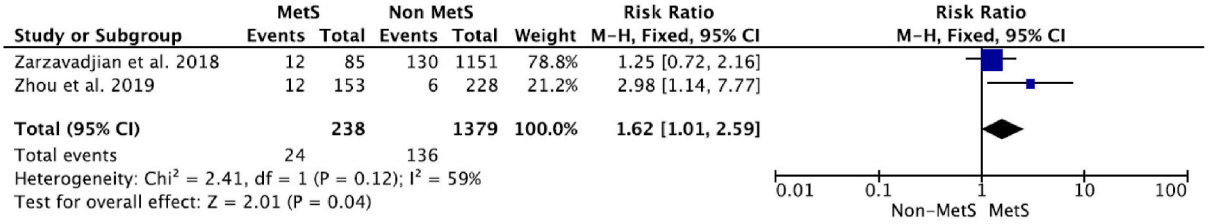
### 3.1.3. Characteristics of studies that assessed preoperative hyperglycemia

Summarized in Table 3, eight studies reported on preoperative hyperglycemia [25,28–34]. Three out of eight studies were classified high-quality level and five studies as moderate level of quality (Supplementary Table 2). The study of Goulart et al. [25] reported on both MetS and hyperglycemia as a component of MetS and was therefore also evaluated in this section. Overall, a total of 9.534 patients were included; 13% had hyperglycemia as defined by various measures and cut-off values. Six out of eight studies reported a mixed population of diabetic and non-diabetic patients. Gustafsson et al. [28] included only non-diabetic patients and Goh et al. [30] only diabetic patients. Four studies used random BG measurements with cut-off values more than or 140 or 180 mg/dL [29,31–33], two studies used FPG values of more than 126 mg/dL [34] and 100/110 mg/dL [25], and two studies used HbA1c with predefined cut-off values of more than 6% and more than 8% [28,30], to define hyperglycemia. The timing to define preoperative hyperglycemia varied widely. Three studies used values within 90 days of surgery [29,30,33], three studies defined hyperglycemia within 1 day before surgery [25,28,31] and two studies did not report timing [32,34].

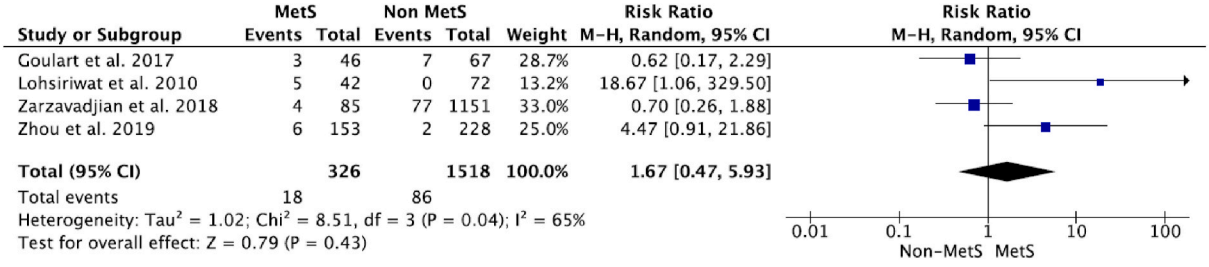
**a**




**b**




**c**




**d**

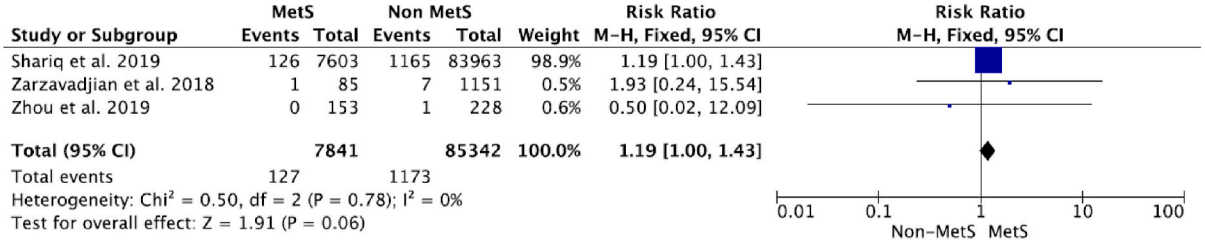



**Fig. 2.** Forest plot showing the relationship between MetS and any complication (**a**), severe complication (Clavien-Dindo III-IV) (**b**), colorectal anastomotic leakage (**c**) and mortality (**d**). Abbreviations: CI, confidence interval; M − H, Mantel Haenszel; MetS, metabolic syndrome; Fixed, fixed-effects modelling, Random; random-effects modelling. For (**a**) and (**c**), incidence rates of MetS according to the ATP III criteria are shown for Goulart et al. [25].

### *3.1.4. Preoperative hyperglycemia and outcome*

Table 4 shows a summary of outcomes regarding studies evaluating preoperative hyperglycemia. While most studies reported on 30-day postoperative outcome, one study had a 90-day follow-up [33] and the study by Goh et al. [30] did not report follow-up time. Except for the two studies that evaluated SSI, studies were not compatible enough in terms of measures and outcomes. Data was therefore ineligible for statistical pooling.

**Any postoperative complication.** Of the two studies that reported on overall complication rate [25,28], Gustafsson et al. showed a threefold increased risk of overall postoperative complications (OR 2.9, CI 95% 1.1–7.9, $P = 0.037$), while Goulart et al. found no significant difference between hyperglycemic and normoglycemic patients.

**Severe complication.** Goh et al. [30], evaluating only diabetic patients with considerably increased HbA1c levels, observed an almost threefold higher risk of CD grade ≥2 (adj. OR 2.479, CI 1.041–5.905, $P = 0.040$), but not a significantly higher risk of severe complications (CD grade ≥3).

**Anastomotic leakage.** Two studies that evaluated CAL as outcome did not find an association with preoperative hyperglycemia [25,33]. In the study of Gustafsson et al. [28], two patients developed anastomotic leakage, both with preoperative levels of HbA1c within normal range (≤6.0%) (significance not determined). Jiang et al. [34] observed that hyperglycemic patients had a significantly higher risk of intestinal

**Table 3**
Characteristics of studies that addressed preoperative hyperglycemia and adverse outcome after colorectal surgery.

| Study, Year | Country | Study design | Population | Definition hyperglycemia | Sample size | Elevated glucose, N (%) | Normal glucose, N | Surgery type | Setting | Age[a] | Study quality[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chen et al., 2019[33] | USA | RCS | DM & Non-DM | BG > 180 mg/dL | 755 | 85 (11%) | 670 | Colorectal | Elective | 57 (45–67) | 9 |
| Gachabayov et al., 2018[31] | USA | RCS | DM & Non-DM | BG > 140 mg/dL | 690 | 113 (16%) | 577 | Colorectal | Elective | 61 (15) | 7 |
| Goh et al., 2016[30] | Singapore | RCS | DM II | HbA1c > 8% | 149[c] | 31 (24%) | 99 | Colorectal | Elective & semi-urgent | 67 (11) | 6 |
| Gustafsson et al., 2009[28] | Sweden | PCS | Non-DM | HbA1c > 6% | 120 | 31 (26%) | 89 | Colorectal | Elective | 66 (31–90) | 8 |
| Jiang et al., 2019[34] | China | RCS | DM & Non-DM | FPG ≥126 mg/dL | 1.876 | 248 (13%) | 1628 | Colorectal | Elective & urgent | 64 (21–98) | 9 |
| Silvestri et al., 2017[32] | Italy | RCS | DM & Non-DM | BG > 180 mg/dL | 687[c] | 17 (3%) | 665 | Colorectal | Elective & urgent | 71 (19–93) | 7 |
| Ziegler et al., 2017[29] | USA | RCS | DM & Non-DM | BG > 140 mg/dL | 5.123[c] | 694 (16%) | 3588 | Colon | Elective | ND | 6 |
| Goulart et al., 2017[25] | Portugal | RCS | DM & Non-DM | FPG ≥110 mg/dL<br>FPG ≥100 mg/dL | 134[c] | 48 (42%)<br>58 (50%) | 65<br>59 | Colorectal | Elective | 68 (13) | 7 |

Abbreviations: BG; blood glucose, DM, diabetes mellitus; FPG fasting plasma glucose; HbA1c, hemoglobin A1c; ND not determined; PCS, prospective cohort study; RCS, retrospective cohort study.
[a] Values are in mean (SD) or median (range).
[b] Scored according to the Newcastle-Ottawa Scale.
[c] Preoperative hyperglycemia could not be defined in all included study patients.

**Table 4**
Summary of results showing relation between preoperative hyperglycemia and outcome after colorectal surgery.

| Study | Follow-up | Any complication | Severe complication | Anastomotic Leakage | Surgical Site Infection | Mortality | Length of stay |
|---|---|---|---|---|---|---|---|
| Chen et al.[33] | ≤90 days | ND | ND | No significant association (OR 1.33, CI 95% 0.50–3.54). No incidence rates | ND | ND | ND |
| Gachabayov et al.[31] | ≤30 days | ND | ND | ND | ↑SSI (28% versus 23%, significance ND) | ND | ND |
| Goh et al.[30] | ND | ND | A significant association with CD grade ≥2 or above (adj. OR 2.479, CI 1.041–5.905), but not with CD grade ≥3 (adj. OR 1.496, 95% CI 0.450–4.978)[a] | ND | ND | Mortality was not observed | ND |
| Gustafsson et al.[28] | ≤30 days | ↑ overall complications (45% versus 25%, OR 2.9, CI 95% 1.1–7.9, $P = 0.037$). | ND | ↑ CAL (6% versus 0%, significance ND) | ND | Mortality was not observed | No significant difference (8.5 (5.4) versus 7.3 (5.6) days). |
| Jiang et al.[34] | ≤30 days | ND | ND | ↑ Intestinal complications (14% versus 8%, $p = 0.002$)[b] | ND | ND | ND |
| Silvestri et al.[32] | ≤30 days | ND | ND | ND | ↑ SSI (41% versus 19%, OR 2.91, 95% CI 1.04–7.72, $P = 0.03$) | ND | ND |
| Ziegler et al.[29] | ≤30 days | ND | ND | ND | ND | ↑ Mortality (7% versus 3%, significance ND) | ND |
| Goulart et al.[25] | ≤30 days | No significant difference in complication rate[c] | ND | No significant difference in CAL rate[c] | ND | ND | ND |

Abbreviations: Adj, adjusted; BG, blood glucose; CAL, colorectal anastomotic leakage; CD, Clavien-Dindo; CI, confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LoS, length of stay; ND not determined; OR, odds ratio; SSI, surgical site infection.
[a] In-hospital complication rates.
[b] Intestinal complications include intestinal obstruction, leakage or bleeding, or peritonitis.
[c] Incidence rates are only shown for hyperglycemic patients.

complications (i.e. leakage, intestinal obstruction, bleeding or peritonitis (14% versus 8%, $P = 0.002$).

**Surgical site infection.** Two studies comprising 1.377 patients, reported the incidence of SSI. As can be seen in Fig. 3, meta-analysis using the fixed-effects model shows that patients with preoperative hyperglycemia are significantly at higher risk of SSI compared to patients with normoglycemia (RR 1.35, 95% CI 1.01–1.81, $P = 0.04$, $I^2 = 60\%$, $P = 0.11$) [31,32].

**Mortality.** Mortality was reported by three studies, two did not observe mortality [28,30] and one study demonstrated higher mortality rates for hyperglycemic patients (7% versus 3%, $P = 0.03$) [29].

**Length of stay.** Lastly, only one study compared LoS in non-diabetic

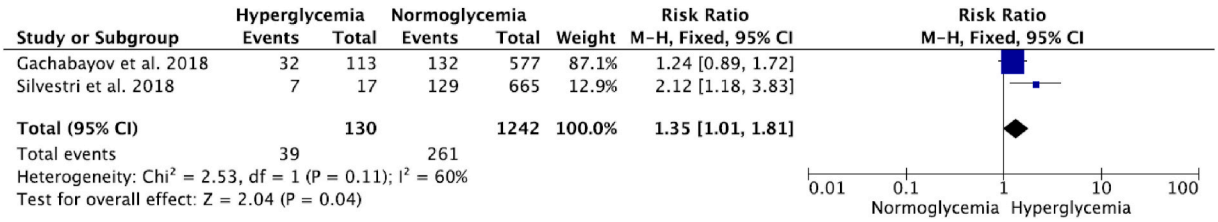



**Fig. 3.** Forest plot showing the relationship between preoperative hyperglycemia and surgical site infection. Abbreviations: CI, confidence interval; M − H, Mantel Haenszel; Fixed, fixed-effects modelling.

patients, and did not find a significant difference (8.5 (5.4) versus 7.3 (5.6) days, p = 0.482) [28] between hyperglycemic and normoglycemic patients.

## 4. Discussion

The purpose of the present systematic review and meta-analysis was to summarize the available evidence on the impact of MetS and preoperative hyperglycemia, as an individual component of MetS, on short-term outcome after colorectal surgery. The prevalence of MetS in patients undergoing colorectal surgery is high, exceeding 35% in half of the included studies. The pooled results show that patients with MetS are more likely to develop severe complications after colorectal surgery than those without MetS. Data on other outcomes including CAL, SSI and mortality are less clear and cannot be answered safely by this study. This lack of clear findings is likely due to shortcomings in the existence of only a handful of studies. Nevertheless, these analyses do demonstrate a non-significant trend toward increased risk ratios. Data on the association of preoperative hyperglycemia, as an individual component of MetS, and adverse outcome demonstrates a negative impact on SSI for hyperglycemic patients.

The number of studies that investigated the relationship of MetS and adverse outcome after colorectal surgery is scarce and results are controversial. Only six studies have determined outcomes following colorectal surgery [22–27]. The recorded prevalence of MetS in the six included varied from 7% to 68%. This substantial range in prevalence could explain the inconsistency in showing risks. In general, studies using the AHA criteria to define MetS found a positive association with adverse outcome [26,27], whereas studies using the NCEP ATP III did not [22,23,25]. Furthermore, several studies used modified criteria to define MetS. It is hard to retrieve lipid profiles, waist circumference or FPG levels from retrospective studies, because these are in general not often assessed preoperatively. Together, this emphasizes the need for prospective cohort studies in order to draw definite conclusions on the prevalence of MetS and to adequately compare study results.

Common problems in patients with MetS are endothelial dysfunction and chronic low-grade inflammation [7]. These conditions may not only cause problems in colorectal surgery, but also in several other surgical procedures. In liver surgery, for instance, Bayani et al. found not only an association between MetS and increased postoperative complications - specifically a 70% higher risk of superficial SSI - but also a more than 2-fold increased risk of mortality [35]. In a systematic review and meta-analyses evaluating patients undergoing orthopedic surgery, MetS was a risk factor for postoperative all-cause complications, SSI, urinary tract infection and 30-day re-admissions [36]. Furthermore, Glance et al. reporting on 310.208 patients undergoing non-cardiac surgery, showed substantial higher rates of postoperative complications, including adverse cardiac events, sepsis and wound infections [6]. Taken together with our findings, these observations support the importance of MetS as a risk factor for poorer prognosis after various forms of surgery.

From the perspective of pathophysiology, assuming the prominent role of insulin resistance, treatment of MetS should be aimed at improving insulin sensitivity. Clinical strategies to reduce MetS include energy restriction, macronutrient manipulation (carbohydrate restriction, enrichment in unsaturated fatty acids) and exercise regimens [38]. The preoperative period could optimally be used to carry out these strategies in terms of multimodal prehabilitation including interventions such as exercise, smoking and alcohol cessation, nutritional support and psychological support [39]. Multimodal prehabilitation aims to improve functional capacity and consequently, reduce surgery-associated morbidity and mortality [40], but could also provide as a strategy to modify abnormalities regarding MetS. To date, the impact on MetS has not been studied. However, it has been well established that insulin resistance can be improved by exercise and dietary interventions [41,42]. In an era of a rapidly increasing prevalence of MetS worldwide, it is paramount to improve the knowledge in this subject.

The impact of preoperative hyperglycemia as a single component of MetS on outcome after colorectal surgery cannot be answered clearly by our study. This is due to high heterogeneity in hyperglycemia cut-off values, assessment methods and a heterogeneous range of complications reported by the included studies. Nevertheless, this study demonstrates a significant increased SSI risk for hyperglycemic patients, with and without diabetes, having a random glucose value of more than 140 or 180 mg/dL. Accordingly, preoperative glycemic screening may be advisably in perioperative care.

There are several limitations in the present study. First, considering that this systematic review comprises only observational studies, the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation rating has to be considered very low [43]. Second, results of the included studies were substantially heterogeneous. Most likely due to the variety of definitions of MetS and hyperglycemia that were used and, subsequently, the wide range of prevalences. Unfortunately, we were unable to evaluate the predictive value by MetS definition as only one study stratified analyses by definition. Third, studies reporting on single complications such as CAL and mortality are often underpowered to detect a statistical difference. It might be better to evaluate clinically relevant postoperative morbidity, as determined by a composite outcome measure that summarizes frequency and severity of postoperative outcome. Concerning future research studies, adequately powered studies are needed to draw definitive conclusions. Ultimately, randomized controlled trials should investigate the potential benefit of preoperative interventions to modify metabolic abnormalities.

## 5. Conclusion

In conclusion, both MetS and preoperative hyperglycemia, as an individual component of MetS, seem to have a negative impact on short-term adverse outcome after colorectal surgery. As a result of relatively few studies meeting inclusion criteria and high heterogeneity across studies, evidence is not conclusive. Nevertheless, the present data offers surgeons, who are often not trained to identify metabolic disorders, food for thought. The identification of MetS is nowadays not part of routine preoperative screening, but might guide preoperative treatment strategies in order to enhance recovery and reduce complications.

## Ethical approval

Not applicable.

## Sources of funding

None.

## Author contribution

MR, GS and AL made substantial contributions to conception and study design. MR, CS, and LJ made substantial contributions to the acquisition and/or analysis of data. MR, GS, RR and AL interpreted the data. MR and CS primarily drafted the manuscript. LJ, GS, AL, RR and GS critically revised it for important intellectual content. All authors gave final approval for this version to be published. 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.

## Registration of research studies

1. Name of the registry: Research Registry.
2. Unique Identifying number or registration ID: reviewregistry1134.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/6076dedfbbb92b001d94e19f/

## Guarantor

M. Reudink MD.
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## Consent

Not applicable.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102997.

## Provenance and peer review

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## Data statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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