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Meta-analysis of patient risk factors associated with post-bariatric surgery leak

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Abstract

Objective: Modifiable risk factors such as diabetes, hyperlipidemia, hypertension, obstructive sleep apnea (OSA), chronic kidney disease (CKD), chronic steroid use and smoking, have been shown in observational studies to negatively affect surgical outcomes. The purpose of this study is to identify and determine the effect of modifiable risk factors on post-operative bariatric surgery leak, as pre-operative risk modification has been shown to reduce the impact on complications.

Methods: Electronic literature searches of MEDLINE, PUBMED, OVID and Cochrane Library databases were performed, including a manual reference check, over the period of 2010 and 2020. 620 articles were screened according to the PRISMA protocol.

Results: Twenty articles were included in the meta-analysis of risk factors. Significant risk factors and the associated effect sizes include: 1. Smoking with an overall OR of 1.31 [1.06, 1.61] and an OR of 1.72 [1.44, 2.05] in Sleeve gastrectomy (SG) patient cohorts; 2. Diabetes with an overall OR of 1.23 [1.08, 1.39] and an OR of 1.33 [1.02, 1.73] in Roux-en-Y patient cohorts; 3. Chronic kidney disease with an overall OR of 2.41 [1.62, 3.59] and 4. Steroid use with an overall OR of 1.57 [1.22, 2.02]. Non-significant risk factors include hypertension with an OR of 0.85, 1.83, OSA with an OR of 1.08 [0.83, 1.39] and hyperlipidemia with an OR of 0.80 [0.61, 1.04]. Combined SG and Roux-en-Y patient cohorts with hyperlipidemia have shown a protective effect of 0.78 [0.65, 0.94].

Conclusions: Significant risk factors for leak post bariatric surgery are smoking in all patients and particularly SG patients, diabetes for all patients and particularly Roux-en-Y patients, and CKD and chronic steroid for all patients. Hyperlipidemia in two combined patient cohorts (SG and Roux-en-Y) appears to have a weak protective effect.

KEYWORDS
bariatric surgery, leak, risk factors

1 | INTRODUCTION

The prevalence of obesity in the United States currently affects 1 in 3 adults and is projected to increase to nearly 1 in 2 adults by the year 2030.[1] Similarly, 31.3% of Australians aged 18 and over are affected by obesity, doubling from 4.9% in 1995% to 9.4% in over a decade.[2] Being overweight or obese is the cause of 8.4% of the total burden of disease in Australia and increases the risk of mortality in proportion to the number of years lived with obesity.[3] Bariatric surgery is recommended as the treatment for type 2 diabetes in national and international guidelines,[4,5] which confers benefits from associated metabolic effects.[6] Patients who have undergone bariatric surgery were found to have significant risk reduction of major adverse cardiovascular event such as myocardial infarction (RR = 0.40, 95% CI = 0.30–0.52, $p < 0.001$), stroke (RR = 0.60, 95% CI 0.46–0.79, $p < 0.001$) and cardiovascular death (RR = 0.43, 95% CI = 0.35–0.54, $p < 0.001$).[7]

Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most prevalent bariatric procedures in Australia, accounting for over 70% of weight loss procedures recorded by the Bariatric Surgery Registry in its seventh annual report of 2018/2019.[8] Bariatric surgical procedures provide good total weight loss outcomes and consequent comorbidity improvement, but also carries the risk of post-operative leak.[9] Most large-volume or multi-center series have reported complication rates of less than 2% with decreasing incidence with increasing experience[10] and annual caseload.[11] The impact of leak on patient morbidity and mortality, though rare, is severe.[12] It is the second commonest cause of death in bariatric surgery and its etiology is multi-factorial.[13]

The progression of a post-operative gastric sleeve leak to further complications can be challenging to manage despite early identification and treatment. Numerous well cited publications have elucidated the technical aspects in the prevention of gastric sleeve leak.[14–16] Pre-operative patient risk factors are potentially modifiable and can be considered in conjunction with the employment of various risk-reducing operative techniques. In a multi-disciplinary environment, risk factors can be rationalized as part of an individualized surgical approach in addition to technical and operative considerations. Risk factors identified in previous publications include: current smokers within a 1-year period, hypertension requiring medication, sleep apnea, hyperlipidemia, history of pulmonary embolus, gastro-esophageal reflux disease, cardiac history, end stage renal failure or requiring hemodialysis, vascular risk, previous foregut surgery, severe chronic obstructive pulmonary disease, steroid use for chronic conditions and patient metrics including age, race, sex and operation being considered.[17]

Our study serves to examine the different risk factors that are predictive of post-operative bariatric surgery leaks and quantify the effect size. This is especially important in patients who are awaiting further treatment upon achieving adequate weight-loss or better control of associated comorbidities. Potential renal transplant candidates awaiting placement on the kidney transplantation wait-list with stringent body mass index (BMI) cut-off of less than 30 kg/m^2, can achieve weight-loss and avoid enteric hyperoxaluria post-Roux-en-Y gastric bypass in a multi-disciplinary setting.[18] Care pathways established to manage patients with clinically severe obesity and advanced heart failure have enabled cardiac transplantation, making metabolic surgery a suitable bridge to therapy.[19] Optimization of identified pre-operative factors, when feasible, can lead to improved outcomes post-operatively in increasingly complex patient cohorts.

2 | OBJECTIVES

This study has identified patient risk factors that contribute to post-operative bariatric surgery leak, specifically patient co-morbidities, and non-technical factors. Patient factors can be considered when rationalizing the most appropriate bariatric procedure for personalized surgical care.

3 | METHODS

This study was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. All authors formed a panel to define the study objective, population, intervention, comparator, and outcome (PICO) parameters. The primary authors conducted a literature search according to inclusion and exclusion criteria, performed critical appraisal and extraction of the articles selected for this study.

Systematic computerized searches of the PubMed, Medline, Embase, the Cochrane Library and Google Scholar were undertaken, limiting articles to those published from 2010 to December 2020. The following MeSH search terms were used: “SG”, “gastric bypass”, “bariatric surgery”, “post-operative complications”, “leak” and “risk factors”.

3.1 | Study selection

The following criteria were used for study inclusion: patients who underwent (1) bariatric surgery, (2) who developed post-bariatric surgery leak and (3) whose pre-operative risk factors were analyzed pertinent to the leak.

The authors excluded articles with (1) single risk factor analysis alone, (2) of single institution or single surgeon case series, (3) lack of correlation of leak rates to pre-operative risk factors, (4) lack of reporting raw data or odds ratio (OR), and (5) non-registry cohort studies. These stringent exclusion criteria are due to the low incidence of post bariatric surgery leaks which ranges from 0.5% to 2%.[13] Using a power calculation in R, the sample sizes ranged from 39,244.3 for an incidence of leak of 2% to 627,908.8 for a leak rate of 0.5%, using an alpha of 0.80 and significance level of 0.05 in a two-sided test (Power calculation in Appendix). Exclusion criteria also extended to non-original research, research performed in a simulated environment, non-human subject research and language of publication other than English, without an English abstract. The time band for this search was limited to January 2010 to December 2020 to allow for a contemporary data representation.

After the initial search, duplicates, and non-English studies (without an English abstract) were removed. Articles were assessed for eligibility by the title, abstract and full text. Reference lists and citations of each article were also searched for articles not otherwise identified. Discrepancies in study selection were discussed by the authors to reach a consensus. All retrieved titles, abstracts and full text were managed with reference manager software EndNote® (Version X9, Thomson Reuters).

3.2 | Data collection process

Two authors (C.S. and S.B,.) extracted the data independently from the final eligible publications and compared the results. To avoid bias, discrepancies were adjudicated by a third author. Data was retrieved from full articles using a standardized data collection form. The following data were collected from each study: first author's name, year of publication, number and ages of patients, BMI, risk factors, rate of post-operative SG leak and follow up. The outcome variables included BMI, hypertension (HTN), hyperlipidemia, diabetes (DM), smoking, obstructive sleep apnea (OSA), chronic steroid treatment (CST), chronic kidney disease (CKD), oxygen dependence and therapeutic anticoagulation, where available.

3.3 | Statistical analysis

The forest plots in this meta-analysis were coded and generated using R[20] using the *metafor*() package.[21] Subgroup analysis was performed using code by Wolfgang Viechtbauer.[21] Should more than 10 publications participate in a forest plot, a funnel plot will be generated to check for asymmetry of the CI and subsequently, an Egger's test. The full code is available in the appendix section of this publication.

3.4 | Quality assessment

The methodology quality of the included studies was assessed using the Oxford Center for Evidence-Based Medicine levels of evidence, ranging from 1 (systematic review of RCTs) to 5 (expert opinion). To assess the risk of bias in observational cohort studies, the Methodological Index for Non-randomized Studies (MINORS)[22] was employed. The 12 items were considered, and values were assigned as follows: 0 (not reported), 1 (reported but inadequate), 2 (reported and adequate). The global score is calculated by adding the values of each domain and a grade assigned from A—C where A is ideal or low risk of bias (score >16), B is likely moderate risk of bias and C is likely high risk of bias. The studies shortlisted are summarized in Table 1, and an evidence grid was generated according to its scores in 12 critical domains as seen in Table A1 (Appendix). The name of the first author and year of publication of article were used for identification.

4 | RESULTS

The PRISMA flow diagram for the performed search is detailed in Figure 1. There were 1079 articles collated from the specified literature search with an additional 6 articles identified during the hand search of references. Of these, 254 duplicate, 3 triplicate and 209 non-relevant articles were excluded. 620 abstracts were screened, of which twenty were included in this meta-analysis. Forest plots for available risk factors were constructed based on a 2×2 table of raw data. R program[20] was used to transform the raw data into odds ratios (OR), CI and *p*-values using the *metafor* package.[21] Sub-group analyses were performed according to the type of surgery, and the heterogeneity between publications was calculated for every plot. The final pooled estimate is demonstrated on a risk grid at the bottom panel of the forest plot. Funnel plots could not be generated for every risk factor as it required a minimum of ten studies with each analysis.

4.1 | Smoking

The forest plot as seen in Figure 2 is subjected to sub-group analysis according to procedure: SG, RYGB or both, recognizing the impact of surgery type. Consistently, smoking had demonstrated to be a risk factor for leak in six SG publications with a pooled OR of 1.72 [1.44, 2.05] in the random effects model. Smoking was not found to be a clinically significant risk factor in the RYGB sub-group with an OR of 1.09 [0.84, 1.42] or in the publication by Alizadeh et al[16] in the combined sub-group (OR 0.89 [0.72, 1.11]). The overall effect size in combining all the publications was clinically significant with an OR of 1.31 [1.06, 1.61], with a narrow confidence interval and $p < 0.001$. There are significant differences in the effects sizes of the subgroup analysis ($p < 0.001$).

A funnel plot, as seen in Figure A1 (Appendix), was constructed for the 11 studies in the corresponding forest plot analyzing smoking status as a risk factor. The Eggers test for funnel asymmetry was performed (code and plot in Appendix), with a *p*-value of 0.0936. This suggested that, except for one outlier, the Funnel Plot was relatively symmetrical.

4.2 | Diabetes mellitus (DM)

Diabetes as a risk factor had an overall OR of 1.23 [1.08, 1.39] as seen in Figure 3. Sub-group analysis found that DM was not a significant risk factor in the SG sub-group, where the effect sizes of individual publications had wide CI in smaller patient populations. In

TABLE 1 Publications reporting on post bariatric surgery leak risk factors

Author	Location	Time band	Study type	Surgery	N	BMI (kg/m^2)	Age (years)	Rate of complications	MINORS score
Masoomi et al 2011[12]	United States of America	2006–2008	Retrospective analysis of multi-center database- national inpatient sample	Laparoscopic or open RYGB	RYGB: 226,452	NR	Mean = 43.6	Leak: 0.7%	B 12/16
Haskins et al 2014[13]	United States of America	2005–2010	Retrospective analysis of multi-center database- (ACS-NSQIP)	Laparoscopic or open RYGB	RYGB: 41,445	NR	NR	Leak: NR	B 20/24
Stenberg et al 2014[14]	Sweden	2007–2012	Retrospective analysis of prospective database Scandinavian obesity registry - (SOReg)	Laparoscopic or open RYGB	RYGB: 26,173	42.7 ± 5.43	41.2 ± 11.03	Leak: 1.8%	B 21/24
Andalib et al 2016[15]	United States of America	2005–2013	Retrospective analysis of multi-center database—(ACS-NSQIP)	AGB, SG, RYGB or BP-DS	114,169 AGB: 26,087 SG: 21,048 RYGB: 65,509 BPDS: 1525	46.37 ± 7.82	44.81 ± 11.62	Leak: 0.58%	B 18/24
Saleh et al 2016[16]	Canada	2009–2011	Retrospective analysis of prospective database—Ontario bariatric network (ONB)	SG or RYGB	SG: 416 RYGB: 4591	NR	44.6 ± 10.3	Leak: SG- 0.96% RYGB- 0.83%	B 13/16
Nienhuijs et al 2016[17]	The Netherlands	2006–203	Retrospective analysis of Catharina hospital bariatric database	Laparoscopic SG	SG: 1041	46.37 ± 7.82	44.8 ± 11.62	Leak: 0.02% Overall: NR	C 15/24
Sánchez-Santos et al 2016[18]	Spain and Portugal	2006-2012	Retrospective multicentre cohort study	Laparoscopic SG	SG: 2882	48.4 ± 9.18	43.9 (14–74)	Leak: 0.02% Overall: 11.7%	C 10/16
Stroh et al 2016[19]	Germany	2005-2013	Retrospective analysis of prospective database—German bariatric surgery registry (GBSR)	Laparoscopic SG	SG: 11,800	F: 51.3 ± 9.6 M: 52.8 ± 9.7	43.7 ± 11.4 (8–79)	Leak: 1.5% Overall: 4.5%	C 6/16
Benedix et al 2017 (same as 2014)[20]	Germany	2005-2014	Retrospective analysis of prospective database—(GBSR)	Laparoscopic SG	SG: 15,756	52.2 ± 9.3	43.7 ± 10.9	Leak: 1.6%	C 18/24
Cesana et al 2017[21]	Italy	2008–2016	Retrospective analysis of multi-center prospective database	Laparoscopic SG	SG: 1738	42.3 (IQR: 38.3-47.1) 43.5 ± 7.2	Median 41.0 (IQR: 33.0-49.0) Mean: 41.2 ± 11.1	Leak: 2.8%	B 14/16

TABLE 1 (Continued)

Author	Location	Time band	Study type	Surgery	N	BMI (kg/m^2)	Age (years)	Rate of complications	MINORS score
Dhar et al 2017[22]	United States of America	2015	Retrospective analysis of prospective database - metabolic and bariatric surgery accreditation and quality improvement program (MBSAQIP)	Laparoscopic SG	SG: 98,292	NR: 3643 (4.1%) 35–39: 20,790 (23.4%) 40–49: 45,044 (50.7%) 50–59: 14,837 (16.7%) 60–69: 3287 (3.7%) ≥70: 1244 (1.4%)	18–29: 9752 (11.0%) 30–39: 22,319 (25.2%) 40–49: 25,910 (29.2%) 50–59: 20,208 (22.7%) ≥60: 10,547 (11.9%)	Leak: 0.3% Overall: 4.5%	B 13/16
Alizadeh et al 2018[8]	United States of America	2015	Retrospective analysis of prospective database - (MBSAQIP)	Laparoscopic SG or RYGB	SG: 92,495 RYGB: 40,983	M/F: 45.7 ± 9.5	45.0 ± 12	Leak: 0.7% Overall: NR	B 13/16
Kumar et al 2018[23]	United States of America	2015	Retrospective analysis of prospective database - (MBSAQIP)	Laparoscopic SG or RYGB	SG: 93,062 RYGB: 41,080	LSG: 44 (40–49) RYGB: 45 (41–51)	LSG: 44 (35–53) RYGB: 45 (36–54)	Leak: SG- 0.76% RYGB- 1.55%	B 21/24
Afraz et al 2019[24]	United States of America	2015—2017	Retrospective analysis of prospective database - (MBSAQIP)	Laparoscopic SG or RYGB	430,936	O2 dep: 45.3 ± 7.9 NO2 dep: 50.7 ± 10.4	O2 dep: 44.5 ± 12 NO2 dep: 55.0 ± 10.3	Leak: O2 dep: 0.41% NO2 dep: 0.69%	B 21/24
Hefler et al 2019[25]	United States of America	2015—2017	Retrospective analysis of prospective database - (MBSAQIP)	Laparoscopic SG or RYGB	430,936 SG: 308,296 RYGB: 115,426	Non-IC: 45.4 ± 7.9 IC: 45.2 ± 7.9	Non-IC: 44.5 ± 12 IC: 48.5 ± 11.2	Leak: 0.4% Overall:	B 20/24
Mazzei et al 2019[26]	United States of America	2015—2016	Retrospective analysis of prospective database - (MBSAQIP)	Laparoscopic SG or RYGB	SG: 280,767	47.35	44.6–48.8	Leak 0.3%–0.6%	B 20/24
Mocanu et al 2019[27]	United States of America	2015—2016	Retrospective analysis of prospective database - (MBSAQIP)	Laparoscopic RYGB	RYGB: 77,596	46.3 ± 8.17	45.2 ± 11.9	Leak: 0.6% Overall: 7.5%	B 14/16
Vidarsson et al 2019[28]	Sweden	2015—2016	Retrospective analysis of prospective database Scandinavian obesity registry - (SOReg)	Laparoscopic RYGB	RYGB: 40,844	NR	NR	Leak: GEJ 0.6%	C 7/16

(Continues)

TABLE 1 (Continued)

Author	Location	Time band	Study type	Surgery	N	BMI (kg/m^2)	Age (years)	Rate of complications	MINORS score
Janik et al 2020[29]	United States of America	2015–2016	Retrospective paired analysis of prospective database - (MBSAQIP)	Laparoscopic SG or RYGB	SG: 29,165 pairs RYGB: 29,165 pairs	Smoker: 46.0 ± 7.6 Non-smoker: 45.7 ± 7.8	Smoker: 41.7 ± 10.8 Non-smoker: 41.5 ± 11.6	Leak: Smoker- 0.59% Non-smoker- 0.32%	B 20/24
Yuce et al 2020[30]	United States of America	2012–2017	Retrospective analysis of multi-center database- (ACS-NSQIP)	Laparoscopic SG or RYGB	133,417	Smoker: 24.3 ± 10.7 Non-smoker: 27.9 ± 11.9	Smoker: 46.2 ± 8.2 Non-smoker: 45.5 ± 8.0	Deep space SSI: Smoker: 0.6% Non-smoker: 0.3%	C 19/24

MINORS Score: A (16/16 or 24/24); B (≥12/16 or ≥20/24); C (<12/16 or <20/24).

Abbreviations: AGB, adjustable gastric band; BP-DS- biliopancreatic duodenal switch; LAGB, laparoscopic adjustable gastric band; NR, not reported; RYGB- Roux-en-Y gastric bypass; SG-sleeve gastrectomy.

the RYGB sub-group, the demonstrated OR was 1.33 [1.02, 1.73]. The differences between sub-groups were not significant ($p = 0.61$) for the random effects model.

4.3 | Hypertension (HTN)

Hypertension has not been shown to increase the risk of leak when the effect sizes were pooled with an OR of 1.25 [0.85, 1.83] as seen in Figure 4. In the combined sub-group, the OR is modestly increased with an OR of 1.15 over a narrow CI [1.09, 1.21], indicating a small but significant effect. The differences between sub-groups were not significant ($p = 0.53$) for this random-effects model.

4.4 | Obstructive sleep apnea

Fewer publications reported on OSA as a risk factor for leaks post bariatric surgery. The forest plot shown in Figure 5 Demonstrated that OSA was not clinically significant as a risk factor for leaks (OR 1.08 [0.83, 1.39]), and groups were not significantly different in sub-group analysis ($p = 0.81$).

4.5 | Hyperlipidemia

Hyperlipidemia had not been shown to a significant affecting post bariatric surgery leak. Figure 6 Shows that two publications reported on pooled outcomes of RYGB and SG,[23,24] demonstrating a clinically significant and protective effects size of 0.78 [0.65, 0.94]. However, when combined with Mocanu's[25] and Masoomi's[24] publications, the pooled effects size was not significant (OR 0.80 [0.61, 1.04]). The groups were significantly different in sub-group analysis ($p = 0.01$).

4.6 | Chronic kidney disease

Chronic kidney disease was considered as a risk factor for post-operative leak in three publications[24,26,27] as in Figure 7. The pooled effect size across the three patient cohorts was clinically significant (OR 2.41 [1.62, 3.59]) and the groups were not significantly different in sub-group analysis ($p = 0.85$).

4.7 | Chronic steroid use

Chronic steroid use had been considered as a risk factor for developing a leak post bariatric surgery by three publications[25,28,29] as in Figure 8. The pooled effects size across the three patient cohorts was clinically significant (OR 1.57 [1.22, 2.02]) and the groups were not significantly different in sub-group analysis ($p = 0.34$).

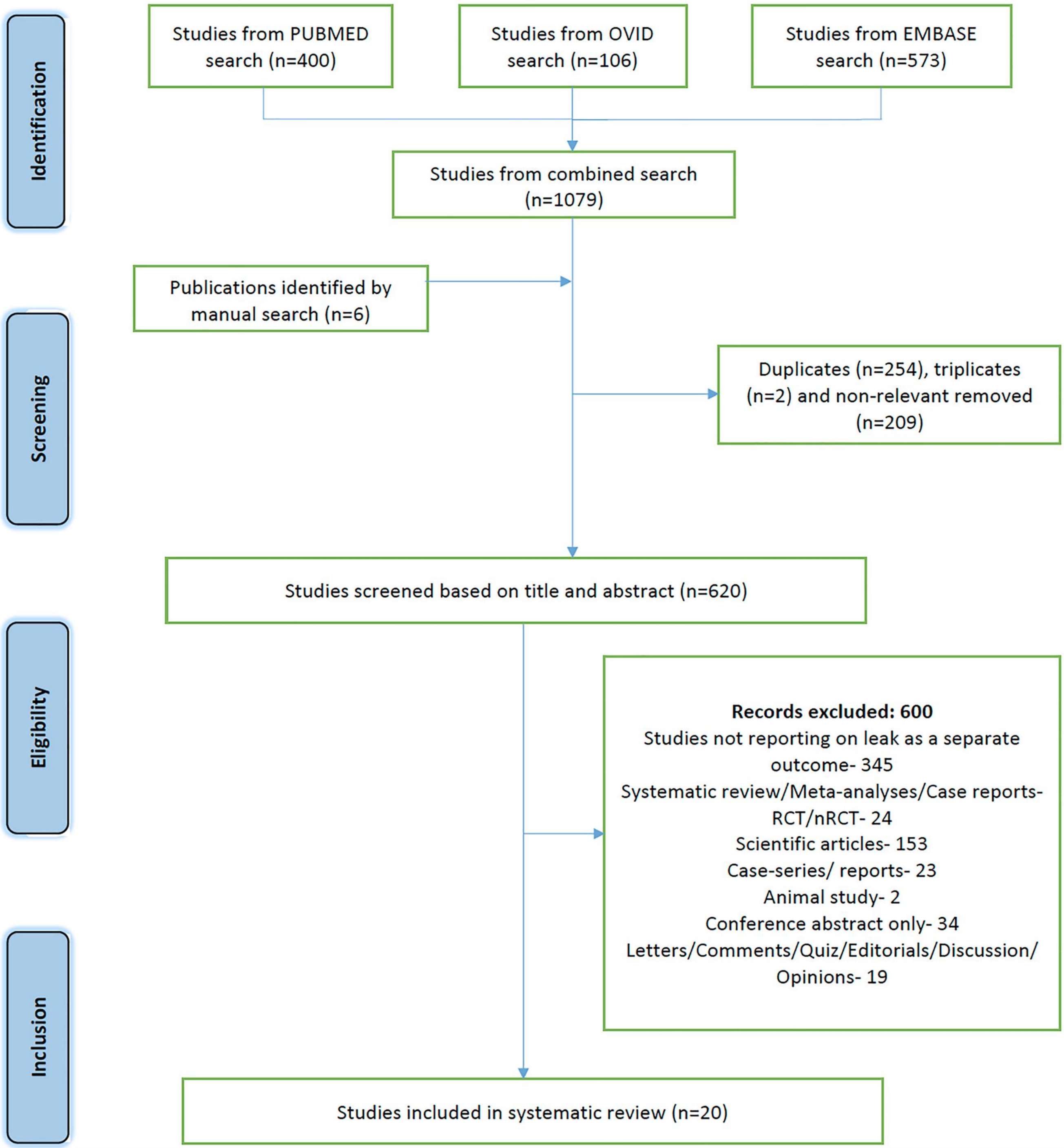

FIGURE 1 PRISMA diagram

5 | DISCUSSION

Bariatric surgery is an efficient means of treating clinically severe obesity, affording most patients durable and predictable weight loss and resolution of comorbidities.[30,31] Safety has improved in bariatric surgery over time as procedures become more standardized with the aid of consensus between surgeons and representative bodies.[32,33] Indications for bariatric surgery as treatment continue to expand to include complex patients[34] and adolescents.[35] As obesity surgical management increases in prevalence, complications become a greater consideration, as we hope to give our patients a better quality of life post-surgery. Post-operative bariatric surgery leaks, although rare, are indeed highly morbid and can affect patient outcomes severely. This publication sought to clarify the risk factors and the associated effect sizes which can allow for pre-operative optimization. Risk reduction is in keeping with current instituted bariatric surgical practices like observing a pre-operative very low energy diet and using adjunct

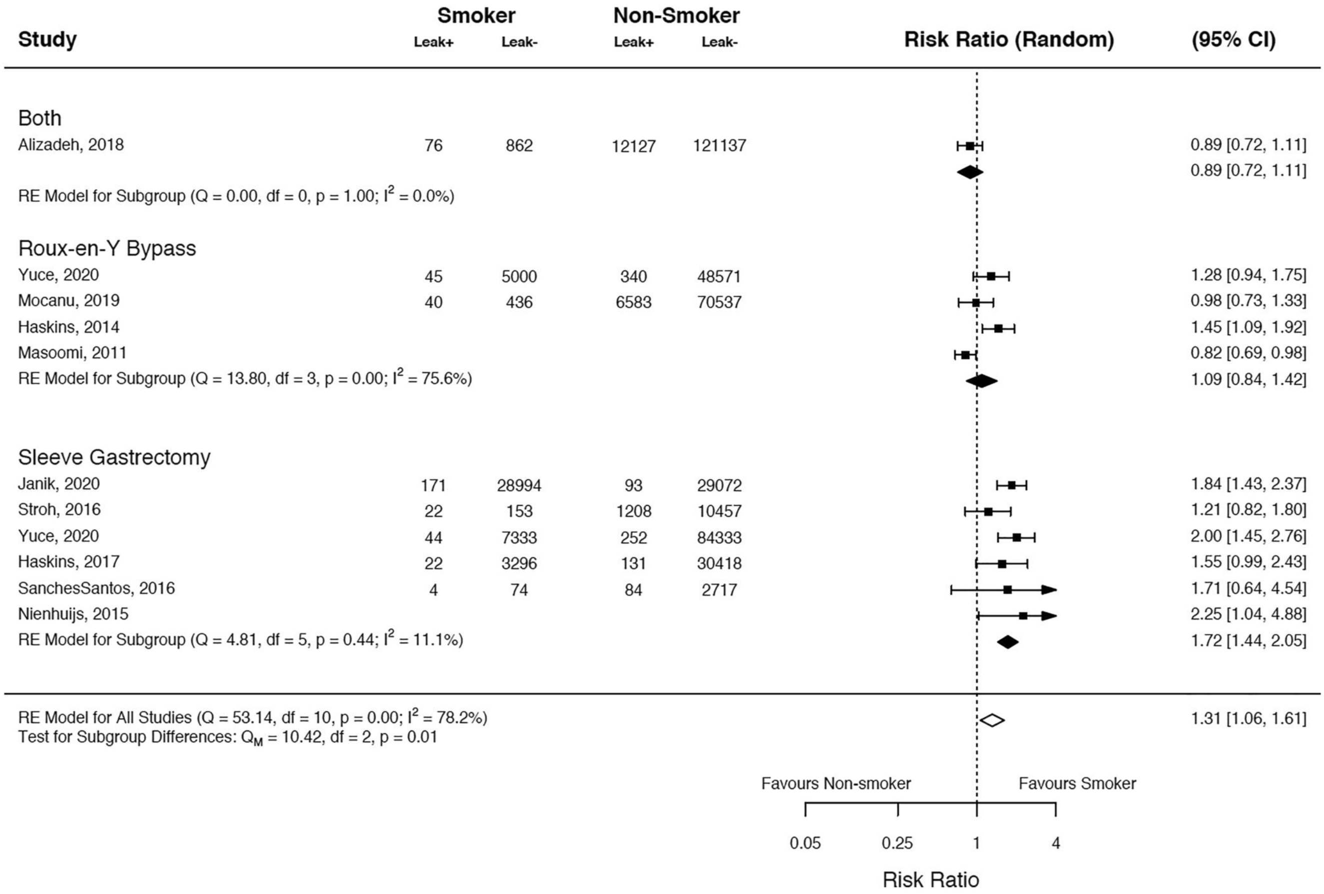

FIGURE 2 Forest plot of multi center publications reporting on the incidence of postoperative leak according to smoking status

surgical techniques to minimize the risk of injury, hemorrhage or staple line disruption.

Earlier publications have identified pre-operative risk factors including limitations in mobility, coronary artery disease, age above 50 years, pulmonary disease, male gender and smoking history as reported by Finks et al of the MBSAQIP database,[36] and similarly by Gupta et al[37] and Maciejewski et al[38] of the ACS-NSQIP database. In an up-to-date iteration of the MBSAQIP analysis, Grieco et al[17] developed a 30-day risk calculator based upon the demographics and outcomes of over 700,000 patients in the United States of America. This calculator is a useful and important tool, and some of the parameters were, unsurprisingly, identified by our meta-analysis as risk factors for post-operative complications. The considered risk factors were: current smoker within 1 year, hypertension requiring medication, sleep apnea, hyperlipidemia, history of pulmonary embolus, gastro-esophageal reflux disease, cardiac risk, dialysis, vascular risk, previous foregut surgery, severe chronic obstructive pulmonary disease, steroid use for chronic condition and patient metrics including age, race, sex and operation being considered.[17] The overlap in the risk factors identified is reflective that the factors that affect tissue healing also contribute to post-operative leaks.

Smokers had been found to have an increased risk in developing post-operative leak undergoing a SG with an OR of 1.71 [1.44, 2.05] compared to those undergoing a laparoscopic RYGB, 1.09 [0.82, 1.42]. It is interesting to note that when combining these effect sizes, the OR was 1.31 [1.06, 1.61], which could be a product of the SG being a more commonly performed procedure than RYGB, and therefore overwhelming the non-significant effect size of smoking on RYGB in developing post-operative leak. The exposure of toxic compounds from smoking causes increased oxidative stress, inflammation and atherogenesis thereby inducing apoptosis of vascular endothelial cells, which leads to vascular dysfunction.[39] Nicotine is a potent vasoconstrictor through endothelium-dependent and endothelium-independent mechanisms.[40] It also causes vascular remodeling leading to arterial stiffness and decreased compliance.[41] Nicotine affects the gastric mucosa by inhibiting mucous synthesis, impairing angiogenesis and promoting gut ischemia by altering its microvasculature,[42] in addition to the relative hypoxia and hypercoagulability caused by chronic carbon monoxide exposure.[43] Smoking thus, renders a new gastric staple-line susceptible to non-healing of the staple line, especially in areas of relative ischemia proximally, in keeping with current The American Society for Metabolic and Bariatric Surgery guidelines.[44]

The potential manifestation of mucosal injury in RYGB patients is marginal ulcers, which have not been considered in this meta-analysis due to lack of comparative data and selection criteria that is,

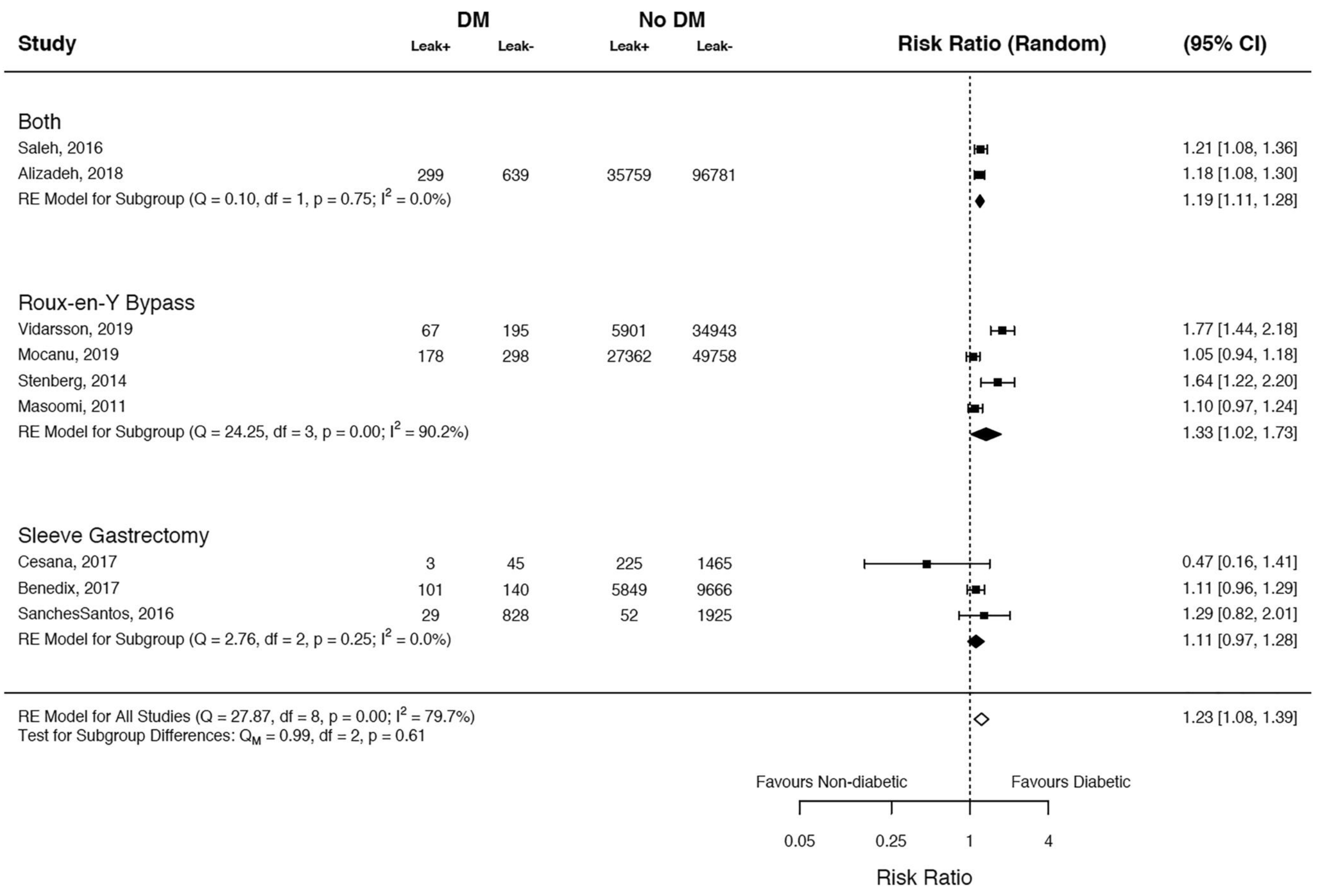

FIGURE 3 Forest plot of multi center publications reporting on the incidence of postoperative leak according to diabetes status

perforated marginal ulcer manifesting as a leak. For patients in whom smoking may be a concern, SG carries a higher risk than a Roux-en-Y gastric bypass, and a longer gastric pouch has an increased risk of ulceration.[45] Factors associated with metabolic syndrome tended to exert a small but significant effect, which can be compounded in patients with multiple comorbidities.

Diabetic status had not increased the risk of post-operative leak in SG patients (OR = 1.11 [0.97, 1.28]), however, in cohorts including RYGB patients the effect size was found to be significant with an OR of 1.33 [1.02, 1.73]. It is important to note, however, that the effect sizes of two of the four studies[24,25] reporting on DM status affecting leak post RYGB were not significant. Both publications had substantial patient populations of 77,596 and 226,452. In patient cohorts where outcomes of both RYGB and SG patients were combined, the effect size was still significant, albeit over a narrower interval 1.19 [1.11, 1.28]. Data was not available to study the effect of insulin dependence or Hba1c control on post-operative leak. The duration of diabetes and therefore the impact on microvasculature in surgical healing, should be a consideration but is under-reported. Diabetic murine models of injury have demonstrated that reduced nascent microvasculature, delayed pruning and refinement of new capillary beds, impairment of capillary maturation resulted in tortuous capillaries and tissue hypoxia.[46] To improve neo-angiogenesis and tissue healing, monitoring Hba1c and optimized blood glucose level control may be helpful. Patients with poorly controlled diabetes or lacking optimal management may benefit from engaging physicians or endocrinologists in the pre-operative for optimisation.

During the initial statistical analysis, hypertension did not appear to increase the risk of leak in patients undergoing SG (1.60 [0.70, 3.63]) or RYGB (0.97 [0.61, 1.54]). Re-analysis of the studies identified an outlier study by Masoomi et al[24] as seen in Table A2 (Appendix), which prompted a repeat analysis of HTN as a risk factor for patient populations including RYGB as the primary bariatric procedure. To perform the analysis without conflating the effect sizes from MBSAQIP populations included, only one MBSAQIP publication dataset was included. The result can be seen in Figure A1 (Appendix), which demonstrates that HTN as a risk factor confers a risk ratio of 1.17 [1.10, 1.24]. This risk ratio is again both narrow and significant. The publications included in our meta-analysis did not distinguish patients with or without hypertension-mediated organ dysfunction, which is an umbrella term covering renal impairment, cardiovascular and cerebrovascular disease.[47] Hypertension is an established risk factor for cardiovascular disease and cerebrovascular events and is an established risk factor for post-operative morbidity and mortality.[48–50] The term "hypertension" broadly covers patients in varying stages or severity of hypertension, which makes analysis of hypertension as a risk factor for post-operative leak difficult. This categorization confers heterogeneity to the data presented in this

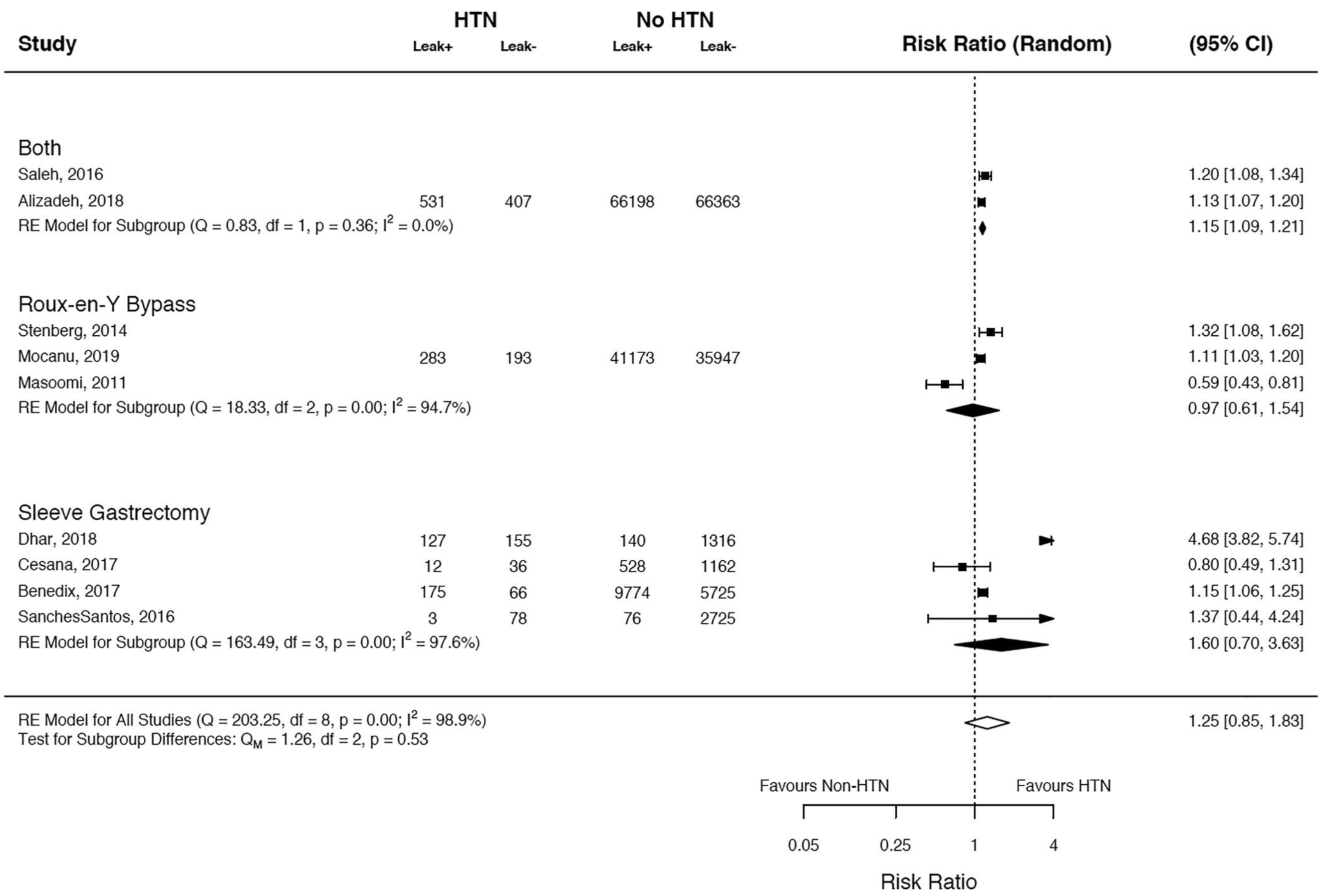

FIGURE 4 Forest plot of multi center publications reporting on the incidence of postoperative leak according to hypertensive status

publication and diminishes its true effect size in patients who have more severe grades of hypertension. In general half of patients with pre-operative hypertension achieve clinical blood pressure measurements of 140/90 mmHg.[51] Whilst there is little evidence supporting the delay of elective surgery for class I or II hypertension patients,[47,52] the extremes of blood pressure are predictive of poorer post-surgical outcomes.[47] In a multi-disciplinary setting, patients being considered for bariatric surgery can be assessed by a bariatric physician who can initiate or optimize treatment as well as assess for cardiovascular risk factors.

The strongest risk factor for post-operative leak is CKD with an OR of 2.41 [1.42, 3.99]. Chronic kidney disease is most commonly caused by DM followed by HTN, which can be viewed as one of the end-stage manifestations of both of these disease processes. The severity of CKD can cause proteinuria, edema and protein malnutrition in the earlier stages (Stage 1–3) and in more advanced stages (Stage 4–5) substantial edema, electrolyte abnormalities, acid-base disorders, relative tissue hypoxia anemia, and secondary or tertiary hypoparathyroidism.[53] Consequent uremia affects the tissue healing of human mesenchymal cells,[54] which can further compound the pathophysiology of advanced kidney disease. It would have been of interest to have enough data to subdivide CKD patients into dialysis and non-dialysis dependent patients. When offering a bariatric procedure in patients with CKD, the complication profile, operative technique and use of safe guards such as leak testing, drains and intra-operative perfusion studies could be considered with the patient and with colleagues in a multi-disciplinary setting.

Patients on chronic steroids also had an increased risk of post-operative leak with an OR of 1.57 [1.22, 2.02], which is in keeping with the hypothesis that steroids affect tissue healing by modulating the cellular signaling involved in angiogenesis.[55,56] Concurrent use of other immunosuppressive agents as well as immuno-modulators could not be considered due to lack of data within our search criteria and may impact further on tissue healing. The chronicity of steroid usage may also impact on tissue healing as it changes the ratio of type I and III collagen, reduces the migration of macrophages and impedes tissue modeling.[57] Patients on CST are also a heterogeneous population with differing disease processes like auto-immune conditions or status post-orthotic organ transplantation, adds to the difficulty of determining the effect of chronic steroid therapy versus the treated primary pathology. Rationalizing immunosuppressive treatment or the weaning period pre-operatively can be attended in conjunction with the treating rheumatologist or specialist physician, in a bid to improve tissue healing in the post-operative period. The authors could not identify an adequate number of publications that reported on the use of non-steroidal medication on the development of post-operative leak in patients undergoing bariatric surgery to be included for meta-analysis.

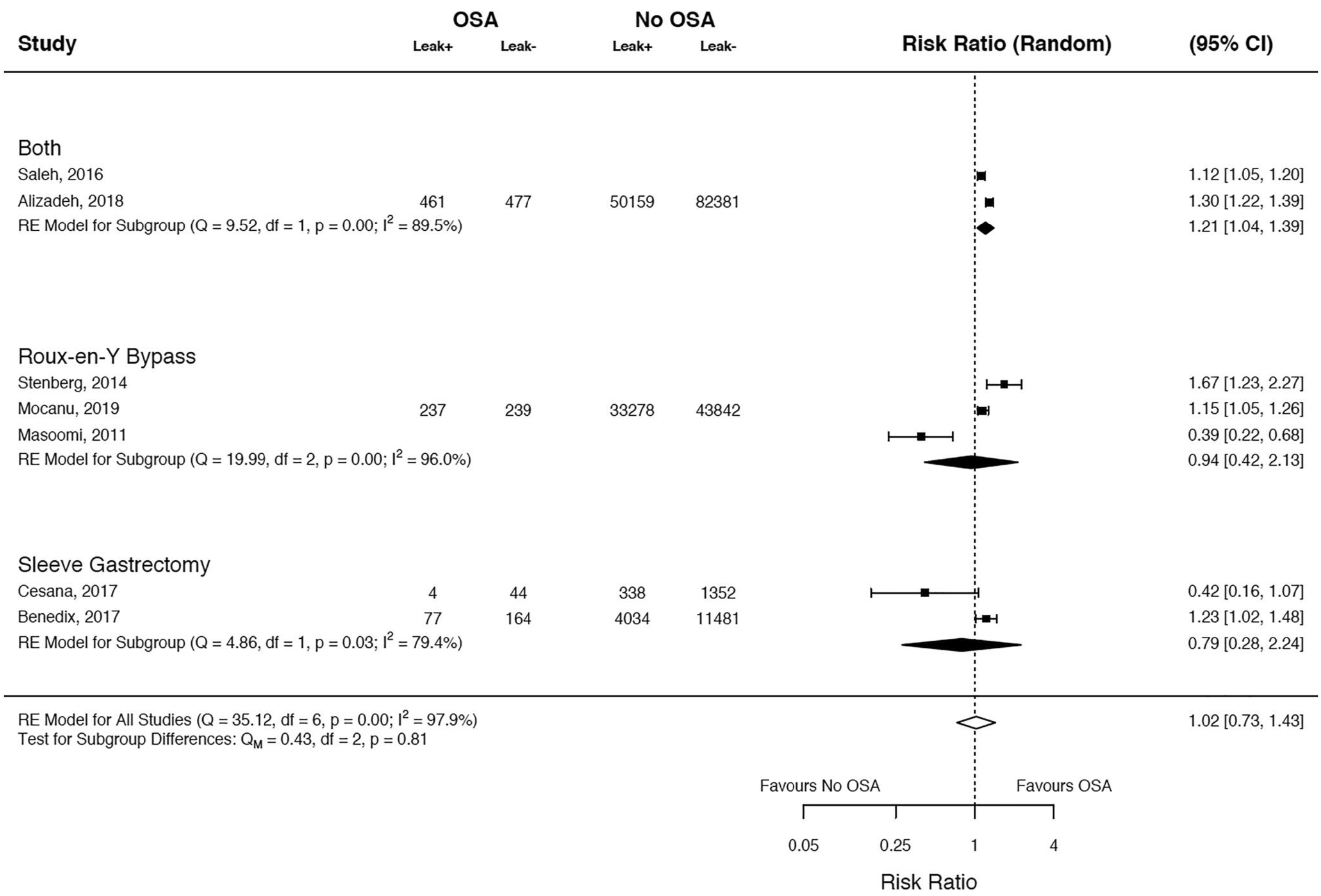

FIGURE 5 Forest plot of multi center publications reporting on the incidence of postoperative leak according to obstructive sleep apnea (OSA) status

Obstructive sleep apnea was only found to be significant in the subgroup analysis including both SG and RYGB with an OR of 1.21 [1.10, 1.33], which is difficult to interpret when other publications did not report a significant relationship. Our literature search has not identified publications on the use of positive pressure ventilation affecting the outcomes post bariatric surgery, though this is a topic the authors found of interest. The utilization of CPAP and the settings at which the machine was used was not able to be analyzed in this meta-analysis, and the negative effects of positive airway ventilation have been refuted in an earlier publication.[58] Hyperlipidemia was found to be a protective factor in the same publications by Alizadeh et al[16] and Saleh et al[27] with an OR of 0.78 [0.65, 0.94]. This protective effect, however, was not demonstrated when combining other relevant publications.

The power calculation performed suggested that patient cohorts of 392,443–627,909 would be required to adequately analyze post-operative leak patients at an incidence of 2% and 0.5% respectively. As such, the studies identified were largely skewed in geography, due to the establishment of large databases like ACS-NSQIP and MBSAQIP. Our publication has been inclusive of multi-center publications to examine a variety of pooled effects sizes in different countries. The databases with associated publications available for analysis were few, and it was difficult to get a fair representation across the different institutions globally. The funding and effort required for the upkeep of large databases may be reflective on the affluence and size of the surgical center, which could be a factor in less endowed health systems and the lack of resulting publications. The small number of publications included in our meta-analysis did not allow for funnel plot generation for each risk factor as more than ten publications were required to do so. The results of this analysis, though significant, did not allow for the establishment of a risk calculator. This is due to the heterogeneity identified in some of the sub-group analyses and the study design could not assess if individual risk factors are actually correlated with post-operative leak or exert a compounding effect. Analyses of multiple databases with machine learning can help generate a best fit model that can be validated with a test population to give the most accurate and meaningful risk calculator.

As databases are prospective with retrospective analysis, there is potential bias and confounding factors. It is assumed that the ethics involved in blinding and randomization diminishes the quality of the evidence presented by this meta-analysis. The authors are cognisant of other factors that may affect choice of operation and access to care such as patient and surgeon preference, the healthcare structure of the country of publication, and the medical industrial regulations specific to each country that can affect choice of surgical instruments and adjunctive treatments. As a result, heterogeneity

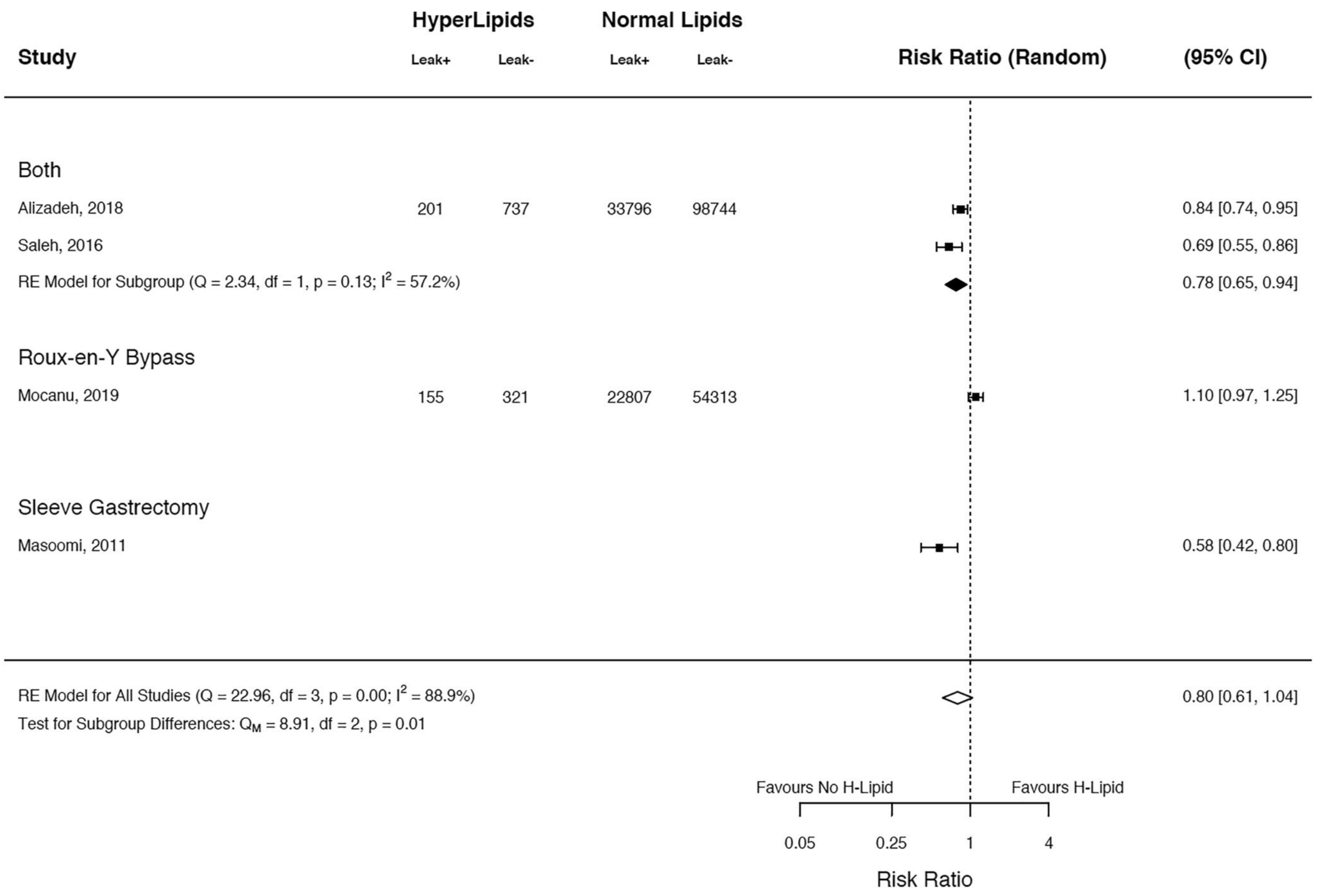

FIGURE 6 Forest plot of multi-center publications reporting on the incidence of postoperative leak according to hyperlipidemia status

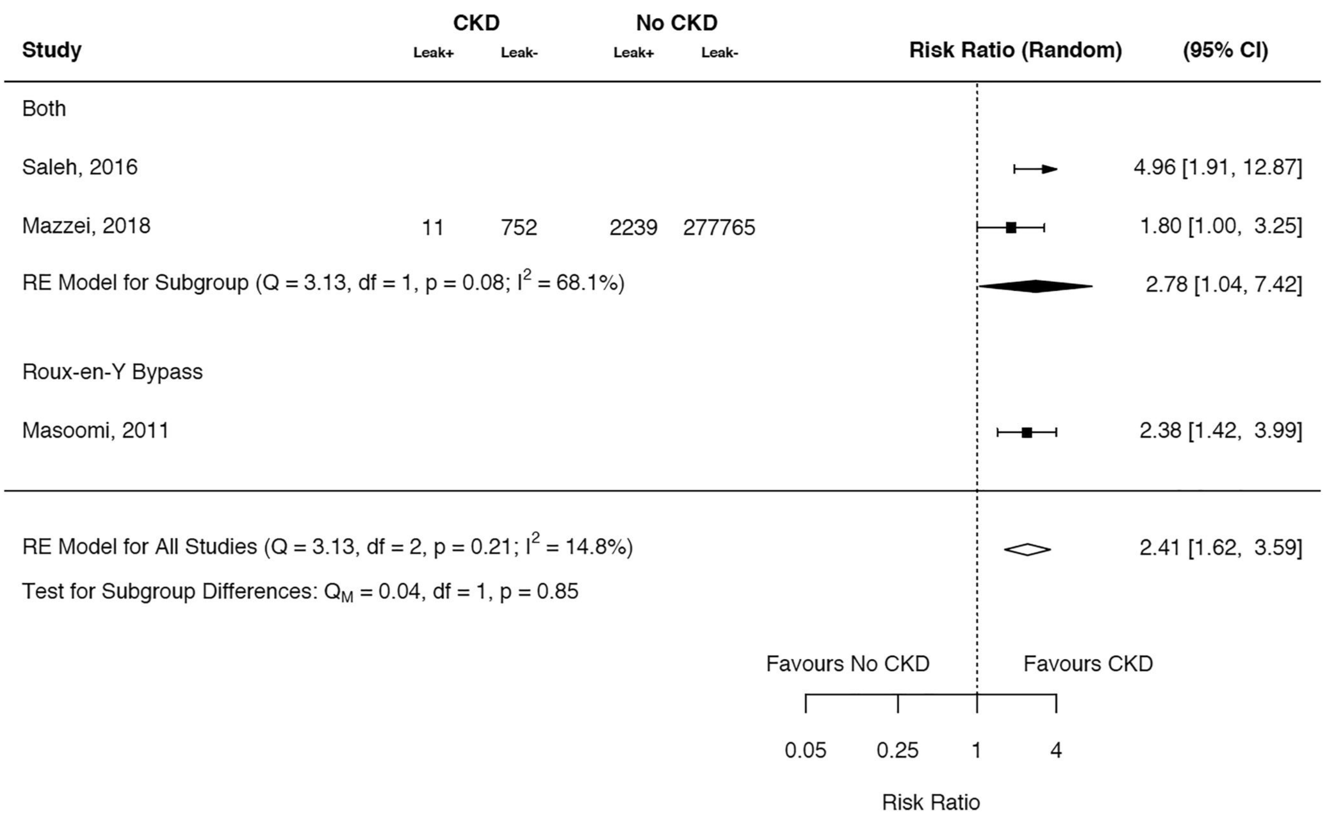

FIGURE 7 Forest plot of multi center publications reporting on the incidence of postoperative leak according to chronic kidney disease (CKD) status

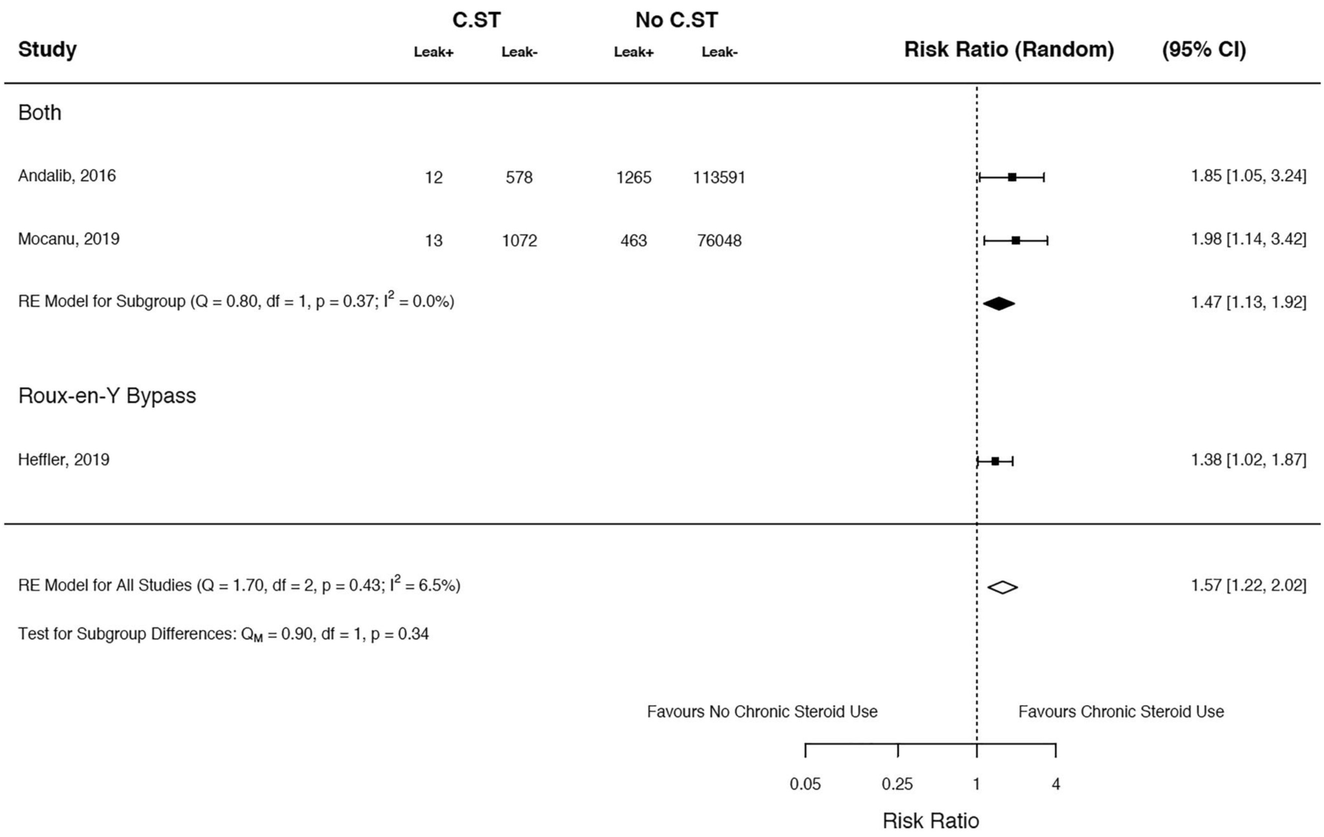

FIGURE 8 Forest plot of multi center publications reporting on the incidence of postoperative leak according to chronic steroid use status

was present in several analyses, which is to be noted when interpreting results. Large cohorts of patients were required to identify the true effect size of patient factors due to the relatively rare occurrence of post-operative leaks.

There is of course a positive publication bias and a lack of reporting of negative results, that can be seen even in the publications selected for this meta-analysis. Factors that were not significant were often not assigned a value or reported as "not significant". The authors have attempted to incorporate non-significant results into the meta-analyses to give a comprehensive assessment on the effect size. There were multiple publications on the same database (MBSAQIP) by different authors, so care needed to be taken to ensure that only one patient cohort in a single time band was represented in each forest plot.

Smokers undergoing SG have an increased risk of post-operative leak compared to smokers undergoing Roux-en-Y gastric bypass. Considering a relatively safer procedure such as RYGB with a shorter pouch, may be reasonable but there is no direct evidence to support this. Patients with metabolic syndrome also have an increased risk regardless of the procedure undergone as each condition associated with metabolic syndrome exerts a small but significant standalone risk factor. Optimization of diabetic factors may improve patient outcomes in either SG or RYGB patients. Validation studies of the treatment of risk factors on post-operative complications would be helpful in terms of patient selection or deferring surgery. Patients with chronic conditions, such as CKD and conditions associated with chronic steroid use, also have an increased risk of post-operative leak, which affects patients undergoing either SG or RYGB. In heavily comorbid patients, a simpler procedure with a smaller risk profile may be the more practical solution.

AUTHOR CONTRIBUTIONS

Calista Spiro: Conceptualization; Methodology; Software; Formal analysis; Investigation; Writing- Original Draft and Review and Editing. **Simon Bennett**: Data curation; Investigation; Writing- Original draft preparation. **Kiron Bhatia**: Supervision; Writing- Reviewing and Editing; Project administration.

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C. Spiro and S. Bennett conducted the systematic review, hand search and meta-analysis. C. Spiro performed the statistics of the meta-analysis using code provided by the metafor() package on the data science platform, R. K. Bhatia oversaw the PRISMA process, reviewed all of the abstracts and full-text articles. All authors were involved in writing the paper and had final approval of the submitted and published versions. This publication received no external funding. Dr Bhatia has agreements with Device Tech and Apollo. Dr Spiro was the Johnson & Johnson industry funded fellow for the year of 2020 and 2021 at the Austin and Repatriation Hospitals. Dr Bennett has no agreements to declare.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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