scientific reports

OPEN

The Metabolic Effects and Effectiveness of the Different Reconstruction Methods used in Gastric Cancer Surgery: A Systematic Review and Meta-Analysis

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Gastric Cancer (GC) is the fifth most common cancer worldwide. Early stages of GC began being detected, giving rise to a new concern, Quality of Life. This study aimed to systematically assess the effects of different GC reconstruction techniques on postoperative type 2 diabetes mellitus (T2DM), hypertension (HBP), and body mass index (BMI) reduction rate and to provide an overview of recent research on oncometabolic surgery (OS). We performed a systematic review and meta-analysis by searching three databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We performed a meta-analysis of risk ratios and mean differences to estimate the impact of duodenal bypass, Roux-en-Y reconstruction, and residual stomach on T2DM, HBP, and BMI reduction rate. Heterogeneity was assessed using the I^2 statistics. At the end of the follow-up, the duodenal bypass group compared to Billroth I had a significantly higher postoperative remission of T2DM and HBP, with a relative risk (RR) of 1.43 (95% confidence interval (95% CI) [1.27; 1.62]) and 1.3 (95% CI [1.00; 1.69]), respectively. Compared with the Billroth II group, Roux-en-Y reconstruction had significantly greater T2DM remission after gastrectomy (RR = 1.19; 95% CI [1.08; 1.31]), while HBP showed no significant differences. Regarding the improvement of HBP, total gastrectomy was significantly superior to subtotal gastrectomy (95% CI [1.01; 2.64]). A trend towards Roux-en-Y Esophagojejunostomy as the best option for T2DM remission was observed (95% CI [0.98; 2.77]; $p = 0.06$). Gastrectomy with Roux-en-Y reconstruction appears to be the most effective treatment for T2DM remission. Further research is needed to assess the impact of OS on metabolic diseases.

Keywords Oncometabolic surgery, Gastric cancer, Gastrectomy, Gastric bypass, Metabolic diseases, Metabolic syndrome

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Gastric Cancer (GC) is the fifth most common cancer worldwide and the fourth leading cause of cancer-related deaths[1]. The standard treatment for gastric carcinoma remains radical resection with total or subtotal gastrectomy[2,3].

The implementation of national screening programs made it possible to identify patients in the early stages of the disease, leading to a decline in GC mortality rates[4,5]. With the rise in life expectancy of patients with GC, a new health factor has emerged: Quality of Life. This topic is particularly important for patients with concurrent chronic diseases such as type 2 diabetes mellitus (T2DM), hypertension (HBP), and dyslipidaemia[6].

Traditionally, bariatric surgery has been used to treat morbid obesity. However, it rapidly became clear its effectiveness in treating chronic comorbidities in obese patients, such as T2DM, dyslipidaemia, and HBP. These conclusions gave rise to the concept of Metabolic Surgery[7].

Recently, based on the similarities between GC and bariatric surgery (including gastric resection and foregut bypass), surgeons have hypothesized that GC surgery could have beneficial effects on glycemic control. These findings led to the emergence of "Oncometabolic Surgery"[8], a dual-purpose surgery with the potential to treat oncologic conditions while simultaneously improving patients' quality of life by ameliorating chronic metabolic diseases with debilitating consequences[9].

The primary purpose of this systematic review and meta-analysis was to provide an overview of recent research findings on oncometabolic surgery (OS). The second goal was to evaluate whether GC surgery helps oncologic patients improve their metabolic status. Additionally, we sought to assess the most suitable reconstructive technique for achieving the best metabolic profile.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10].

Eligibility criteria

We included all observational studies and randomized controlled trials analyzing patients that underwent gastrectomy for GC with concurrent metabolic diseases (T2DM, HBP, visceral fat, and dyslipidaemia).

We included studies assessing the outcomes of complete or partial remission of T2DM and HBP, body mass index (BMI) reduction rate, visceral and subcutaneous fat reduction rate, changes in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG).

We excluded studies with small sample sizes (i.e., less than ten patients) or those that did not specify the reconstruction method used. All the reports identified as animal trials, editorials, correspondence, video reports, reviews, or meta-analyses were excluded. We did not apply a language restriction.

Information sources and search strategy

We searched three databases (PubMed, Scopus, and Web of Science) through December 2023. This search was conducted using the following Query: ((Bariatric Surgery) AND (Gastric Cancer)) OR (Oncometabolic). This Search Query was reinforced by a Grey Literature.

Study selection and data collection process

The study selection was divided into two phases. In the screening phase, after duplicate removal, each study was independently assessed and selected by title and abstract reading by two reviewers (MC, CO). In the second phase, study selection was based on full-text reading. Any disagreements were resolved by a third researcher (HSS).

Regarding the data collection process, both reviewers (MC, CO) extracted data from the selected articles separately using a predesigned data extraction sheet developed according to the Cochrane Handbook[11]. For each study, the following information was extracted: authors' identification, year of publication, country, study design, number of participants, follow-up, participants' inclusion and exclusion criteria, general characteristics of the participants (age, gender, mean duration T2DM, mean BMI, mean weight, mean hemoglobin A1c (HbA1c), mean fasting plasma glucose (FPG), mean systolic and diastolic blood pressure, TC, LDL, HDL, TG, and visceral and subcutaneous fat area), the metabolic diseases evaluated by the study (T2DM, HBP, adiposity, and dyslipidaemia), GC type and stage, neoadjuvant or adjuvant therapy, type of surgery (total or partial gastrectomy), reconstruction method (Roux-en-Y, Billroth I, and Billroth II) and outcome measures.

Quality assessment

The quality of the articles was independently analyzed by two reviewers (MC, CO) using the National Institutes of Health quality assessment criteria for observational studies[12], and the Cochrane risk of bias tool for randomized control trials[13].

The first tool consists of a form with 14 yes-or-no questions (related to research question, study population, exposure, outcome, blinding, follow-up, and statistical analysis), obtaining a final quality rating (ranging from good to poor) to classify the study according to its potential risk of bias (Supplementary Table 1).

The second tool includes stratification of the risk of selection, performance, detection, attrition, reporting bias, and other sources biases and the classification of the studies as high, low, or unclear (Supplementary Fig. 1).

Quantitative synthesis of results
We performed meta-analyses of relative risks for dichotomous variables (complete and partial remission of T2DM and HBP), and mean differences for continuous variables (BMI reduction rate). BMI reduction rate is a measure that is calculated as [(preoperative BMI – postoperative BMI) ÷ (preoperative BMI)] × 100.

For each outcome, the pooled meta-analytical measure, and the respective 95% confidence interval (95% CI) were obtained. We performed a random-effects meta-analysis using the restricted maximum likelihood approach.

Heterogeneity was assessed using Cochran's Q test *p*-value and I^2 statistic. Heterogeneity was considered high for *p*-values of the Cochran's Q test lower than 0.10 or I^2 above 50%. To explore potential sources of heterogeneity, we performed leave-one-out sensitivity analyses and, for analyses including more than ten primary studies, meta-regression analyses, testing follow-up time, preoperative BMI, and BMI reduction rate as moderator variables**.**

A *p*-value lower than 0.05 was considered statistically significant. This meta- analysis was performed using meta package of software R**.**

Results
Study selection
During the initial search, 2799 records were identified. After excluding duplicates, 1529 articles remained. After the screening phase, 31 articles were fully read, of which 25 were included. Through Grey Literature, 7 articles arose, and 6 of them were included. The quantitative synthesis comprised 18 papers out of the 31 included in the qualitative synthesis (Fig. 1)[10].

Study characteristics
A summary of the study's characteristics is presented in Table 1. The 18 articles included in the meta-analysis comprised of 3453 patients. Of the 31 eligible studies, 18 were retrospective studies[8,14–30], 11 were prospective studies[31–41], and 2 were randomized controlled trials[42,43]. The articles were published between 2012 and 2022 and were conducted in Korea, Japan, Taiwan, China, and Brazil. The minimum follow-up time of the included studies was 3 months (Zhang et al. [37]), with five studies having a follow-up period lower than 12 months, fourteen studies between 12 and 24 months and twelve studies higher than 24 months.

Two types of gastrectomy (subtotal and total) and three different reconstruction methods were studied: Billroth I (BI), Billroth II (BII), and Roux-en-Y (RY; conventional and long-limb).

Although the definition of complete remission and improvement of T2DM and HBP demonstrated small differences between studies, all of them used the reduction or absence of medication as complete or partial remission criteria.

Risk of bias of individual studies
Supplementary table and Fig. 1 display the findings of the risk of bias assessments of the included studies.

Regarding observational studies, none of the studies justified their sample size, nor was the participants' level of exposure hidden from the outcome assessors. Concerning the eighth and tenth parameters related to the level and assessment of exposure in observational studies, we considered them not applicable to all articles.

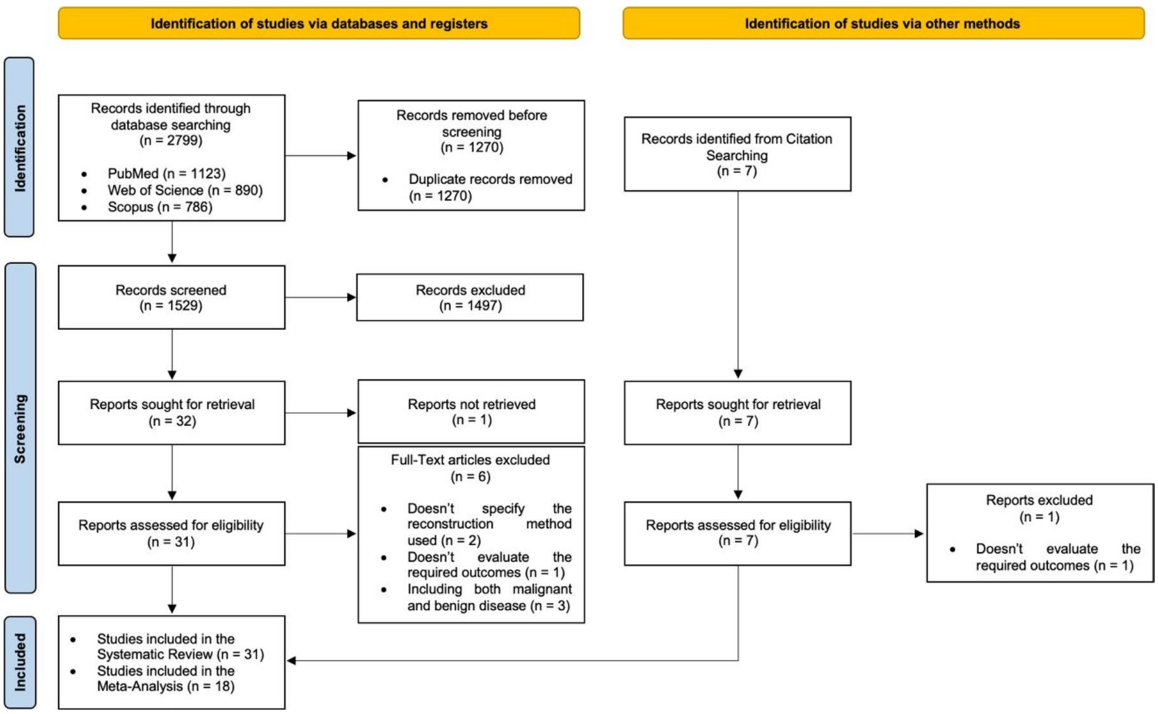

Fig. 1. Flow diagram of study selection.

Study, year	Country	Study design	Nº patients	Mean Age (years)	Male (%)	Mean follow- up (months)	GC ataging	Neoadjuvant or adjuvant therapy	Interventio n type	Mean BMI (kg/m2)	BMI reductio n ratio (%)	Mean HbA1c (%)	Mean FPG (mg/dL)	Mean duration of T2DM (months)	Mean SBP (mmHg)	Mean DBP (mmHg)	Mean TC (mg/dL)	Mean LDL (mg/dL)	Mean HD L (mg/dL)	Mean TG (mg/dL)	Mean SFA (cm^2)	Mean VFA (cm^2)
Lee et al.[24]	Korea	RS	220	64.5	77.8	12	I, II, III	Adjuvant Therapy	BI, BII, RYGJ, RYEJ	23.9	7,82	–	150.9	–	–	–	–	–	–	–	–	–
Kang et al.[25]	Korea	RS	75	67	72	35	–	Adjuvant Therapy	BI, BII, RYEJ	23.8	8.03	7.4	–	–	–	–	176.77	–	–	–	–	–
Kim et al.[36]	Korea	RS	403	63.8	76.2	33.7	–	–	RYEJ, BI, BII	24.7	9.8	–	–	–	–	–	–	–	–	–	–	–
Zhang et al.[37]	China	PS	21	55.3	83.33	3	I, II, III	No	BII	22.4	–	7	140.0	–		–	–	–	–	–	–	–
Hayashi et al.[35]	Brazil	PS	164	68.3	57.2	36	–	–	RYEJ, RYGJ	25.85	8.5	–	116.25	–	–	–	179.65	–	–	–	–	–
An et al.[34]	Korea	PS	64	62.7	67.2	12	I	No	BI, BII, RYEJ	24.7	10.22	7.2	149.63	6.6	–	–	–	102.6	43.17	138.13	–	–
Kim et al.[40]	Korea	PS	15	62.1	66.67	12	I, II, III	Neoadjuvant and Adjuvant Therapy	LRYGJ, LRYEJ	< 30	13.89	–	–	136.9	–	–	–	–	–	–	–	–
Tanaka et al.[30]	Japan	RS	152	62.8	69.74	6	I, II, III	Adjuvant Therapy	BI, RYGJ	22.6	9.36	–	–	–	–	–	–	–	–	–	118.15	77.9
Wei et al.[29]	China	RS	67	65.7	70	57.4	I, II, III, IV	Adjuvant Therapy	BII, RYEJ	–	14.53	–	–	–	–	–	–	–	–	–	–	–
Wang et al.[15]	Taiwan	RS	69	70.3	76.8	67.8	–	–	RYGJ, RYEJ, BI, BII	24.8	15.7	–	149.2	–	–	–	–	–	–	–	–	–
Xiong et al.[19]	China	RS	54	52.2	68.52	6	I, II, III, IV	–	LRYGJ, LRYEJ	–	–	10.6	102.6	105.6	–	–	–	–	–	–	–	–
Tanaka et al.[42]	Japan	RCT	221	64.1	67.9	12	–	Adjuvant Therapy	BI, RYGJ	22.55	9.22	–	–	–	–	–	–	–	–	–	121.5	88.25
Kwon et al.[28]	Korea	RS	49	65.2	82.3	24	I, II, III	Adjuvant Therapy	BI and BII	25.07	7.58	7.3	145	–	120	75	162	–	–	–	–	–
Zhu[23]	China	RS	292	64.9	69.5	24	–	No	BI, BII, RYEJ	22.4	10	–	102.6	97.2	–	–	–	–	–	–	–	–
Liu[32]	China	PS	93	59	50.54	12	–	–	BI, RYGJ, RYEJ	29.31	–	9.27	184.86	–	–	–	–	–	–	–	–	–
Pak[20]	Korea	RS	90	65.4	70	24	I, II, III	–	BI, BII, RYEJ	24.8	11	7.1	151.0	25.6	119	–	–	–	–	–	–	–
Kim et al.[36]	Korea	PS	30	63.9	46.7	12	I, II, III, IV	Adjuvant Therapy	LRYGJ	26.8	15.25	7.6	144.7	100.8	–	–	–	–	–	–	–	–
Ho et al.[21]	Taiwan	RS	579	57	67.7	47.1	–	–	RYEJ	–	–	–	–	–	–	–	–	–	–	–	–	–
Choi[43]	Korea	RCT	40	62.6	65	12	I, II, III	No	RYGJ, BI	25.65	–	7.4	135.15	–	–	–	–	–	–	–	–	–
Guner et al.[22]	Korea	RS	238	62.9	75	24	I, II	No	BI, BII	24.3	–	7.2	137	96	–	–	–	–	–	–	–	–
Lee et al.[8]	Korea	RS	42	68.7	68.6	60	I, II, III	–	BI, BII, RYEJ	25.1	–	6.9	139.6	152.4	–	–	–	–	–	–	–	–
Min Jeong Park[41]	Korea	PS	52	65	73.08	12	I, II, III	Adjuvant Therapy	BI, BII, RYGJ, RYEJ	24.94	–	–	–	–	–		–	–	–	–	144.70	128.18
Lin et al[26]	China	RS	455	69.4	56.76	99	I	No	BII, RYGJ	21.6	–	–	–	100	123	74	163	–	54	81	–	–
Kim et al.[38]	Korea	PS	66	62	65.3	12	Ia, Ib	No	BI, BII, RYGJ, RYEJ	25.5	–	–	–	–	125	82	178	111	45	110	–	–
Park et a.[31]	Korea	PS	40	60	80	12	I	Adjuvant Therapy	LRYGJ, RYGJ	29.6	9.63	5.8	–	–	136	84.25	–	–	–	–	–	–
Kim et al.[27]	Korea	RS	1305	58.55	65.4	12	Ia, Ib, IIa	No	BI, BII, RYGJ	23.63	–	–	–	–	–	–	182	–	–	–	–	–
Kim et al.[16]	Korea	RS	226	63.05	77	12	I	No	LRYGJ, BII	25.59	11	7.25	149.55	–	–	–	–	–	–	–	–	–
Continued																						

Study, year	Country	Study design	N° patients	Mean Age (years)	Male (%)	Mean follow- up (months)	GC ataging	Neoadjuvant or adjuvant therapy	Interventio n type	Mean BMI (kg/m2)	BMI reductio n ratio (%)	Mean HbA1c (%)	Mean FPG (mg/dL)	Mean duration of T2DM (months)	Mean SBP (mmHg)	Mean DBP (mmHg)	Mean TC (mg/dL)	Mean LDL (mg/dL)	Mean HD L (mg/dL)	Mean TG (mg/dL)	Mean SFA (cm^2)	Mean VFA (cm^2)
Peng et al.[18]	China	RS	143	65.1	63.6	6	–	–	BI, BII, RYEJ, RYGJ	23.4	12.82	–	–	–	–	–	–	–	–	–	–	–
Park et al.[33]	Korea	PS	20	60.1	70	6	I, II	No	BI, LBII, LRYGJ	25.8	8.91	7.8	121.4	36	–	–	–	–	–	–	–	–
Lee et al..[39]	Korea	PS	41	62.4	80.5	12	Ia, Ib	No	BI, BII, RYGJ, RYEJ	24.5	6.45	7.3	132.5	81.6	–	–	–	–	–	–	–	–
Choi et al.[14]	Korea	RS	48	60.73	83.1	12	I, II	No	LRYGJ, LRYEJ	23.77	11.34	7.45	122.21	–	–	–	–	–	–	–	–	–

Table 1. General characteristics of the included studies. *GC* gastric cancer, *BMI* body mass index, *HbA1c* hemoglobin A1c, *FPG* fasting plasma glucose, *T2DM* type 2 diabetes mellitus, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TG* triglycerides, *SFA* subcutaneous fat area, *VFA* visceral fat area, *RS* retrospective study, *PS* prospective study, *BI* Billroth I, *BII* Billroth II, *RYGJ* Roux-en-Y Gastrojejunostomy, *RYEJ* Roux-en-Y Esophagojejunostomy, *LRYGJ* Long-limb Roux-en-Y Gastrojejunostomy, *LRYTG* Long-limb Roux-en-Y Esophagojejunostomy.

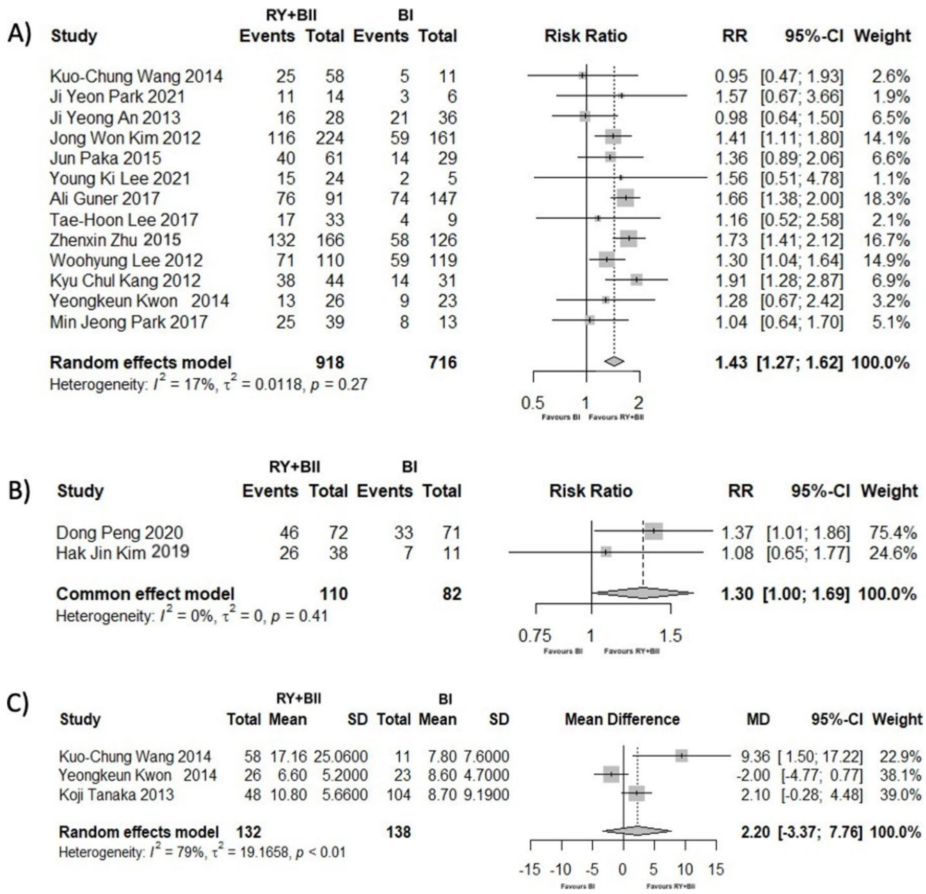

Fig. 2. (**A**) Forest Plot showing the outcomes of complete or partial remission of T2DM after gastrectomy, comparing duodenal bypass to BI reconstruction, at the end of the follow-up period. (**B**) Forest Plot showing the outcomes of complete or partial remission of HBP after gastrectomy, comparing duodenal bypass to BI reconstruction, at the end of the follow-up period. (**C**) Forest Plot showing the outcomes of BMI reduction rate after gastrectomy, comparing duodenal bypass to BI reconstruction, at the end of the follow-up period.

Most studies had a low risk of bias for the evaluated parameters. Twenty-three (79.31%) articles were classified as good, and six (20.69%) as fair.

Five studies (17.24%) with a follow-up duration of < 12 months did not have a sufficient timeframe to identify potential associations between exposure and outcomes, as their follow-up duration was judged inadequate to properly assess the outcomes.

The two randomized controlled trials included in the qualitative synthesis were considered to have an overall low risk of bias. Only one parameter, the random sequence generation, in Tanaka et al.[42], was recognized as having high risk of selection bias.

Comparison of the duodenal bypass reconstruction techniques (Roux-en- Y and Billroth II) with Billroth I

Type 2 diabetes mellitus

The frequency of patients who achieved diabetic remission at the end of follow- up period was evaluated in 13 studies[8,15,17,20,22–25,28,33,34,39,41].

Patients who underwent gastrectomy with duodenal bypass reconstruction had 1.43 times more probability of T2DM improvement or remission compared to the BI reconstruction (RR = 1.43; 95% CI [1.27; 1.62]; $p < 0.001$). The heterogeneity between studies was moderate but not significant ($I^2 = 16.90\%$; $p = 0.27$) (Fig. 2A).

Heterogeneity ceased to be observed using leave-one-out sensitivity analyses by omitting An et al.[34] (Supplementary Table 2). To further explore the potential sources of heterogeneity, a meta-regression analysis was performed. None of the variables analyzed (follow-up time, preoperative BMI, and BMI reduction rate) were identified as heterogeneity moderators (Supplementary Table 3).

Hypertension

Two studies[18,38] including 192 patients examined partial or complete HBP remission after duodenal bypass or BI reconstruction.

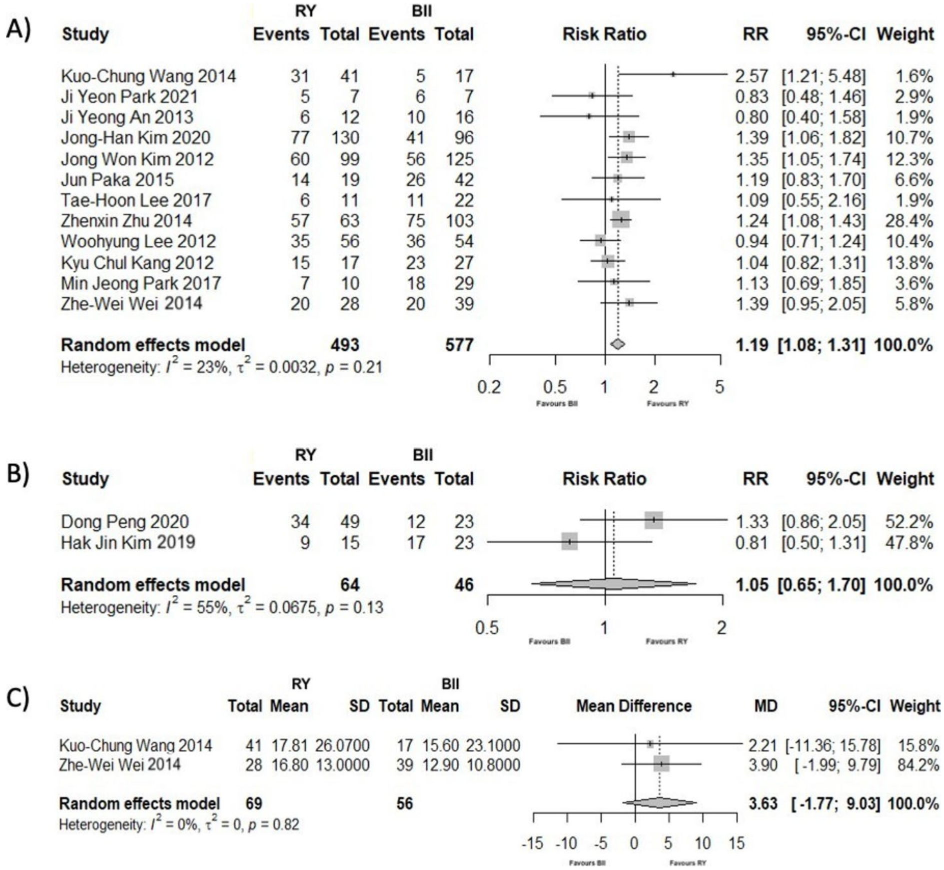

Fig. 3. (**A**) Forest Plot showing the outcomes of complete or partial remission of T2DM after gastrectomy, comparing RY to BII reconstruction, at the end of the follow-up period. (**B**) Forest Plot showing the outcomes of complete or partial remission of HBP after gastrectomy, comparing RY to BII reconstruction, at the end of the follow-up period. (**C**) Forest Plot showing the outcomes of BMI reduction rate after gastrectomy, comparing RY to BII reconstruction, at the end of the follow-up period.

After gastrectomy, patients who received RY or BII reconstruction had a 1.3 higher likelihood of improving or having their HBP resolved (RR = 1.30; 95% CI [1.00; 1.69]; $p = 0.048$), with no heterogeneity being detected ($I^2 = 0\%$; $p = 0.41$) (Fig. 2B).

BMI reduction rate

Three studies[15,28,30] (270 patients) compared surgical techniques regarding their BMI reduction rate after gastrectomy at the end of follow-up. There were no significant differences between BI and duodenal bypass reconstruction techniques in this parameter (MD = 2.20; 95% CI [− 3.37; 7.76]; $p = 0.44$). In addition, there was a high degree of heterogeneity within studies ($I^2 = 79.20\%$; $p < 0.01$) (Fig. 2C).

Comparison of the two duodenal bypass procedures, Roux-en-Y and Billroth II

Type 2 diabetes mellitus

Twelve studies[8,15–17,20,23–25,29,33,34,41] assessed the frequency of patients who had T2DM remission or improvement at the end of the follow-up period. The patients to whom gastrectomy with RY was performed had a 1.19 times greater chance of partial or complete remission compared to those with BII reconstruction (RR = 1.19; 95% CI [1.08; 1.31]; $p < 0.001$). The degree of heterogeneity was moderate, although not statistically significant ($I^2 = 23.40\%$; $p = 0.21$) (Fig. 3A).

Using leave-one-out sensitivity analyses, the heterogeneity decreased significantly ($I^2 = 3.60\%$) by omitting Wang et al.[15] (Supplementary Table 4). None of the variables analyzed in meta-regression (follow-up time and preoperative BMI) were identified as heterogeneity moderators (Supplementary Table 5).

Hypertension

Two studies[18,38] (110 patients) analyzed HBP remission or improvement at the end of the follow-up period. There were no significant differences between the RY and BII groups (RR = 1.05; 95% CI [0.65; 1.70]; $p = 0.84$), with heterogeneity being substantial ($I^2 = 55.40\%$; $p = 0.13$) (Fig. 3B).

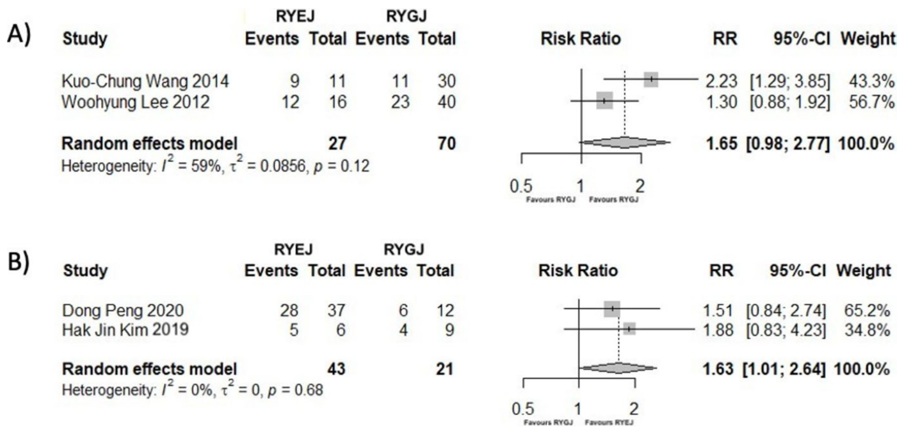

Fig. 4. (**A**) Forest Plot showing the outcomes of complete or partial remission of T2DM, comparing RYEJ to RYGJ, at the end of the follow-up period. (**B**) Forest Plot showing the outcomes of complete or partial remission of HBP, comparing RYEJ to RYGJ, at the end of the follow-up period.

BMI reduction rate

At the end of the follow-up period, the BMI reduction rates from two studies[15,29] were compared (125 patients). No significant differences were observed between RY and BII reconstruction techniques (MD = 3.63; 95% CI [− 1.77; 9.03]; $p = 0.19$; I^2=0%) (Fig. 3C).

Comparing Roux-en-Y between total gastrectomy and subtotal gastrectomy

Type 2 diabetes mellitus

To determine the impact of the residual stomach on T2DM remission, we compared RY reconstruction between total and subtotal gastrectomy, Roux-en-Y Esophagojejunostomy (RYEJ) and Roux-en-Y Gastrojejunostomy (RYGJ).

After total or subtotal gastrectomy with RY reconstruction, two studies[15,24] (97 patients) evaluated complete or partial remission of T2DM. Figure 4A shows a trend favouring total gastrectomy, although no significant difference was observed (RR = 1.65; 95% CI [0.98; 2.77]; $p = 0.06$; $I^2 = 59.40\%$).

Hypertension

We examined Roux-en-Y reconstruction between total and subtotal gastrectomy to explore the impact of residual stomach on remission of HBP.

Two studies[18,38] (64 patients) assessed the improvement or remission of HBP who underwent RYEJ or RYGJ. After RYEJ, patients had a 1.63 higher probability of improving their HBP (RR = 1.63; 95% CI [1.01; 2.64]; $p = 0.046$), with no heterogeneity detected ($I^2 = 0\%$; $p = 0.68$) (Fig. 4B).

Discussion

Summary of evidence

The mechanism underlying GC surgery as a metabolic surgery shares many similarities with bariatric Roux-en-Y Gastric Bypass (RYGB). Both rely on reduction of gastric volume and anatomical reconstruction of the stomach[22]. BI reconstruction preserves gastric tract continuity. In contrast, in reconstruction techniques that involve duodenal bypass, BII or RY, food bypasses the duodenum and proximal jejunum, reaching the distal ileum earlier. These two reconstruction techniques resemble bariatric surgery more than BI[14].

Bariatric and Oncometabolic Surgery share many concepts, yet they also exhibit significant differences. One major drawback is their substantially different target population, candidate patients for OS tend to be older, frailer, and lighter[9]. Consequently, in contrast to obese individuals receiving bariatric surgery, inferior outcomes are to be anticipated in oncological patients undergoing gastrectomy. Patients with GC are less likely to be obese. Therefore, the effect of weight loss is smaller than what is expected in bariatric patients. Another disparity is their age: oncological patients are generally older. Ageing exponentially increases surgical morbidity and mortality, leading to higher and more severe preoperative comorbidities and postoperative risks[44]. Lastly, in conventional GC surgery, the bypass length is usually shorter than in bariatric RYGB, leading to a weaker enteric effect[14].

Therefore, GC surgical techniques can be adjusted, thoroughly evaluated, and tailored to optimize therapeutic benefits without sacrificing oncological safety[45] for a particular and cautiously selected patient group. OS involves adapting and choosing the best surgical method available for optimal oncologic and metabolic control.

To the best of our knowledge, this is the first meta-analysis exploring the impact of duodenal bypass (RY or BII), residual stomach, and the various GC reconstruction techniques on postoperative T2DM, HBP, and BMI reduction rate in patients with GC.

Duodenal Bypass demonstrated a significantly higher efficiency in the improvement of T2DM compared to BI reconstruction. For BII, the remission rate ranged from 13 to 83.5%, and for RY, it ranged from 30.7 to 90.5%. This wide variability may be attributed to distinct patient characteristics, different follow-up periods, lack of technical standardization, different lengths of the biliopancreatic and alimentary limbs, or the fact that almost all included studies, the primary goal was the resection of the tumor rather than the improvement of glycemic control.

The mechanism underlying T2DM remission after gastrectomy is similar to that in bariatric surgery. Two theories have been developed to explain this phenomenon: Foregut and Hindgut Hypotheses[46]. According to the Foregut Hypothesis, bypass of the duodenum alters levels of postprandial hormones, improving glucose control by enhancing insulin release and sensitivity. On the other hand, the Hindgut Hypothesis suggests that early contact of nutrients with the distal small intestine induces an antidiabetic effect by increasing GLP-1, which enhances insulin release and reduces postprandial hyperglycemia by slowing gastric emptying. Lastly, we must highlight the essential role of gut hormones in remission, not only in T2DM but also in HBP, dyslipidaemia, and cardiovascular events. Studies have demonstrated that, independent of weight loss, proximal intestinal bypass promotes T2DM improvement via incretins/anti-incretins, gut hormones, alteration in the gut microbiome, or altered bile acid signaling[28,47,48].

According to several studies, the most significant independent predictors were the duration and severity of T2DM[8,14,15,20–22,25,28,34,36,40,41] (preoperative diabetes duration, insulinogenic index, and HbA1c level) and weight loss[8,17,20,22,34,36,40] (preoperative BMI, and BMI reduction rate). Several previous bariatric and gastrectomy studies have reported pancreatic β cell function as having an important role in T2DM remission[49,50]. Patients with shorter T2DM duration have greater β cell activity[15]. Therefore glycemic control would be more effective in GC patients with a shorter diabetes diagnosis time, not requiring insulin therapy, and with lower preoperative HbA1c levels[8,20,21,25,28,36,41]. Weight loss, higher preoperative BMI, and higher BMI reduction rate, even in nonobese patients, were also important factors in the improvement of glucose metabolism[8,17,20,22,36,38].

Hypertension is a modifiable risk factor that is intimately linked to cardiovascular and cerebrovascular diseases and can affect the quality of life of cancer survivors[38]. Three articles[18,31,38] from this qualitative synthesis evaluated the influence of gastrectomy and its different reconstruction methods on blood pressure control in patients with a BMI< 30 kg/m^2. Remission and improvement of HBP after gastrectomy ranged from 53.1 to 67.4%. Two studies[18,38] included in this quantitative synthesis showed significant superiority of duodenal bypass reconstruction over BI. However, no discernible difference was established between RY and BII. A statistically significant difference was observed in the extent of gastrectomy, demonstrating the superiority of RY Esophagojejunostomy. These findings were consistent with those in Peng et al., that reported that total gastrectomy was associated with a greater remission rate of HBP, and that no noticeable superiority was seen among the three reconstructive techniques for subtotal gastrectomy[18]. Both studies acknowledge that additional factors such as lifestyle modifications may play an important role.

The effect of GC surgery on metabolic control has been evaluated in several studies involving oncologic patients with BMI< 30 kg/m^2. In fact, most have shown that T2DM, HBP, and dyslipidaemia improve following gastrectomy in non-obese patients[23,25,28,31,38,41]. However, although it has been proven that weight loss plays a crucial role in the metabolic status of patients with GC, suggesting that patients with a lower BMI are less likely to benefit from metabolic surgery, it is not the only contributing factor, nor is it statistically significant on its own[20]. Weight loss and the effects of duodenal bypass appear to work synergistically to improve metabolic control after gastrectomy, even in non-obese patients[22]. This suggests that while weight loss plays a role, other mechanisms, also significantly contribute to metabolic outcomes.

Cerebrovascular, cardiac, and respiratory diseases are common causes of death in patients with early GC[52]. One of the main findings of Lee et al. was that patients who underwent gastrectomy for early GC had a similar overall mortality as the general Korean population, but a significantly lower cardiovascular mortality[53]. Multiple studies included in this systematic review showed a significant lowering of TC, TG, and LDL levels and a rise of HDL after gastrectomy[25–28,31,34,38].

Lin et al.[26] states that GC patients who had undergone subtotal gastrectomy (BII and RY reconstruction) had significantly lower TC and TG levels, BMI, decreased waist circumferences, and occurrence of T2DM and Metabolic Syndrome. Lee et al. reinforced the correlation between weight loss and patients' lipid profiles. After gastrectomy, a significant reduction in body weight and visceral fat might improve lipid metabolism and prevent atherosclerotic changes, leading to a reduction in cardiovascular mortality[53].

One retrospective study and one randomized controlled trial (373 patients)[30,42] evaluated the influence of RY and BI on visceral fat reduction after gastrectomy. Visceral fat accumulation has been identified as an underlying cause of metabolic syndrome[54]. These two studies showed that both duodenal bypass and gastrectomy promoted significant visceral fat loss.

Long-limb RY reconstruction has recently emerged as an option in GC surgery. Studies have suggested that increasing the length of biliopancreatic and alimentary limbs leads to better metabolic outcomes after gastrectomy[43]. Currently, no consensus on the optimal limb length has been established. Long-limb RY reconstruction typically refers to a modification of the standard procedure where the lengths of the anastomosis limbs exceed the traditional measurements. In conventional RY reconstruction surgery for gastric cancer, the length of the alimentary limb ranges from 40 to 50 cm, and the biliopancreatic limb is generally about 30–40 cm in length[9].

Seven studies (433 patients)[14,16,19,31,33,36,40] investigated the effect of long-limb RY reconstruction on T2DM improvement, ranging from 50.8 to 85%. These studies showed that a longer modification of RY resulted in better outcomes for T2DM, HBP, and dyslipidaemia. Kim et al. reported a statistically significant superiority of long-limb RY over the conventional BII in a multicenter retrospective cohort of 226 patients for up to 1 year after surgery[16]. Choi et al. found that the results of long-limb Roux-en-Y gastrojejunostomy (LRYGJ) in oncologic, diabetic, nonobese patients were similar to that of metabolic surgery in obese diabetic patients[14]. A prospective study of 40 patients compared long-limb RY with conventional RY for T2DM and HBP. It disclosed that the complication rate of OS group did not differ from the conventional group. Although no significant difference was observed between the two methods, the results showed higher remission rates for both T2DM (LRYGJ 77.8% and RYGJ 50%) and HBP (LRYGJ 68.8% and RYGJ 41.2%). Lastly, it reported an improvement in dyslipidaemia

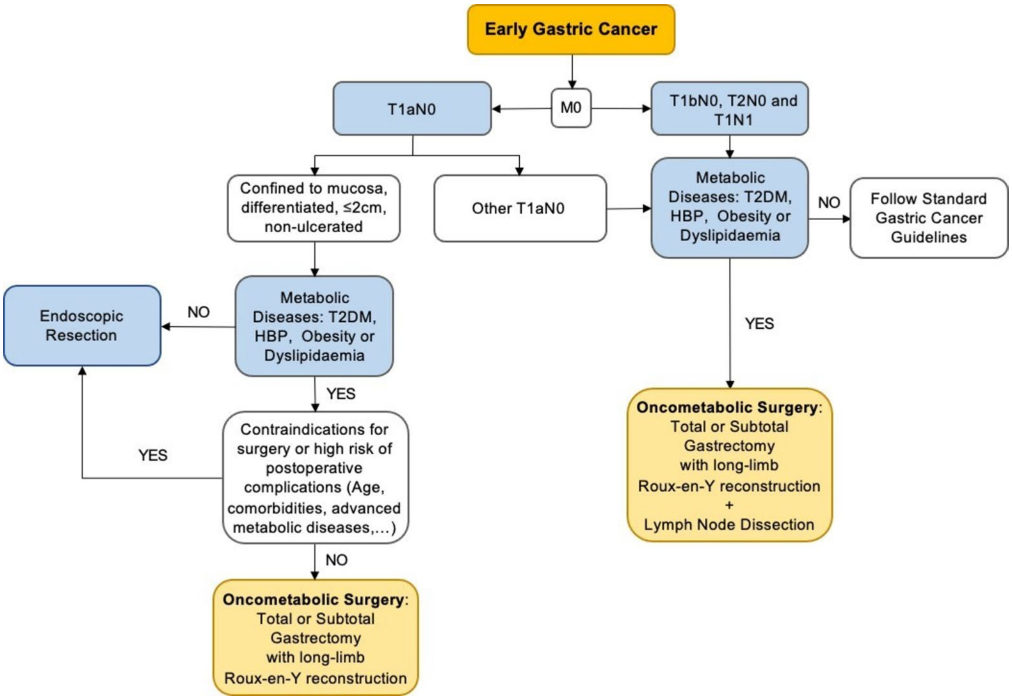

Fig. 5. Potential treatment algorithm for early gastric cancer patients with metabolic diseases. (Adapted from Kim et al.[33] and ESMO Clinical Practice Guidelines[55].

in 61.5% of patients in the OS group. However, this study had a small sample size, and its primary endpoint was nutritional safety not OS efficacy[31].

Who would benefit from OS? Patients with longer life expectancies, with localized early-stage GC, who would require ongoing care for their metabolic comorbidities: younger oncologic patients with shorter duration of T2DM, HBP, and dyslipidaemia, especially those who cannot adequately control their comorbidities by optimal lifestyle modification or pharmacotherapy. Although numerous studies have shown excellent outcomes in individuals with normal BMI, this surgery would be particularly favorable for patients with obesity. Figure 5 shows a potential treatment algorithm for patients with early GC and concomitant metabolic diseases, based on the ESMO Clinical Practice Guidelines[55].

Limitations

Most included studies were based in Asia, specifically Korea, China, Japan, and Taiwan, except for Hayashi et al.[35], which was from Brazil. The characteristics of Asian patients are distinct from those observed in other regions. There is a higher percentage of GC and less obesity in East Asia. This might be due to several risk factors, such as dietary patterns and the high prevalence of *Helicobacter pylori* infection[56].

Second, most studies employed different criteria for remission and improvement of T2DM. Nevertheless, all studies used one common criterion: reduction or cessation of medication as indicators of partial or complete remission, respectively. In regard to T2DM, the majority of these studies adhered to the American Diabetes Association (ADA) criteria for defining complete and partial remission. According to the ADA, complete remission is characterized by a fasting blood glucose (FBS) level of less than 100 mg/dL and an HbA1c level below 6.0%, maintained for 1 year without the use of antidiabetic medication. Partial remission, on the other hand, is defined as a fasting blood glucose level between 100 and 125 mg/dL and an HbA1c level below 6.5%, which was maintained for 1 year in the absence of antidiabetic medication[8,14,16,20,24,29,33,43]. For HBP, both studies used reduction or cessation of medication as the criteria for determining partial or complete remission[18,38].

Another limitation was the inability to analyze other key outcomes such as dyslipidaemia, visceral fat reduction, and other metabolic diseases. Data on such outcomes were not presented in the primary studies.

The influence of neoadjuvant and adjuvant therapy on glycemia, hypertension, and dyslipidemia in these patients was not deeply explored in the included studies, it is important to note that only one study briefly addressed the impact of adjuvant therapy. Lee et al. states that adjuvant chemotherapy in advanced stages could potentially influence glucose management. The most prevalent side effects are diminished appetite, nausea, vomiting, and growth hormone deficiency post-chemotherapy, which can impact insulin secretion[24]. Further research is needed to explore the influence of neoadjuvant and adjuvant therapies on glycemia, HBP, and dyslipidemia in gastric cancer patients. This area of study is crucial to better understand the comprehensive impact of these therapies on metabolic parameters and to optimize treatment outcomes.

Patients with GC and concurrent HBP after gastrectomy have rarely been reported. Further investigation is required on this subject as well as studies with larger sample sizes and longer follow-up times.

Most of the included studies reported weight reduction primarily using BMI reduction rates, which are commonly used in gastric cancer surgery, rather than the standard metrics used in bariatric surgery, such as %TWL, %EWL, or %EBMIL.

Further research on the efficiency of long-limb RY reconstruction with larger sample sizes and long-term outcomes is needed to compare its results with those of traditional BII and RY gastrectomy. In addition, a standard biliopancreatic limb length should be established to obtain optimal results.

All the outcomes analyzed in this meta-analysis were evaluated at the end of the follow-up period. Such periods ranged between 6 and 67.8 months. Three studies[18,30,33] had a follow-up of 6 months, and four studies[8,15,17,25] had follow- ups over 24 months. At both extremes, we observed significant improvements in the metabolic status. To evaluate whether this variation influenced heterogeneity, a meta- regression analysis was performed, which showed that this variable was not a heterogeneity moderator.

Lastly, some of our results demonstrated low to high heterogeneity. This heterogeneity might be due to disparity in patient characteristics, lack of standardization of biliopancreatic and alimentary limb lengths, and outcomes not being the primary goal of the study.

Conclusion

Our systematic review and meta-analysis demonstrated that both conventional and modified gastrectomy were effective in the improvement of metabolic diseases. However, RY reconstruction after gastrectomy is the most effective method for altering GC patients' metabolic status.

The concept of OS could change the surgical oncology paradigm. Its future lies in surgeons actively selecting patients with specific characteristics (T2DM, obesity, HBP, dyslipidaemia, GC, and younger age) and modifying the traditional GC operation based on the principles of metabolic and bariatric surgery.

Future perspectives

Research on OS has mainly focused on T2DM rather than cardiovascular diseases or other metabolic comorbidities such as HBP, dyslipidaemia, obesity, and non-alcoholic fatty liver disease.

Further research with longer follow-up periods is needed to reflect the impact of OS on survival rates, quality of life and the safety of this procedure.

OS provides a glimmer for the prospective widening of the criteria for metabolic and bariatric surgery in the treatment of T2DM in non-obese, non- oncologic patients.

In future GC guidelines, OS should be considered as an option for patients with obesity or metabolic diseases.

Data availability

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

Received: 15 June 2024; Accepted: 6 September 2024
Published online: 08 October 2024

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Acknowledgements

First and foremost, we would like to thank Dr José Maximino Costa because, without his assistance and support, the progress and completion of this dissertation would not have been possible. The authors would like to acknowledge all the Obesity Integrated Responsibility Unit (CRI-O) group members.

Author contributions

Study concepts: M.P.C., H.S.S. Study design: M.P.C., H.S.S., B.S.—Pinto Data acquisition: M.P.C., Carolina Rodrigues Oliveira Quality control of data and algorithms: M.P.C., C.O., H.-S.S., B.S.-P. Data analysis and interpretation: M.P.C., C.O., H.-S.S., B.S.-P. Statistical analysis: M.P.C., B.S.-P. Manuscript preparation: M.P.C. Manuscript editing: M.P.C., C.O., H.-S.S., B.S.-P. Manuscript review: M.P.C., C.O., H.-S.S, B.S.-P., F.A.-C., R.B., E.B., S.C.

Competing interests

The authors declare no competing interests.

Ethics approval

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

Informed Consent

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

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-72456-2.

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