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ORIGINAL ARTICLE

Contrast-enhanced ultrasound assessed renal microvascular perfusion may predict postoperative renal complications following colorectal surgery

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Abstract

Colorectal surgery is associated with an above-average mortality rate of approximately 15%. During surgery, maintenance of vital organ perfusion is essential in order to reduce postoperative mortality and morbidity, with renal perfusion of particular importance. Oesophageal Doppler monitors (ODM) are commonly used to try and provide accurate measures of fluid depletion during surgery; however, it is unclear to what extent they reflect organ perfusion. In addition, it is not known whether macro- and/ or microvascular perfusion indices are associated with renal complications following colorectal surgery. Thirty-two participants scheduled for colorectal surgery had three measures of macro- and microvascular renal blood flow via contrast enhanced ultrasound (CEUS), and simultaneous measures of cardiac output indices via ODM: (i) pre-operatively; (ii) intra-operatively at the mid-point of operation, and (iii) after the conclusion of surgery. The Postoperative Morbidity Survey (POMS) was used to assess postoperative complications. Intra-operatively, there was a significant correlation between renal microvascular flow (RT) and renal macrovascular flow (TTI) (ρ = 0.52; p = 0.003). Intra-operative TTI, but not RT, was associated with cardiac index (ρ = −0.50; p=0.0003). Intra-operative RT predicted increases in renal complications (OR 1.46; 95% CI 1.03–2.09) with good discrimination (C-statistic, 0.85). Complications were not predicted by TTI or ODM-derived indices. There was no relationship between RT and TTI before or after surgery. ODM measures of haemodynamic status do not correlate with renal microvascular blood flow, and as such are likely not suitable to determine vital organ perfusion. Only CEUS-derived measures of microvascular perfusion were predictive of postoperative renal complications.

KEYWORDS
cancer, imaging, renal, surgery, ultrasound

1 | INTRODUCTION

For patients undergoing surgery, mortality is around 4%,[1] with the development of postoperative complications a key predictor of postoperative mortality.[2] Colorectal surgery in particular has heightened complication rates of 15%–30%.[3] During surgery, maintenance of adequate vital organ perfusion via fluid therapy and optimisation of cardiovascular performance is essential in order to reduce postoperative mortality and morbidity. More specifically, acute kidney injury (AKI) is associated with an increase in postoperative mortality[4,5] and therefore strategies to help predict and avoid its occurrence may improve outcomes for patients undergoing surgery.

Due to the limitations of traditional indices such as heart rate and blood pressure (BP)[6] for the measurement of cardiovascular performance during surgery, cardiac output (CO) and stroke volume (SV) devices, such oesophageal Doppler monitors (ODM) were developed. These devices aim to provide more accurate measures of volume status and cardiovascular performance during surgery and are recommended by the UK National Institute for Health and Care Excellence (NICE) in patients undergoing major or high-risk surgery or other surgical patients in whom a clinician would consider using invasive cardiovascular monitoring.[7] However, it is unclear how CO measures of large vessel blood flow relate to microvascular organ perfusion, which may be a more important physiological measure to prevent organ dysfunction. Some studies in healthy research volunteers have suggested that ODM-derived CO indices may be poor predictors of organ microvascular blood flow.[8]

Insufficient renal microvascular blood flow may promote AKI,[9] and poor microvascular perfusion of other vital organs is also associated with postoperative complications.[10] Most current monitors used in anaesthetic practice, including CO monitors, are unable to accurately assess microvascular blood flow, which may explain inconsistent results regarding their use to reduce mortality in patients undergoing surgery.[11–13]

Contrast-enhanced ultrasound (CEUS) is a method to monitor real-time renal microvascular perfusion.[14–16] The administration of microbubbles that absorb ultrasound (US) waves allows real-time imaging of the microcirculation, which may provide useful additional clinical information during surgery as compared with CO monitors. However, the clinical significance of poor renal microvascular perfusion during surgery has been little studied. Therefore, the aims of this study were to test: (i) the feasibility of CEUS as a method to assess renal microvascular perfusion *during* surgery; (ii) whether CEUS-derived indices of renal microvascular perfusion correlate with traditional macrovascular indices of CO, SV and BP; and (iii) whether reductions in macro- and/or microvascular perfusion indices are associated with renal and general complications following colorectal surgery.

2 | RESULTS

We recruited 32 participants, of whom 7 (22%) were American Society of Anaesthetists (ASA) Grade 1, 21 (66%) ASA Grade 2 and 4 (12%) ASA Grade 3. The mean age was 64.6 ± 12 years. The median POMS score was 3 [IQR 2–4]. Renal complications developed in four (12.5%) of the study population. The median length of stay was 6.5 days [IQR 4–8].

Ten of the 32 participants underwent laparoscopically assisted procedures with an open abdomen. Anaesthetic techniques were comparable between all participants, with all receiving neuro-axial blockade via an epidural (3 participants) or spinal anaesthesia (29 participants) followed by a general anaesthetic. No intra-operative complications of CEUS occurred. Fluid administration varied significantly between participants (0.16 ± 0.06 mL/kg/min), with total fluid administered correlated with operative time (r = 0.58, p < 0.001; Table 1). CEUS measures were performed successfully at all three time points for all patients. Feedback from theatre staff and surgeons reported minimal and acceptable delays with intra-operative CEUS.

Mean percentage change in RT (microvascular blood flow) from induction was −5% to time point 2 and −7% to time point 3. Changes in TTI (macrovascular blood flow) from induction followed a similar pattern to changes in RT (to time point 2 = −6%, to time point 3 = −13%). Measures of RT and TTI showed no relationship to each other, or to ODM-derived indices or clinical outcome measures when recorded in the induction or postoperative phases. There was no significant correlation between intra-operative RT and MAP (ρ = −0.15; p = 0.41; Figure 1A), SV (ρ = −0.06; p=0.72; Figure 1B) or CI (ρ = −0.22; p = 0.22; Figure 1C). However, there was a significant correlation between intra-operative RT and TTI (ρ = 0.52; p = 0.003; Figure 1D) and also between intra-operative TTI and CI (ρ = −0.50; p = 0.0003).

Increases in intra-operative RT (reduced microvascular flow) predicted increases in renal complications (OR 1.46; 95% CI 1.03–2.09). The C-statistic was 0.85 indicating good discrimination (Figure 2). After adjusting for P-POSSUM predicted morbidity and fluid volume, results for this relationship remained significant (OR 1.72; 95% CI 1.01–2.92). Intra-operative TTI did not predict renal complications on univariate or multivariate analysis. Renal complications were also not predicted by intra-operative SV, MAP or CI.

For postoperative complications assessed using POMS, increases in intra-operative RT (reduced microvascular flow) alone did not predict increases in overall complications. However, when adjusting for P-POSSUM predicted morbidity and fluid volume, it did become a significant predictor (OR 1.37; 95% CI 1.05–1.79). Similarly, intra-operative TTI did not predict overall complications on univariate analysis but did on multivariate analysis (OR 1.29; 95% CI 1.09–1.52). On univariate analysis SV, MAP nor CI predicted overall complications. CI was, however, a significant predictor on multivariate analysis (OR 0.43; 95% CI 0.21–0.87).

3 | DISCUSSION

The results of this pilot study show that in patients undergoing colorectal surgery, none of the traditional measures of haemodynamic

TABLE 1 Patient surgical characteristics

Participant ID	Procedure	P-POSSUM Morbidity	P-POSSUM Mortality	Operation duration (mins)	POMS Score
1	Lap assisted anterior resection	25.5	1.1	177	5
2	Anterior resection	12.7	0.5	570	3
3	High anterior resection	17.5	0.7	450	1
4	Anterior resection	21.6	1.0	165	2
5	Low anterior resection	28.7	1.3	405	3
6	Low anterior resection	19.9	0.8	270	5
7	Anterior resection	76.1	8.6	360	3
8	Lap assisted right hemi	81.6	14.3	240	5
9	Panproctocolectomy	39.4	2.1	285	2
10	Extended right hemi	73.3	9.1	190	5
11	Lap assisted right hemi	49.8	3.6	180	4
12	Low anterior resection	25.5	1.1	225	2
13	Anterior resection	11.0	0.4	540	4
14	Lap assisted right hemi	27.5	1.3	150	1
15	Lap assisted right hemi	51.2	3.5	105	3
16	Anterior resection	21.6	1.0	330	3
17	Anterior resection	25.5	1.1	135	3
18	AP resection	25.5	1.1	120	1
19	Lap assisted abdominal perineal excision	31.2	1.2	295	5
20	Right hemi	21.6	1.0	180	1
21	Extended right hemi	27.5	1.3	190	3
22	Anterior resection	35.7	1.8	660	5
23	Lap assisted left hemi	55.2	4.1	420	2
24	Anterior resection	25.0	1.1	345	2
25	Abdominal perineal excision	58.2	3.9	300	5
26	Lap assisted anterior resection	11.0	0.4	300	3
27	Right hemi	30.8	1.6	165	2
28	Lap assisted anterior resection	41.8	2.6	300	2
29	Lap assisted right hemi	32.1	1.5	240	1
30	Panproctocolectomy	73.5	5.8	330	4
31	Ileal resection	9.3	0.4	240	1
32	Panproctocolectomy	18.5	0.8	300	2

status, including ODM-derived measures of CI, correlate with renal microvascular blood flow as assessed by CEUS. As expected, macrovascular organ blood flow was correlated with CI. Only CEUS-derived measures of microvascular perfusion were predictive of renal complications.

Despite the advantages of CO assessed indices of cardiovascular performance over traditional methods such as BP measurements, their use in directing fluid therapy during major surgery has provided conflicting results.[8,13,17,22] This may be due to the fact that CO monitors are unable to accurately assess organ microvascular perfusion. Our previous study demonstrated that CO as assessed by ODM in healthy volunteers did not correlate with CEUS assessed renal microvascular blood flow.[8] Similarly, in this study of patients undergoing colorectal surgery, we found no correlation between CI, SV or MAP when compared with our measure of renal microvascular perfusion. This suggests that CO may be a poor predictor of vital organ perfusion in patients undergoing surgery.

Previous studies have suggested that insufficient microcirculation may be associated with postoperative complications.[23] For example, poor intestinal microvascular blood flow has been shown to increase the risk of an anastomotic leak during colorectal surgery.[24] Sublingual microcirculation has been shown to be associated with postoperative complications in high-risk patients undergoing major abdominal surgery.[25] It must, however, be noted that this finding is not unequivocal, with other studies examining sublingually assessed microcirculation reporting no association between poor microcirculation and postoperative outcomes.[25]

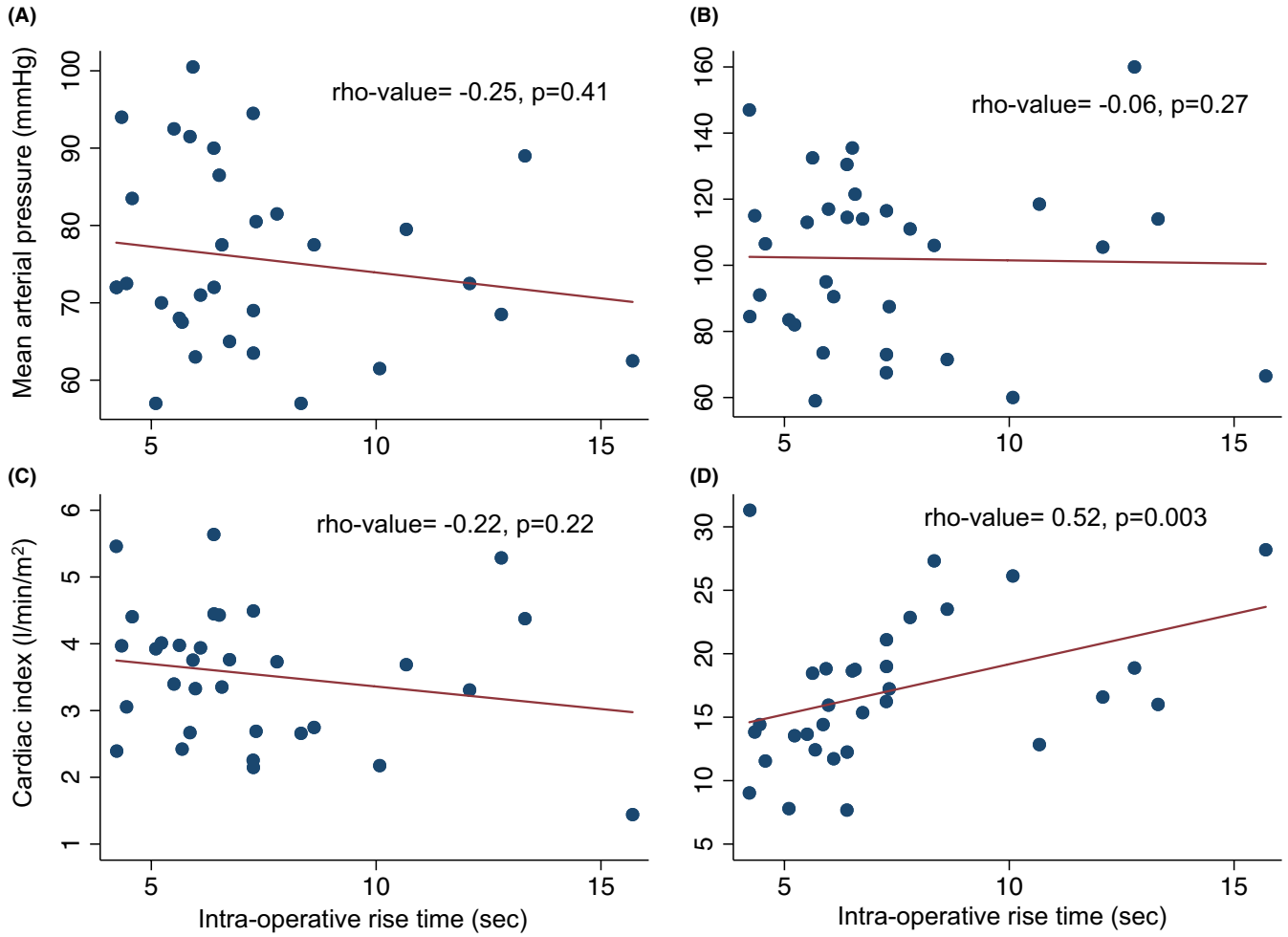

FIGURE 1 Relationship between intra-operative renal microvascular perfusion (intra-operative rise time in seconds (Y axis)) and A, Mean arterial pressure in mm Hg; B, Stroke volume in mL; C, cardiac index in L/min/m^2 (cardiac output in L/min divided by body surface area in m^2); D, Renal macrovascular blood flow as time to inflection in seconds

However, sublingually assessed microcirculation may not reflect microcirculatory changes in specific vital organs, such as the kidney.

Specific to the kidney, the architecture of the renal microcirculation makes it very susceptible to hypoxic injury.[4,26] This had led to calls to ensure adequate fluid status and inotropic support to maintain renal microperfusion, although it has been acknowledged that to date there is no reliable test to monitor renal blood flow when fluid challenges and inotropes are given.[5,27,28] CEUS may offer this monitoring to ensure optimum real-time renal perfusion and potentially reduce renal complications secondary to poor blood flow and renal hypoxia.

Currently available methods of assessing bedside renal blood flow such as Doppler ultrasound only give an indication of global macro- and not microvascular blood flow.[29] Other methods such as MRI and scintigraphy are not applicable to theatre environments making repeat assessments following surgical interventions difficult.[30] CEUS measurements of renal perfusion have been tested in multiple settings and have been found to correlate well with alterations in renal blood flow induced with agents such as dopamine and valsartan, whilst experience in renal transplants suggests good

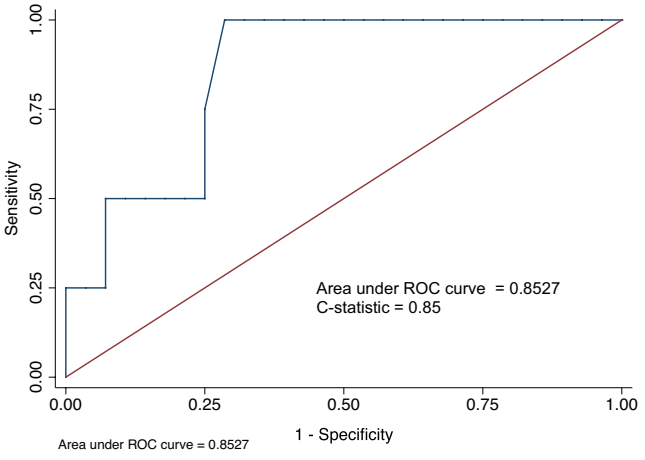

FIGURE 2 Area under the receiver operating characteristic (ROC) curve (C-statistic = 0.85) for average intra-operative rise time (microvascular perfusion) in discriminating postoperative renal complications

correlation between CEUS assessed renal blood flow and serum creatinine.[31–33]

Our previous work with CEUS in healthy volunteers in a laboratory setting[8] has demonstrated that interventions such as intravenous fluid therapy that induce increases in CO may not affect visceral microvascular blood flow. As previous studies have found an association between poor microvascular perfusion and an increase in postoperative complications,[10,25,34–36] this may explain the mixed results from trials using ODM guided fluid therapy. Explanations for these findings may involve the autoregulatory mechanisms inherent within the kidney, where increases in blood pressure may be compensated for with decreases in renal blood flow. However, the use of CEUS to assess real-time microvascular perfusion allows the search for novel therapies or selection of inotropes that optimise renal microvascular perfusion. For example, the β agonist ephedrine may be a better choice compared with the α agonist phenylephrine for optimising renal perfusion.

We do acknowledge that there are limitations with this current work. Firstly, our definition of renal complications was taken from the POMS score giving an incidence of 12.5%. Due to the relatively low number of included patients, we were unable to use more traditional definitions of acute kidney injury such as the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) score, with acute kidney injury having a reported incidence of around 5%[37] on RIFLE scoring. Secondly, although previous studies have demonstrated good correlation between CEUS assessed microvascular blood flow and thermodilution [18] and end organ microvascular perfusion,[19,20] real-time MRI imaging is considered the gold standard for imaging renal microvascular perfusion and to date CEUS measures have not been compared with arterial spin labelling (ASL) MRI. Thirdly, again due to patient numbers, we were unable to adjust for multiple confounders that may have affected the incidence of renal complications such as age, concurrent medications and use of inotropes.

In conclusion, we have shown that CEUS assessed renal microvascular blood flow is feasible in a surgical population. In addition, we have shown that traditional macrovascular indices do not appear to correlate with microvascular indices. Moreover, poor renal microvascular perfusion appears to be associated with renal complications following surgery, which may explain the equivocal results from trials of ODM guided fluid administration. These results require validation in larger studies.

4 | METHODS

4.1 | Participants and ethics

Ethical approval was obtained from the National Research Ethics Service in the UK (13/EM/0408), with the study registered on Clinicaltrials.gov before study commencement (NCT02136277). All participants provided written informed consent prior to participation in the study when they attended their pre-operative assessment clinic. The majority of patients underwent surgical procedures for colorectal cancer resections, although some did undergo surgery for inflammatory bowel disease. Inclusion criteria included patients undergoing colorectal surgery; fully open or laparoscopically assisted open procedures, aged 18–80 years, no metastatic disease and able to give informed consent. Exclusion criteria included oesophageal varices, recent acute coronary syndrome, known right to left shunts, severe pulmonary hypertension, uncontrolled hypertension, pregnancy or breast-feeding, known sensitivity to the CEUS contrast agent and prolonged QT syndrome.

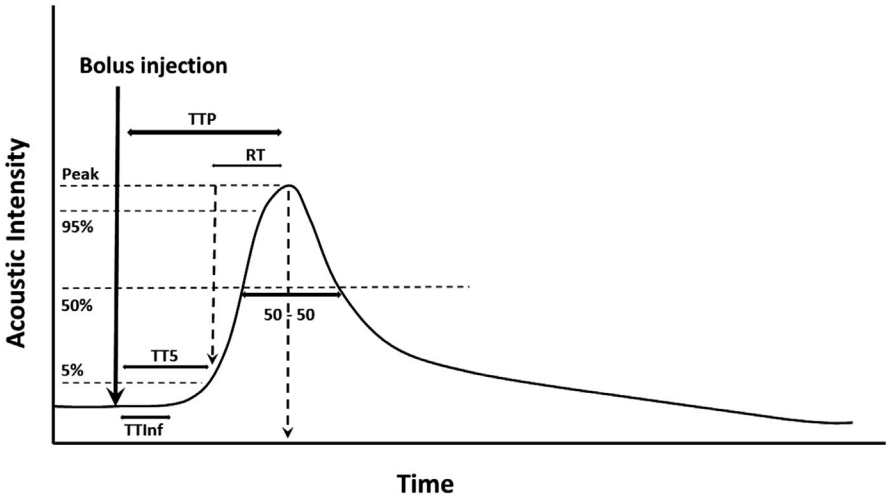

FIGURE 3 Annotated time-intensity curve for contrast enhanced ultrasound (CEUS). TTInf, time to inflection: time from injection until 1% of maximum acoustic intensity (AI); TT5, time to 5% perfusion (maximum AI); RT, rise time: time from 5% to 95% of maximum AI; TTP, time to peak (maximum) AI

All patients underwent general anaesthesia with monitoring provided at the discretion of the attending anaesthetist, although as a minimum included pulse oximetry, ECG and non-invasive BP monitoring. Administration of intravenous fluids and vasopressors in order to maintain cardiovascular homeostasis was also at the discretion of the anaesthetist. Anaesthetists did not have access to the data from the CEUS assessment of microvascular blood flow.

4.2 | Cardiac output monitoring

To assess CO indices an ODM (Deltex Medical, UK) was inserted by a member of the research team via a nasal or oral route[8,17] with the participant under general anaesthesia. Final CO values were converted to cardiac index (CI) values by division by body surface area (BSA).

Both CO and CEUS measurements were taken at the following time points: (1) as soon as possible after transfer to the operating theatre following the induction of anaesthesia; (2) intra-operatively at the mid-point of operation, at a time deemed appropriate by the operating surgeon; (3) after the conclusion of the surgery and prior to the emergence from the general anaesthesia.

4.3 | Contrast enhanced ultrasound assessments

The CEUS was used to assess both macro and microvascular renal organ perfusion. Whilst the patient was on the operating table, a sterile Philips iU22 US probe was placed on the participant's abdomen to visualise the kidney. 0.5 mL of SonoVue contrast agent was then administered intravenously as a bolus via a cannula with two 30 second video captures of the kidney. To assess macrovascular organ blood flow time to inflection (TTI; defined as time from injection until 1% of peak acoustic intensity is achieved) was used. Rise time (RT), defined as time from 5% to 95% of maximum acoustic intensity, was used to assess microvascular organ perfusion (Figure 3). All acoustic intensity analysis was performed using Philips Q-Lab ultrasound quantification software. Each of these measures was repeated twice at each time point, with an average of the readings at each time point used. Previous studies have demonstrated good correlation between CEUS assessed microvascular blood flow and thermodilution[18] and end organ microvascular perfusion.[19,20]

4.4 | Clinical outcomes

We used the Postoperative Morbidity Survey (POMS) to record postoperative complications in a standardised manner.[21] This score evaluates postoperative complications graded in categories including pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound complications and pain. It assigns a score of 1 if any of these complications develop within each category out of a possible total of nine. We also specifically evaluated whether or not the participant had a renal complication, defined within POMS as oliguria of <500 mL/24 h, increased serum creatinine >30% from pre-operative levels or a urinary catheter in situ for a non-surgical reason.

4.5 | Statistical analysis

Sample size calculations demonstrated that for an α of 0.05 and 1-β of 0.85, 32 subjects were needed to detect a 25% difference in microvascular blood flow, with a coefficient of variation 0.43 as seen from our previous CEUS studies.[8] Descriptive data are reported as mean ± SD, median [inter-quartile range] or number (%) as appropriate. Correlation between macrovascular and microvascular indices was assessed using Pearson's or Spearman's correlation as appropriate (normality testing using the Shapiro-Wilk test). To assess the ability of haemodynamic indices to predict renal complications we used binary logistic regression presented as odds ratios (OR) and 95% confidence intervals (CI). We assessed linearity of predictors using the lowess command in STATA with logit-transformed outcomes. We assessed goodness of fit using calibration plots. Model discrimination was assessed using the C-statistic (area under ROC curve). For POMS score, we performed ordinal logistic regression. To adjust for confounders, we added P-POSSUM predicted morbidity and intra-operative fluid volume administered to the final models. Participants with missing covariate data were excluded from the analysis (n = 2). All analyses were performed using Stata version 15.

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CONFLICT OF INTEREST

No authors have a conflict of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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

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