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REVIEW ARTICLE

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Postoperative morbidity and mortality after surgical resection of small bowel neuroendocrine neoplasms: A systematic review and meta-analysis

Enes Kaçmaz[1,2] | Jeffrey W. Chen[1,2] | Pieter J. Tanis[1,2] | Els J. M. Nieveen van Dijkum[1,2] | Anton F. Engelsman[2,3]

[1]Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Cancer Center Amsterdam, ENETS Center of Excellence, Amsterdam UMC, The Netherlands

[3]Department of Surgery, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

Correspondence
Anton F. Engelsman, Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, Boelelaan 1117, Amsterdam 1081 HV, The Netherlands.
Email: a.f.engelsman@amsterdamumc.nl

Abstract

Although small bowel resection is generally considered a low risk gastrointestinal procedure, this might not be true for small bowel neuroendocrine neoplasms (SB-NEN) as a result of potential central mesenteric involvement. We aimed to determine the reported morbidity and mortality after resection of SB-NEN in the literature and assess the effect of hospital volume on postoperative morbidity and mortality. A systematic review was performed by searching MEDLINE and Embase in March 2021. All studies reporting morbidity and/or mortality after SB-NEN resection were included. Pooled proportions of overall morbidity (Clavien-Dindo I-IV), severe morbidity (Clavien-Dindo III-IV), 30-day mortality, 90-day mortality and in-hospital mortality were calculated, as well as the association with hospital volume (high volume defined as the fourth quartile). Thirteen studies were included, with a total of 1087 patients. Pooled proportions revealed an overall morbidity of 13% (95% confidence interval [CI] = 7%-24%, I^2 = 90%), severe morbidity of 7% (95% CI = 4%-14%, I^2 = 70%), 30-day mortality of 2% (95% CI = 1%-3%, I^2 = 0%), 90-day mortality of2% (95% CI = 2%-4%, I^2 = 35%) and in-hospital mortality of 1% (95% CI = 0%-2%, I^2 = 0%). An annual hospital volume of nine or more resections was associated with lower overall and severe morbidity compared to lower volume: 10% vs 15% and 4% vs 9%, respectively. Thirty-day mortality was similar (2% vs 1%) and 90-day mortality was higher in high-volume hospitals: 4% vs 1%. This systematic review with meta-analyses showed severe morbidity of 7% and low mortality rates after resection of SB-NEN. The currently available literature suggests a certain impact of hospital volume on postoperative outcomes, although heterogeneity among the included studies constrains interpretation.

KEYWORDS

complications, morbidity, mortality, neuroendocrine neoplasm, small bowel, surgery

1 | INTRODUCTION

Small bowel neuroendocrine neoplasms (SB-NEN) are rare tumours of the small bowel with an incidence of one to four per 100,000 person years.[1,2] Patients are often amenable for surgery, in either a curative or palliative setting (50% stage I-III, 40% patients with liver metastases).[2-4] Surgery consists of a partial small bowel resection or right hemicolectomy with mesenteric lymphadenectomy, and is sometimes combined with resection or debulking of liver or peritoneal metastases. Open surgery is still considered the standard approach, although minimally invasive surgery is emerging as an alternative technique in selected patients.[5-10] The timing of the resection is still a subject of debate (ie, prevent or relieve obstructive symptoms) and remains unanswered by recent guidelines.[11]

One of the challenges of SB-NEN surgery is the safe and complete resection of mesenteric lymph nodes, which are present in > 80% of patients.[2,12] Because mesenteric tumour masses can have a close relationship with the main mesenteric trunks, vascularisation of the small bowel may be at risk during central mesenteric dissection. Other potential complications after surgery for SB-NEN include postoperative haemorrhage, surgical site infections, abscess and anastomotic leakage.[13]

It is a common assumption among healthcare providers that clinics with higher volumes of specific procedures have lower morbidity and mortality rates; for example, as reported for pancreatic and colorectal surgery.[14,15] Besides surgical experience, anesthesia management might also be relevant. This is especially the case for patients undergoing surgery for hormonally active NEN because intra-operative carcinoid syndrome develops in up to 55% of patients, regardless of preoperative prophylactic octreotide infusions.[16] Recently, Hallet et al[17] investigated the association between anaesthesiologist volume and postoperative morbidity after complex gastrointestinal surgery. Interestingly, cases performed by high-volume anaesthesiologists had significantly less complications with a Clavien-Dindo grade III-V.

Because of the low incidence of SB-NEN, there is a restricted amount of literature compared to other high incidence gastrointestinal malignancies, and evidence is mostly based on observational studies. The aim of the present systematic review and meta-analyses was to determine the incidence of morbidity and mortality in patients with SB-NEN who undergo resection of the primary tumour, and to assess any potential association with hospital-volume.

2 | MATERIALS AND METHODS

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology guideline.[18,19] The protocol of this study was registered in PROSPERO (www.crd.york.ac.uk/prospero) under registration number CRD42020185001.

2.1 | Eligibility criteria

We aimed to identify all studies reporting on morbidity and mortality after SB-NEN resection. Both prospective and retrospective studies that were published in English after the year 2000 were included. Case reports, conference abstracts and reviews were excluded. In the case of a mixed population (ie, pancreatic NEN and SB-NEN), studies were excluded if no separate data were reported for patients with SB-NEN. Studies including patients with concomitant hepatectomies in more than 20% of the patients were excluded from analyses to limit heterogeneity. In the case of publications with overlapping patient cohorts, the study with the largest cohort size was included for analysis.

2.2 | Literature search strategy

A search was performed in MEDLINE (PubMed) and Embase (Ovid) on 8 March 2021. The key words and Medical Subject Headings (MeSH) terms used for both databases were: ileal/jejunal neoplasms, neuroendocrine tumours, surgery, postoperative complications, morbidity and mortality. The complete search string is provided in (Table S1). Additional hand screening was performed with respect to the reference lists of included articles.

2.3 | Study selection

Study selection was performed according to the PRISMA statement. Abstracts were screened for eligibility by two independent researchers (EK and JWC), using Rayyan software (Qatar Computing Research Institute, Doha, Qatar).[20] Any discrepancies were resolved by discussion. Subsequently, two independent researchers (EK and JWC) screened full texts and selected studies for inclusion in the systematic review and meta-analysis.

2.4 | Data collection and outcome parameters

Data collection was performed by one author (EK). Collected data included study characteristics (author, country, publication year, inclusion period), patient characteristics (age, sex, disease stage), operative characteristics (type of operation, surgical approach) and postoperative events. Outcome parameters were overall morbidity, severe morbidity, 30-day mortality, 90-day mortality and in-hospital mortality.

Overall morbidity was defined as Clavien-Dindo grade I-IV and severe morbidity was defoned as grade III-IV.[21] All study authors were contacted to complete and correct extracted data. Low volume centres were defined as an annual case load equal or below the third quartile, whereas high-volume centres were defined as those with an annual case load higher than the third quartile.

2.5 | Risk of bias

Risk of bias was assessed by one author (EK) using the Joanna Briggs Institute ([JBI] Faculty of Health Sciences, The University of Adelaide, South Australia) checklist for case series. The predefined criteria for each of the 10 questions in the JBI checklist (low, unclear or high risk of bias) were modified to suit the present study and are provided in (Table S2). A risk-of-bias graph displays overall risk of bias for each item on the JBI checklist across all included studies.

2.6 | Statistical analysis

Postoperative events were classified according to the Clavien-Dindo classification in case the study authors did not already do so.[21] The annual hospital volume was estimated per publication using the formula: total number of patients/inclusion period in years. Subgroup analyses were performed for studies reporting outcomes after minimally invasive surgery. Categorical values are presented as numbers with percentages, whereas continuous data as presented as the mean ± SD or the median with interquartile range (IQR). Reported medians were converted to means using the method described by Wan et al.[22] Pooled proportions were calculated for the different outcome parameters. The results are presented in forest plots, providing an estimate of the mean proportion with a 95% confidence interval (CI). Heterogeneity was assessed using the I^2 statistic. $I^2 > 50\%$ was considered to indicate a moderate amount of heterogeneity, which resulted in use of the random effects model, and $I^2 > 75\%$ was considered to indictae a substantial amount of heterogeneity, for which a meta-analysis was not performed. Funnel plots were made to estimate publication bias. Meta-analyses were performed with a random effects model using the meta package, version 4.15-1 in Rstudio, version 1.2.5033 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study selection

In total, 2416 studies were identified through the electronic search (without duplicates). After the screening and selection process, 13 studies involving 1087 patients were included (Figure 1).[8,23-35]

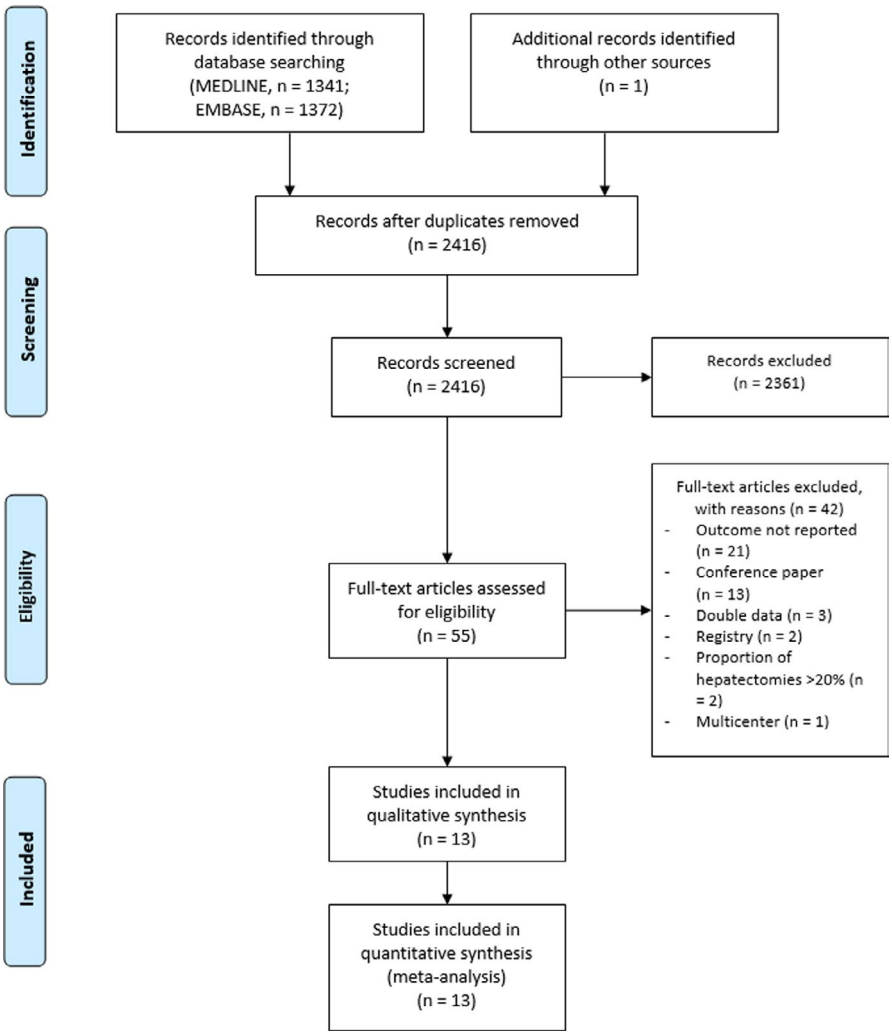


FIGURE 1 PRISMA flow chart

TABLE 1 Study characteristics

Author	Country	Inclusion period	Patients (*n*)	Annual volume (*n*/year)	Age, years, mean	Males, *n* (%)	Disease stage, *n* (%)		
							I-II	III	IV
Addeo et al[23]	France	1997-2018	44	2	63	20 (45)	0	0	44 (100)
Evers et al[35]	Germany	2000-2020	65	3	61	38 (58)	11 (17)	54 (83)	0
Figueiredo et al[8]	France	1996-2012	73	5	56	40 (55)	NR	NR	43
Fisher et al[32]	USA	2001-2018	17	1	57	9 (53)	0	0	17 (100)
Folkestad et al[31]	Norway	1998-2018	186	9	65	101 (54)	23 (12)	101 (54)	61 (33)
Horwitz et al[33]	USA	2014-2018	14	4	64	7 (50)	0	7 (50)	7 (50)
Kaçmaz et al[7]	Netherlands	2003-2019	34	2	67	21 (62)	0	16 (47)	17 (53)
Norlen et al[25]	Sweden	1985-2010	312	12	63	NR	NR	NR	NR
Pasquer et al[26]	France	2000-2013	107	8	62	62 (58)	NR	NR	75 (70)
Pasquer et al[27]	France	2013-2015	21	11	55	11 (52)	0	8 (38)	13 (62)
Pedrazzani et al[28]	Italy	2014-2019	5	1	70	0	0	3 (60)	2 (40)
Reissman et al[29]	Israel	2002-2012	20	2	60	8 (40)	0	10 (50)	10 (50)
Wang et al[34]	USA	2003-2012	189	21	NR	80 (42)	0	0	189 (100)
Total			1087	4 (2-9)[a]	62	397 (51)[b]	34 (6)[b]	199 (33)[b]	478 (62)[b]

Abbreviations: MIS, minimally invasive surgery; NR, not reported.

[a]Median (interquartile range).

[b]Proportions are calculated for studies who presented these variables.

TABLE 2 Surgical characteristics

Author	Surgical approach	Emergency resection	Procedure, *n* (%)				Hospital stay, days (mean ± SD)
			Total	Segmental resection	Ileocolic resection	Right hemicolectomy	
Addeo et al[23]	Open	NR	44	18 (41)[a]	0	26 (59)	NR
Evers et al[35]	NR	NR	65	24 (37)	0	41 (63)	NR
Figueiredo et al[8]	61 (84) open, 12 (16) MIS	9 (12)	73	45 (62)[b]	25 (38)	0	NR
Fisher et al[32]	NR	NR	17[c]	NR	NR	NR	NR
Folkestad et al[31]	Open	45 (24)	186[d]	112 (60)	33 (18)	35 (19)	NR
Horwitz et al[33]	Open	0	14	7 (50)	7 (50)	0	13 ± 21
Kaçmaz et al[7]	11 (32) open, 23 (68) MIS	4 (12)	34	20 (59)	8 (24)	6 (17)	8 ± 6
Norlen et al[25]	Open	NR	312	312[e]	NR	NR	NR
Pasquer et al[26]	Open	NR	107	58 (54)	9 (8)[f]	40 (18)[f]	NR
Pasquer et al[27]	Open	NR	21	21 (100)	0	0	NR
Pedrazzani et al[28]	MIS	NR	5	0	0	5 (100)	7 ± 6
Reissman et al[29]	MIS	NR	20	20 (100)[g]	NR	NR	6 ± NR
Wang et al[34]	Open	NR	189	189 (100)	NR	NR	NR
Total			1087	826 (76)	82 (8)	153 (14)	9

[a]Three of 18 resections were combined with a major liver resection.
[b]Seven of 45 procedures were segmental resection + ileocolectomy.
[c]Ileal resection, right hemicolectomy, or an extended right hemicolectomy.
[d]Six of 186 procedures were not described.
[e]A distal small bowel resection was often combined with a right hemicolectomy, but unknown in how many cases.
[f]Ileocolectomy and hemicolectomies were combined in an unknown amount of procedures with segmental resections.
[g]All patients had consequent cholecystectomy.
[h]Eighty-six of 103 patients had 5-fluorouracil gel foam strips sutured in the mesentery.

3.2 | Study characteristics

Four (29%) studies had a prospective design,[27,28,32,33] whereas the others were retrospective design studies.[7,8,23,25,26,29,31,34,35] Thirty-three percent of patients had stage III disease and 62% of patients had stage IV disease (Table 1). Segmental bowel resections were performed in 76% of the cases, and were combined with concomitant liver resections or cholecystectomy in some cases (Table 2). These additional procedures were performed in addition to the resection of the primary tumour and/or metastases: Horwitz et al[33] performed small bowel resections after endovascular embolisation of encased mesenteric vessels; Reissman et al[29] performed a prophylactic cholecystectomy to avoid future cholecystitis caused by somatostatin analogue usage or peptide receptor radiotherapy; and Wang et al[34] secured gel foam strips soaked with 5-fluorouracil in the mesenteric tumour resection site in 86 of 189 (46%) patients. Minimally invasive surgery was performed in 60 of 1087 (1%) patients.

3.3 | Postoperative morbidity

Overall morbidity was reported in 12 studies (901 patients) with a pooled overall morbidity rate of 13% with high heterogeneity (95% CI = 7%-24%, random effects model; I^2 = 90%). Severe morbidity was reported in 11 studies (589 patients), with a pooled severe morbidity rate of 7% (95% CI = 4%-13%, random effects model, I^2 = 70%) (Figure 2A). Seven studies (313 patients) reported details on the type of postoperative complications that occurred (Table S3).[8,23,26,27,29,33] The two most common postoperative complications were intra-abdominal bleeding (9/313, 3%) and ileus (8/313, 3%). Reoperations were performed in six of 313 (2%) patients (Table S3).

3.4 | Postoperative mortality

Thirty-day mortality was reported in all studies, accounting for 1087 patients. The pooled 30-day mortality rate of these studies was 2% (95% CI = 1%-3%, fixed effects model, I^2 = 0%) (Figure 2B). Ninety-day mortality was reported in 12 studies, including 775 patients. The pooled 90-day mortality rate of these studies was 2% (95% CI = 2%-4%, fixed effects model, I^2 = 0%) (Figure 2C). In-hospital mortality was reported in 10 studies with a total of 400 patients. The pooled in-hospital mortality rate of these studies was 1% (95% CI = 0%-2%, fixed effects model, I^2 = 0%) (Figure 2D).

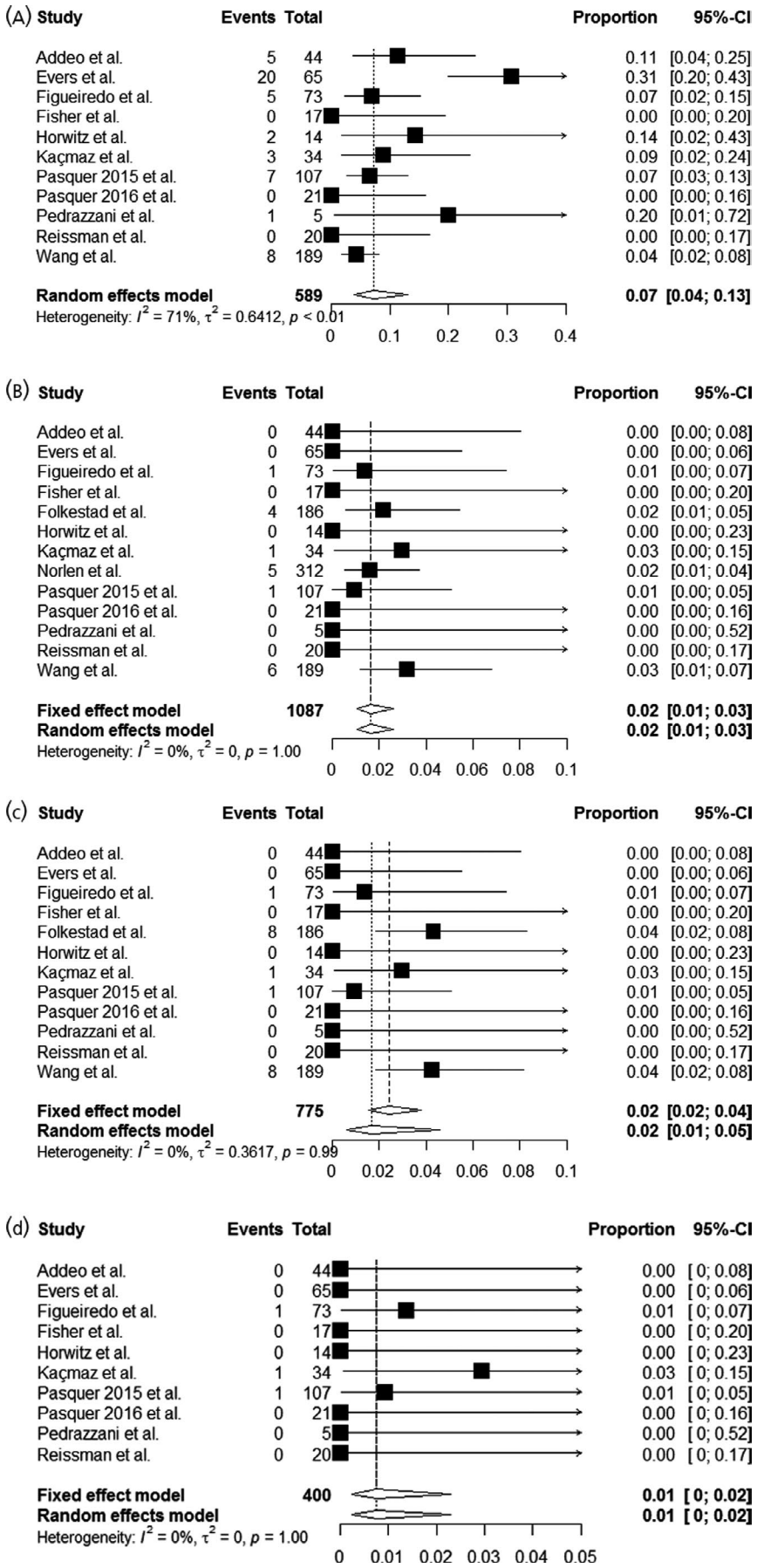


FIGURE 2 Pooled proportions for (A) severe morbidity, Clavien-Dindo grade III-IV, (B) 30-day mortality, (C) 90-day mortality and (D) in-hospital mortality. CI, confidence interval

TABLE 3 Pooled proportions for postoperative outcomes, stratified for median number procedures per year

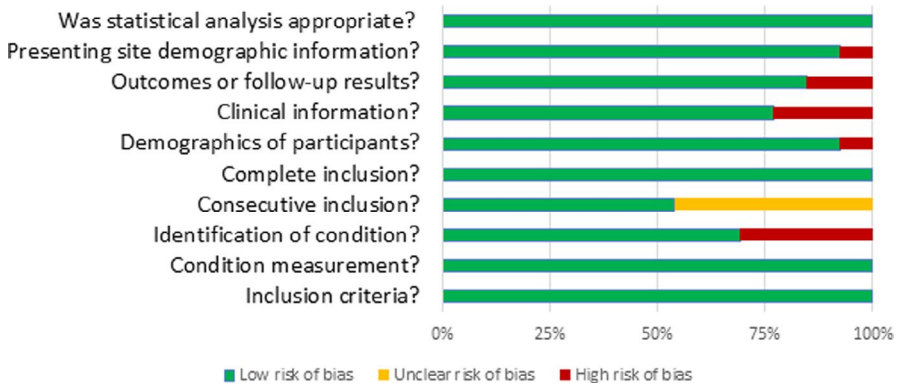
	Procedures per year	
Outcomes[a]	8 or less	9 or more
30-day mortality	1% (95% CI = 0%-2%), $I^2 = 0\%$	2% (95% CI = 1%-3%), $I^2 = 0\%$
90-day mortality	1% (95% CI = 0%-2%), $I^2 = 0\%$	4% (95% CI = 2%-6%), $I^2 = 0\%$
In-hospital mortality	1% (95% CI = 0%-2%), $I^2 = 0\%$	N/A[b]
Overall morbidity	15% (95% CI = 6%-31%), $I^2 = 89\%$	10% (95% CI = 5%-20%), $I^2 = 81\%$
Severe morbidity	9% (95% CI = 6%-16%), $I^2 = 0\%$	4% (95% CI = 2%-7%), $I^2 = 0\%$

Abbreviations: CI, confidence interval.

[a]Forest plots of individual analyses are presented in (Figure S4).

[b]This proportion could not be calculated as only one study reported this outcome.

FIGURE 3 Risk of bias graph. Overall risk of bias across all included studies



3.5 | Hospital volume and minimally invasive surgery

The median (IQR) annual hospital volume of SB-NEN resection was 4 (2-9) and the fourth quartile consisted of nine or more resections per year (defined as high-volume). Thirty-day mortality was similar (2% vs 1%) and 90-day mortality rates were higher in high volume centres (4% vs 1%) (Table 3; Figure S1A-D). High annual volume was associated with lower overall and severe morbidity compared to low volume: 10% vs 15% and 4% vs 9%, respectively (Figure S1F-I). Funnel plots estimating publication bias are presented in (Figure S5A-D). Herein, a skewed distribution is observed in the low volume hospitals, whereas outcomes in high volume hospitals are more centred. Pooled overall and severe morbidity rates were 20% (95% CI = 12%-32%, fixed effects model, $I^2 = 0\%$) and 7% (95% CI = 3%-16%, fixed effects model, $I^2 = 0\%$), respectively, after minimally invasive surgery (Figure S2A,B).

3.6 | Critical appraisal and risk of bias

Figure 3 presents the overall risk of bias for each item of the JBI checklist across all included studies. The study-level risk of bias for each individual study is presented in (Table S4). The majority of studies were retrospective.[7,8,23,25,26,29,31,34,35] A high risk of bias (ie, incomplete data) was present for clinical information in three of 13 studies (23%)[8,23,25] and for postoperative outcomes in two of 13 (15%) studies.[29,32] Funnel plots estimating publication bias are presented in (Figures S3A-D and S4A,B). The in-hospital mortality analysis was particularly skewed, and all but one study remained within the 95% CIs (severe morbidity analysis).

4 | DISCUSSION

This systematic review with meta-analysis on morbidity and mortality after resection of SB-NEN consisted of 13 studies with a total of 1087 patients. The meta-analyses revealed a severe morbidity rate of 7%, a 30-day mortality rate of 2%, a 90-day mortality rate of 2% and an in-hospital mortality rate of 1%. Analysis of annual hospital volume revealed that high volume centres appeared to have lower morbidity rates but a higher 90-day mortality rate, which probably reflects differences in case-mix and methodological issues.

Albers et al[13] recently analysed data concerning postoperative complications using the EUROCRINE registry, a European online endocrine surgical quality registry. They included 133 patients across 23 centres from nine different countries who underwent resection of a SB-NEN. Severe morbidity occurred in 11% of the patients, which is slightly higher than that observed in the present study (6%), and the mortality was 1%, which is similar. Under-reporting of complications might be one explanation for

the observed differences, whereas mortality is a more reliable outcome parameter in general. Only a minority of studies in the present review had a prospective design, illustrating the risk of underestimation of morbidity.

Current analyses show that overall and severe morbidity was lower in centres with a higher annual volume. Remarkably, 30- and 90-day mortality was slightly higher in high volume centres, at 1% and 3%, respectively, compared to low volume centres. This might be a result of the studies that could be included for the different endpoints. The study by Wang et al[34] included only stage IV patients and was the proportionally most weighted study for 90-day mortality analyses. Other factors that might have resulted in discrepancies between the different endpoints might be related to differences in the quality of the reported data or populations characteristics (ie, patient comorbidities, tumour stage, type and extensiveness of surgery) among the eligible studies for each of the meta-analyses. This hypothesis is supported by the funnel plots presented in Figure S5A-D: substantial publication bias is present in the low volume hospital papers, whereas outcomes are around the estimated effect size in high volume centres. Therefore, the reported mortality rates in low volume hospitals might not reflect the true mortality rates. Indication for surgery differs between clinics, in which some prefer to operate electively, whereas others prefer to delay the resection to a later stage with an increased risk for an emergency resection as a result of obstruction, perforation or ischaemia. In a retrospective cohort study, Folkestad et al[31] found that 24% of patients underwent an emergency resection. The diagnosis of SB-NEN was unknown in 58% of emergency resection cases, and significantly more postoperative deaths occurred as a result of surgical complications compared to an elective resection (9% vs 0%, respectively).

Morbidity and mortality rates after minimally invasive surgery did not differ from the overall group (ie, including MIS patients). A comparison between open and MIS was performed in two studies, in which one study found less complications after MIS, whereas the other found no differences.[7,8] Well-designed prospective studies might be able to clarify the differences between open and MIS regarding postoperative morbidity and mortality.

By pooling data and excluding studies with > 20% concomitant hepatectomies, the present study is more representative than individual cohort studies. However, the findings of the present study should be seen in the light of certain limitations. Although excluding studies with > 20% concomitant hepatectomies limited (some) heterogeneity, it failed to do so in the severe morbidity analyses, which had an I^2 of 71%. Some moderately sized studies reported no severe morbidities, whereas some smaller sized studies did. This suggests that differences between centres exist (eg, different expertise, surgical approach or complex surgical oncology units). Also, variables that could potentially have an influence on postoperative outcomes (ie, individual surgeon volume, location of mesenteric mass, body mass index, Charlson comorbidity index, American Society of Anaesthesiologists score) were not readily available or could not be deduced, and hence could not be corrected for or taken into account when interpreting the data. Ideally, a random effects meta-regression could have been considered to assess such sources of heterogeneity across the included studies. Similarly, several details about surgical treatment were not uniformly available. The results of the in-hospital mortality rate should be interpreted with caution because the funnel plot (Figure S1D) is skewed, which could represent the presence of reporting bias. Also, the majority of the publications had a retrospective design and did not report on consecutive cases, which might have introduced selection bias. Finally, the periods for which postoperative morbidity was reported by studies were only known for four of 13 studies, which makes the comparison of reported outcomes less effectual.

The most common postoperative complication was ileus, which could be attributable to extensive manipulation of the small bowel and the mesentery for lymphadenectomy. We have previously described techniques to prevent (potential) ischaemic complications with the use of fluorescence angiography as a consequence of mesenteric lymphadenectomy.[36] The complications that followed were intra-abdominal bleeding, wound/bladder infections and anastomotic leaks, which are relatable to gastrointestinal surgery in general, and hence multifactorial in aetiology.

We recommend that surgical studies clearly report morbidity/mortality outcomes. To achieve this, reporting of morbidity/mortality outcomes could be added to reporting guidelines, or made a mandatory condition for publication in journals. Future studies should also include the indication for surgery, whether patients were operated in a progressive disease stage with or without abdominal complaints or whether they were operated in a stable disease stage as a more pre-emptive resection of the primary tumour to prevent future complications of the primary tumour and/or mesenteric metastases. Centralisation of care for this rare disease has potential advantages because quality improvement programmes, innovation and clinical research all require a certain volume in general. However, the present review does not clearly indicate a certain volume-outcome relationship, with contradictory associations regarding morbidity and mortality, probably because of several methodological issues. We plan to set-up an international surgical registry of SB-NEN surgery to clarify the contradictory findings regarding morbidity and mortality, as well as investigate postoperative complications using standardised definitions, assessed at pre-defined time-points.

5 | CONCLUSIONS

This systematic review with meta-analyses showed relatively low morbidity and mortality rates after resection of SB-NEN. Contradictory associations of morbidity and mortality with hospital volume were found, which are probably related to heterogeneity among the eligible studies for different endpoints.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Enes Kaçmaz: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Visualisation; Writing – original draft; Writing – review & editing. **Jeffrey W. Chen:** Data curation; Writing – review & editing. **Pieter J. Tanis:** Conceptualisation; Supervision; Writing – review & editing. **Els J. M. Nieveen van Dijkum:** Conceptualisation; Supervision; Writing – review & editing. **Anton F. Engelsman:** Conceptualisation; Supervision; Writing – review & editing.

PEER REVIEW

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Enes Kaçmaz https://orcid.org/0000-0001-7265-3893

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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