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Original Article

Composite endpoint for liver and colon simultaneous surgery: a proposed approach to reduce sample size of future clinical trials

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ABSTRACT

Background: With expanding indications for resection of colorectal liver metastasis (CRLM), simultaneous resections for primary colon cancer (CC) with synchronous colorectal liver metastases (sCRLM) has increased. sCRLM remains debated, however, and only a handful, often underpowered, trials have evaluated this approach. We sought to develop a composite postoperative endpoint (composite endpoint for liver and colorectal simultaneous surgery [CELCSS]) combining colon- and liver-specific complications to reduce sample size requirements in future prospective randomized clinical trials.
Methods: Patients who underwent simultaneous resection for CC and sCRLM between 2012 and 2021 were identified from the American College of Surgeons National Surgical Quality Improvement Program database. CELCSS components were selected using univariable logistic regression. Associations among CELCSS, prolonged length of stay (LOS), and 30-day mortality were assessed. Sample size estimates were calculated for CELCSS and its individual components. Separate training and internal validation cohorts were used for model development and testing.
Results: Among 1591 patients in the training cohort, 24.3% (n = 386) had a positive CELCSS. Components included postoperative bleeding (6.5%), colon anastomotic leak (15.4%), reoperation (4.8%), bile leak (4.1%), and posthepatectomy liver failure (3.5%). CELCSS-positive patients more frequently underwent major resection (34.5% vs 18.6%; P < .001), but there was no difference regarding American Society of Anesthesiology classification or receipt of neoadjuvant therapy (P > .5). CELCSS demonstrated good predictive performance for prolonged LOS (area under the curve [AUC], 0.71 training; 0.72 testing) and 30-day mortality (AUC, 0.70 training; 0.71 testing). Of note, CELCSS reduced the required sample size by 41.4% to 88.5% compared with individual complications.
Conclusion: CELCSS is a strong predictor of outcomes and may be used as a postoperative endpoint to improve clinical trial feasibility by reducing required sample size.

Introduction

The incidence of colon cancer (CC) in the United States has increased over the last decade and now represents the third most common malignancy and third leading cause of cancer-related mortality [1]. Moreover, 1 in 2 patients diagnosed with CC will develop metastases during their disease course, and as many as 30% present with metastatic disease at the time of diagnosis. The liver is the most frequent site of metastasis, and surgical resection remains the gold-standard treatment for hepatic metastases, whether performed upfront or after preoperative systemic therapy for conversion/downsizing of disease [2–4].

The presence of synchronous colorectal liver metastases (sCRLM) at diagnosis is generally a negative prognostic factor relative to survival [2]. Among patients with sCRLM, the operative approach can include the traditional “primary-first” approach, which involves resection of the primary tumor followed by chemotherapy and subsequent hepatic resection [5,6]. An alternative staged strategy—usually reserved for

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patients with rectal cancer—prioritizes liver resection first, followed by subsequent resection of the primary tumor [7–9]. In addition, a simultaneous approach involving resection of the primary and CRLM at the same operative setting may be used [10–13]. In fact, some surgeons have argued that—in well-selected patients—the simultaneous approach may decrease total days in the hospital and overall costs, while not increasing the risk of complications [14–16]. However, the “optimal” surgical strategy for patients with sCRLM remains controversial and is often debated. To date, only 1 randomized surgical trial (the METASYNC trial) has investigated simultaneous versus stage resection for sCRLM, which demonstrated comparable postoperative morbidity for the 2 operative approaches [17]. The lack of high-quality data may, in part, be caused by most surgical clinical trials being underpowered owing to poor accrual and low sample size, which has led to an increased risk of inadequate power and the risk of a type II statistical error [17,18]. Therefore, the current study sought to develop a potential approach to address the issue of underpowered clinical trials within this complex and multidisciplinary field.

Composite endpoints have been proposed as a means to merge several siloed outcomes of interest into a single composite metric. Because the occurrence of any single outcome is inherently less likely to occur than the sum of the individual outcomes in the composite metric, “events” are more frequent and lower statistical power is generally needed to examine the composite outcome. To date, composite endpoints have been used to assess the quality of complex surgical interventions in several different abdominal and thoracic surgical procedures [19–24]. However, no surrogate endpoint has been proposed related to the outcomes of patients undergoing simultaneous colon and hepatic resection. Therefore, the current study aimed to develop and internally validate a composite postoperative endpoint for postoperative morbidity after simultaneous resection of CC and sCRLM. Such a tool may reduce the required sample size to detect meaningful differences in surgical clinical trials aimed at examining outcomes among patients being treated with different operative approaches for sCRLM.

Methods

Data source and patient selection

The study cohort was identified from the 2012–2021 American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, using the “Colectomy” and “Hepatectomy” procedure-targeted participant use data files (PUFs). Patients were selected by primary procedure based on Current Procedural Terminology (CPT) codes and assessed for concurrent colon or liver resection. To identify simultaneous resections, hepatectomy CPT codes were used to detect concurrent hepatectomy among patients who also were in the colectomy PUF, whereas colectomy CPT codes were used to identify concurrent colectomy in the hepatectomy PUF. Diagnosis of metastatic CC was further confirmed using International Classification of Diseases, 9th Revision (ICD-9), and International Classification of Diseases, 10th Revision (ICD-10) codes and procedure-targeted PUF variables (Supplementary Table 1). The 2 datasets were merged and linked based on the unique, deidentified case ID [25–27].

Propensity score matching (PSM) analysis was used to generate 1:1 matched cohorts based on PUF of origin to control for selection bias. The following covariates were included in the PSM analysis: age, sex, diabetes, history of smoking, chronic obstructive pulmonary disease, ascites, dialysis, steroid use, American Society of Anesthesiology (ASA) classification, need for preoperative transfusion, inpatient or outpatient admission, preoperative international normalized ratio, operative time, neoadjuvant therapy receipt, probability of mortality, and probability of morbidity. The use of PSM to adjust for case mix was based on previously published studies [28]. This study has been conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The institutional review boards of Ohio State University approved this study.

Variables of interest

Baseline demographic and clinical characteristics of the cohort included age, sex, ASA classification, neoadjuvant therapy, extent of liver resection (ie, major/minor), operative time, use of minimally invasive surgery, and length of stay (LOS). Complications of interest included postoperative bleeding, colon anastomotic leak, reoperation, bile leak, and posthepatectomy liver failure (PHLF), which were identified using ICD-9 and ICD-10 codes or using the appropriate variables in each procedure-targeted PUF (Supplementary Table 1). Major liver resection was defined as resection involving 3 or more Couinaud liver segments [29].

Primary outcomes of interest included prolonged LOS, defined as > 15 days between index operation and discharge, and 30-day mortality [20]. Selection of potential predictors for these outcomes was informed by previously developed composite endpoints and the METASYNC [17,19,20]. The components of the composite endpoint for liver and colorectal simultaneous surgery (CELCSS) were selected in line with previously developed composite endpoints designed for the same purpose [19,20]. In particular, regarding hepatic resection, the composite endpoint of liver surgery (CELS) included bile leak, PHLF, and posthepatectomy hemorrhage—the latter corresponding to postoperative bleeding related to the liver resection. Intraoperative blood loss was not included owing to the lack of validated quality cutoff values [20]. Similarly, the pancreatic surgery composite endpoint (PACE), in addition to postoperative hemorrhage, included reoperation as a non–organ-specific variable [19]. These components were included among the primary outcomes in the METASYNC trial [4]. Anastomotic leak was also included as a colon-specific complication, which was similar to the METASYNC study [17]. As such, the CELCSS components included bile leak, PHLF, postoperative bleeding, leak of intestinal anastomosis, and reoperation. CELCSS was considered positive if a patient experienced 1 or more of these complications [17,19,20].

Statistical analysis

Missing values were addressed using multiple imputation by chained equations with fully conditional specification [30,31]. In particular, hepatectomy-specific complications such as PHLF and bile leak were systematically missing in the colectomy dataset, whereas data on colon anastomotic leak were systematically missing in the hepatectomy dataset [32]. Patients with missing data for other composite endpoint variables were excluded. Thirty imputed datasets (m = 30) were generated via a random forest method across all variables, with a maximum of 50 iterations per chain (maxit = 50) and a fixed seed for reproducibility (seed = 555) [33]. The final dataset was randomly split into training and testing cohorts in an 80:20 ratio.

Continuous variables were reported as median with IQR, and categorical variables were reported as frequency with percentages. Comparisons between continuous and categorical variables were conducted using the Wilcoxon rank-sum test and the χ^2 test or Fisher’s exact test, respectively. Univariable logistic regression was used to assess the association between CELCSS and prolonged LOS or 30-day mortality. The predictive performance of CELCSS for these outcomes was evaluated using sensitivity, specificity, receiver operating characteristic curves, and area under the curve (AUC). Logistic regression assessed calibration for prolonged LOS and postoperative mortality in both training and testing cohorts. The ability of CELCSS to predict prolonged LOS and 30-day mortality was internally validated in the testing cohort.

Theoretical sample size calculations for a randomized clinical trial (RCT) were performed to estimate the minimum number of patients necessary per arm, assuming an alpha of 0.05 and a beta of 0.20 (2-sided testing) and a 25% to 75% relative reduction in incidence of either a single CELCSS component of the composite endpoint itself [20]. The calculation was based on a 2-sided comparison of proportions, using the following standard formula for independent samples:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^{*}[p_1(1-p_1) + p_2(1-p_2)}{(p_1 - p_2)^2}$$

in which n represented the sample size per group, p_1 and p_2 were the expected event rates in the control and intervention groups, respectively, $Z_{1-\alpha/2}$ is the standard normal deviate corresponding to the chosen 2-sided significance level (α), and $Z_{1-\beta}$ corresponded to the desired power (1−β) [34].

The α and β assumptions were selected in accordance with parameters used by Nickel et al. [19] and Kawashima et al. [20] to ensure methodological consistency and comparability with previously validated approaches. The scenarios assumed 25%, 50%, and 75% relative risk reductions to illustrate the progressive decrease in required sample size as the expected relative risk reduction increased. Subgroup analyses were performed among patients undergoing major liver resection to evaluate the discriminatory performance of CELCSS by the extent of liver resection. AUC, sensitivity, and specificity of CELCSS were recalculated for this subgroup in both training and testing cohorts. Further subanalyses of patients who only underwent major resection, as well as using organ-space SSI as a surrogate for bile leak and anastomic leak were performed. All tests were 2 sided, and $P < .05$ was considered statistically significant. All statistical analyses were performed using R version 4.4.3 (R Project for Statistical Computing).

Results

Baseline training cohort characteristics and development of CELCSS

The training cohort included 1591 patients who underwent simultaneous colon and liver resection. Median age was 58 years (IQR, 49–67 years); most were male (n = 890; 55.9%) and had ASA class 3 to 4 (n = 1188; 74.8%). Neoadjuvant therapy was administered to 925 patients (58.1%), and 77.6% of individuals (n = 1234) underwent minor liver resection. Among CELCSS-positive patients, the most common complication was colon anastomotic leak (n = 245; 63.5%), followed by postoperative bleeding (n = 104; 26.9%), reoperation (n = 76; 19.7%), bile leak (n = 65; 16.8%), and PHLF (n = 55; 14.2%) (Table 1).

On univariable analysis, several factors were associated with prolonged LOS including bile leak (odds ratio [OR], 5.13; 95% CI, 2.82–9.00; $P < .001$), PHLF (OR, 7.19; 95% CI, 3.92–12.84; $P < .001$), anastomotic leak (OR, 4.96; 95% CI, 3.36–7.29; $P < .001$), and reoperation (OR, 15.57; 95% CI, 9.44–25.70; $P < .001$). In contrast, postoperative bleeding was not associated with LOS of > 15 days ($P = .144$) (Table 2). Factors associated with 30-day mortality included predictive postoperative bleeding (OR, 3.93; 95% CI, 1.10–11.05; $P = .017$), bile leak (OR, 6.61; 95% CI, 1.84–18.84; $P < .001$), PHLF (OR, 7.95; 95% CI, 2.21–22.83; $P < .001$), anastomotic leak (OR, 4.10; 95% CI, 1.57–10.23; $P = .003$), and reoperation (OR, 7.55; 95% CI, 2.39–20.35; $P < .001$) (Table 2).

Overall, 386 patients (24.3%) were classified as being CELCSS positive in the training cohort (Table 1). CELCSS-positive patients more frequently underwent major resection (n = 133 [34.5%] vs n = 224 [18.6%]) and had a longer median LOS (8 days [IQR, 5–13] vs 6 days [IQR, 5–8]) than CELCSS-negative patients (all $P < .001$) (Fig. 1). The CELCSS score correlated with both prolonged LOS (n = 79 [20.5%] vs n = 45 [3.7%]; $P < .001$) and 30-day mortality (n = 12 [3.1%] vs n = 7 [0.6%]; $P < .001$) (Table 1 and Fig. 2). There was no difference between CELCSS-positive and negative patients relative to age ($P = .140$), ASA class ($P = .500$), or receipt of neoadjuvant therapy ($P = .600$).

In the training cohort, CELCSS was associated with prolonged LOS (OR, 6.63; 95% CI, 4.54–9.83; $P < .001$) and 30-day mortality (OR, 6.54; 95% CI, 1.57–32.43; $P = .011$). The ability of CELCSS to predict prolonged LOS was very good with an AUC of 0.71 (95% CI, 0.67–0.76), a sensitivity of 0.63, and a specificity of 0.79; for 30-day mortality, the AUC was 0.70 (95% CI, 0.58–0.81) with a sensitivity of

Table 1
Baseline characteristics of the training cohort.

Characteristic	N	Overall, N = 1591[a]	No CELCSS, n = 1205[a]	CELCSS, n = 386[a]	*P* value[b]
Age	1591	58.0 (49.0, 67.0)	58.0 (49.0, 67.0)	59.0 (50.0, 67.0)	.14
Sex	1591				.3
Female		701.0 (44.1)	540.0 (44.8)	161.0 (41.7)	
Male		890.0 (55.9)	665.0 (55.2)	225.0 (58.3)	
ASA	1588				.5
1–2		400.0 (25.2)	308.0 (25.6)	92.0 (23.8)	
3–4		1188.0 (74.8)	894.0 (74.4)	294.0 (76.2)	
Neoadjuvant therapy	1591				.6
No		666.0 (41.9)	509.0 (42.2)	157.0 (40.7)	
Yes		925.0 (58.1)	696.0 (57.8)	229.0 (59.3)	
Major resection	1591				< .001[c]
No		1234.0 (77.6)	981.0 (81.4)	253.0 (65.5)	
Yes		357.0 (22.4)	224.0 (18.6)	133.0 (34.5)	
Operative time	1591	304.0 (233.0, 390.0)	303.0 (227.0, 382.0)	311.0 (248.0, 416.0)	.013[c]
Minimally invasive surgery	1591				.010[c]
No		1275.0 (80.1)	948.0 (78.7)	327.0 (84.7)	
Yes		316.0 (19.9)	257.0 (21.3)	59.0 (15.3)	
Length of stay	1575	6.0 (5.0, 9.0)	6.0 (5.0, 8.0)	8.0 (5.0, 13.0)	< .001[c]
Postoperative bleeding	1591	104.0 (6.5)	0.0 (0.0)	104.0 (26.9)	< .001[c]
Colorectal anastomotic leak	1591	245.0 (15.4)	0.0 (0.0)	245.0 (63.5)	< .001[c]
Reoperation	1591	76.0 (4.8)	0.0 (0.0)	76.0 (19.7)	< .001[c]
Bile leak	1591	65.0 (4.1)	0.0 (0.0)	65.0 (16.8)	< .001[c]
PHLF	1591	55.0 (3.5)	0.0 (0.0)	55.0 (14.2)	< .001[c]
30-d mortality	1591				< .001[c]
No		1572.0 (98.8)	1198.0 (99.4)	374.0 (96.9)	
Yes		19.0 (1.2)	7.0 (0.6)	12.0 (3.1)	
LOS of > 15 d	1591				< .001[c]
No		1467.0 (92.2)	1160.0 (96.3)	307.0 (79.5)	
Yes		124.0 (7.8)	45.0 (3.7)	79.0 (20.5)	

ASA, American Society of Anesthesiologists; LOS, length of stay; PHLF, posthepatectomy liver failure.

[a] Median (quartile 1, quartile 3); number (percentage).

[b] Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's exact test.

[c] Statistically significant.

Table 2
Univariable logistic regression for prolonged LOS and 30-day mortality.

Variable	Prolonged LOS		30-d mortality	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Bleeding	1.60 (0.81–2.90)	.144	3.93 (1.10–11.05)	.017[a]
Anastomotic leak	4.96 (3.36–7.29)	< .001[a]	4.10 (1.57–10.23)	.003[a]
Bile leak	5.13 (2.82–9.00)	< .001[a]	6.61 (1.84–18.84)	< .001[a]
Reoperation	15.57 (9.44–25.70)	< .001[a]	7.55 (2.39–20.35)	< .001[a]
PHLF	7.19 (3.92–12.84)	< .001[a]	7.95 (2.21–22.83)	< .001[a]
CELCSS	6.63 (4.54–9.83)	< .001[a]	6.54 (1.57–32.43)	.011[a]

CELCSS, composite endpoint for liver and colorectal simultaneous surgery; LOS, length of stay; OR, odds ratio; PHLF, posthepatectomy liver failure.

[a] Statistically significant.

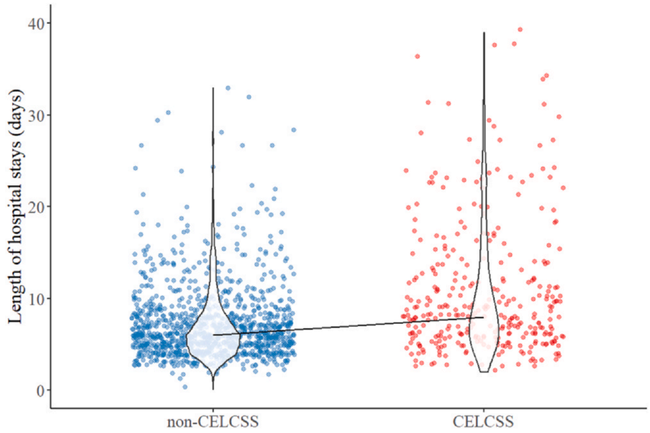

Figure 1. Jitter plot showing the difference in length of stay between CELCSS-positive and CELCSS-negative patients in the training cohort. CELCSS, composite endpoint for liver and colorectal simultaneous surgery.

Table 3
Performance metrics of the composite endpoint as a predictor of prolonged LOS and 30-day mortality.

Metric	Endpoint: LOS of > 15 d		Endpoint: 30-d mortality	
	Training	Testing	Training	Testing
AUC	0.71 (0.67–0.76)	0.72 (0.62–0.82)	0.70 (0.58–0.81)	0.71 (0.53–0.89)
Sensitivity	0.63	0.63	0.63	0.63
Specificity	0.79	0.82	0.76	0.8

AUC, area under the curve; LOS, length of stay.

0.63 and a specificity of 0.76 (Table 3). Calibration curves demonstrated strong agreement between predicted probabilities based on CELCSS and observed outcomes in both training and testing cohorts (Supplementary Fig. 1 and 2).

Validation of CELCSS

Among 397 patients in the internal validation cohort, 21.2% of individuals (n = 84) were positive for CELCSS, which correlated with longer median LOS (8.5 days [IQR, 6–12] vs 6 days [IQR, 5–8]; *P* < .001) than CELCSS-negative patients (Supplementary Table 2). In the testing cohort, CELCSS demonstrated good discriminatory ability to predict prolonged LOS with an AUC of 0.72 (95% CI, 0.62–0.82), a sensitivity of 0.63, and a specificity of 0.82; coherence with the training cohort was demonstrated by the calibration curve (Supplementary Fig 1B). Similarly, CELCSS demonstrated good predictive performance for 30-day mortality with an AUC of 0.71 (95% CI, 0.53–0.89), a sensitivity of 0.63, a specificity of 0.80, and an overall agreement with the training cohort (Table 3 and Supplementary Fig 2B).

CELCSS as a tool to reduce clinical trial sample size

The calculation of sample size requirements for clinical trials was based on estimating complication incidence rates needed to achieve varying levels of minimal clinically important risk reduction. For a 25% relative risk reduction, using CELCSS as the primary endpoint would require 1420 enrollees compared with 12,312 using PHLF, 10,356 using bile leak, 8804 using reoperation, 6330 using postoperative bleeding, and 2462 using anastomotic leak as individual endpoints. To achieve a 50% relative risk reduction, the required sample size would be 310 patients using CELCSS vs 2644 using PHLF, 2226 using bile leak, 1892 using reoperation, 1362 using postoperative bleeding, and 534 using anastomotic leak as individual endpoints (Table 4, Fig. 3).

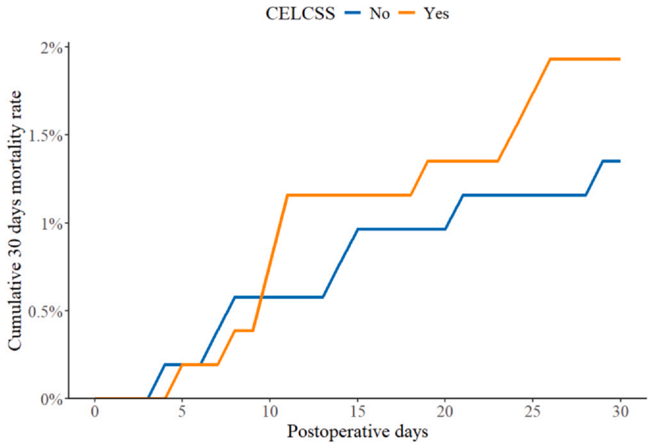

Figure 2. Cumulative incidence of 30-day mortality among the CELCSS-positive and CELCSS-negative patients. CELCSS, composite endpoint for liver and colorectal simultaneous surgery.

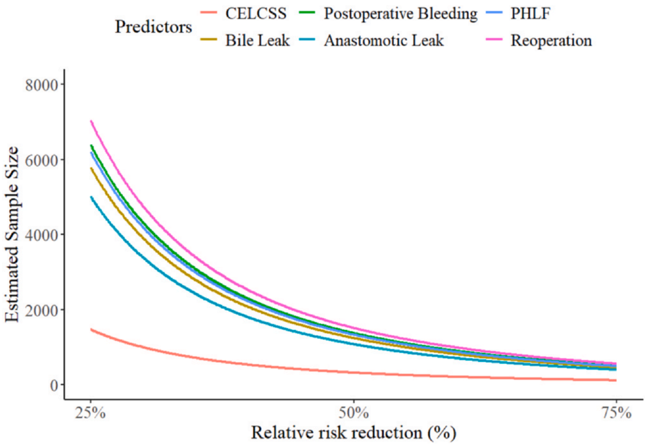

Figure 3. Estimated sample size based on assumed relative risk reduction for CELCSS and each of its components. CELCSS, composite endpoint for liver and colorectal simultaneous surgery; PHLF, posthepatectomy liver failure.

A subanalysis was performed among patients who underwent major hepatic resection. CELCSS remained associated with higher odds of prolonged LOS (OR, 7.57; 95% CI, 3.62–17.4; $P < .001$) and 30-day mortality (OR, 8.71; 95% CI, 1.39–167.87; $P = .049$). CELCSS was a good predictor of prolonged LOS with an AUC of 0.74 (95% CI, 0.68–0.81), a sensitivity of 0.78, and a specificity of 0.68. Similarly, the composite endpoint demonstrated good predictive performance for 30-day mortality with an AUC, sensitivity, and specificity of 0.66 (95% CI, 0.5–0.82), 0.83, and 0.64, respectively (Supplementary Table 3). The subanalysis involving only patients who underwent major resection (Supplementary Tables 4 and 5) , as well as the sensitivity analysis of SSI (Supplementary Tables 6–8) demonstrated comparable reductions in sample size and model performance to the main analysis.

Discussion

The optimal surgical approach for synchronous CC and CRLM resection remains a topic of debate. Simultaneous resection of CC tumors and CRLM may allow for shorter LOS, reduced overall hospitalization costs, and quicker time to initiation of adjuvant therapy [14,26,35–37]. Other studies have suggested that a staged approach may be preferable owing to a lower risk of severe complications [25,38]. Most available evidence comes from retrospective studies, which, although informative, cannot replace the rigor of RCTs [39–47]. To date, only one randomized surgical trial (the METASYNC trial) has investigated simultaneous vs staged resection for sCRLM [17]. Of note, data from this study failed to demonstrate a difference in postoperative morbidity between the two operative approaches, which may have been caused by being underpowered owing to low sample size and a type II statistical error [17,18]. Traditionally, studies assessing optimal surgical strategies have relied on individual complications as endpoints for postoperative morbidity [17,27,48]. Although providing increased specificity, individual siloed endpoints often fail to capture the overall risk associated with surgery. In addition, the low incidence of any one of the individual outcomes impedes powering trials, complicates study design, and limits feasibility owing to the very large cohorts needed for accrual [19,21]. To address these limitations, we introduced the CELCSS—a composite endpoint incorporating key uncommon complications related to hepatectomy and colectomy, as well as major clinical events. The treatment of CRLM continues to evolve. In particular, there is a growing interest in how to manage synchronous CRLM, as evidenced by new trials on simultaneous colon and liver resection [49,50]. The current study represented an important first attempt to apply a methodology to devise a composite endpoint to assess 2 distinct surgical procedures using a combined metric. The intent was to conceptualize simultaneous colon and hepatic resections as a single, integrated episode of care. Although the findings require further investigation and external validation, the proposed methodological framework helps inform future clinical trials evaluating simultaneous resection. CELCSS demonstrated robust predictive performance for both prolonged LOS and 30-day mortality. By offering a more comprehensive and statistically efficient measure of postoperative morbidity risk, CELCSS has the potential to reduce required sample sizes substantially and improve the power and feasibility of future RCTs evaluating simultaneous CC and CRLM resection.

Although several retrospective studies have compared staged strategies (liver-first and primary-first) with simultaneous resection for sCRLM, data on morbidity and mortality have been inconsistent [17,40,41,43–47,51]. In most retrospective studies, patients selected for simultaneous resection were typically lower risk and underwent less extensive liver and colon resections, thus introducing selection bias [39–45,52]. In fact, a recent meta-analysis of more than 30 studies reported no statistically significant difference in outcomes between simultaneous and staged approaches; however, the two cohorts were imbalanced, with the simultaneous resection group including fewer patients with advanced CRLM and markedly fewer patients who underwent a major hepatectomy, further highlighting the need for RCTs [52]. This trend was also observed in the current cohort, given that more than 75% of patients underwent a minor liver resection. Given that the extent of resection is a well-established predictor of postoperative complications and mortality in liver surgery, this finding underscores the potential for selection bias when comparing staged with simultaneous resection for sCRLM [26]. Notably, a recent analysis in the United States (2004–2014) demonstrated a 37% increase in the utilization of simultaneous resection, which was associated with reduced postoperative complications, mortality, LOS, and hospital costs [16]. Given the growing adoption of simultaneous CC and CRLM resection, advances in chemotherapy, and the oncology field's shift toward personalized treatment, there is a pressing need for prospective RCTs to understand the precise role of simultaneous vs staged resection of sCRLM to inform clinical guidelines.

More than two decades ago, Boudjema et al. [17] conducted the only randomized trial comparing simultaneous vs staged resection, which enrolled a limited number of patients. Interestingly, even in the METASYNC trial, which was a randomized study, the frequency of complex procedures was unevenly distributed among the two study arms—with more patients undergoing a major liver resection in the staged-surgery arm [53]. In this study, there was no difference in morbidity among patients in the staged vs simultaneous group, possibly owing to differences in cohort characteristics or a type II statistical error. Although the approach to calculating sample size differed, the METASYNC trial primary outcomes were the same as the CELCSS components. If the METASYNC trial had used our proposed methodology, the required sample size for each endpoint would have been substantially larger, given the assumed 20% absolute difference between arms. Because the double triangular test used in METASYNC also depended on outcome incidence, applying a composite endpoint like CELCSS could have improved the trial's statistical efficiency and reduced the necessary sample size. Nonetheless, CELCSS still requires external and long-term validation before broader application. Unfortunately, many surgical trials do not report or justify sample size calculations or fail to reach target accrual, resulting in a high proportion of underpowered studies [54]. Increasing the number of observations is an effective way to control random error, and sample size determination should be made a priori, with careful attention to the variables involved in the calculation [55]. The adoption of composite outcomes based on consensus in the field may simplify outcome assessment and aligns with the principles of "textbook outcomes" and benchmarking, which have been increasingly adopted and embraced [19]. Recent composite endpoints, such as the CELS by Kawashima et al. [20] and PACE by Nickel et al. [19], have been developed in response to this need [54]. Combining different outcomes into a composite endpoint increases statistical precision, reducing the required sample size, as well as potential cost and duration of clinical trials [56–58]. One of the main downsides of composite endpoints is the potential loss of information resulting from the combination of multiple individual outcomes [59]. The present study aimed to propose a practical approach to evaluate postoperative outcomes in a complex surgical setting in which numerous clinical events may occur during the postoperative course. In such a context, developing a summary measure—intended to complement, rather than replace, the assessment of individual clinically relevant complications—may help capture overall quality of the surgical procedure. Moreover, composite outcomes can help avoid competing risks in outcome assessment and are particularly valuable when assessing rare events [58,60].

The CELCSS offers several important advantages over conventional short-term surgical endpoints among patients undergoing simultaneous colectomy and hepatectomy. To the best of our knowledge, this was the first study to incorporate both colon- and liver-specific components into a single composite endpoint, serving as a robust predictor of short-term outcomes after simultaneous primary CC and synchronous CRLM resection. Of note, the proposed

Table 4
Estimated required sample size depending on different predicted relative risk reductions.

Estimated sample size				
Variable	Incidence	Relative risk reduction		
		25%	50%	75%
CELCSS	0.24	1420	310	116
Bile leak	0.04	10,356	2226	824
Postoperative bleeding	0.07	6330	1362	504
Anastomotic leak	0.15	2462	534	198
PHLF	0.03	12,312	2644	980
Reoperation	0.05	8804	1892	702

CELCSS, composite endpoint for liver and colorectal simultaneous surgery; PHLF, posthepatectomy liver failure.

CELCSS endpoint had an AUC of ≥ 0.70 to predict prolonged LOS and 30-day mortality in both the training and internal validation cohorts. By streamlining the assessment of outcomes after complex, multidisciplinary procedures for sCRLM, CELCSS may obviate the need to interpret each complication separately [19,21,22]. Furthermore, the use of CELCSS markedly reduced the sample size needed to detect clinically meaningful risk reductions in postoperative morbidity, thereby potentially decreasing the cost and duration of clinical trials, improving completion rates, and strengthening the overall evidence base [19,21]. Of note, assuming a predicted 25% relative risk reduction, the CELCSS allowed for a reduction in sample size of 88.47% compared with PHLF alone, 86.29% compared with bile leak alone, 83.87% compared with reoperation alone, 77.57% compared with postoperative bleeding alone, and 42.32% compared with anastomotic leak alone. Owing to its simplicity, ability to simultaneously capture a broad spectrum of uncommon complications, and statistical efficiency, CELCSS may enhance the feasibility of prospective studies while maintaining consistency with established outcome frameworks [19,21].

The results of this study should be interpreted in light of several limitations. The ACS maintains strict quality control over data integrity; however, the retrospective nature of the study (even based on prospectively collected data) may suffer from selection bias. In addition, the analysis was conducted based on the procedure-targeted PUFs for colectomy and hepatectomy. Therefore, the study did not include rectal cancer patients and lacked NSQIP data on proctectomy, which is a high-risk procedure that warrants future dedicated analyses. Given that the ACS-NSQIP database only included data for the first 30 postoperative days, it was not possible to evaluate CELCSS as a predictor of long-term outcomes (eg, overall/disease-free survival). In a large national database, a certain degree of ICD/CPT code misclassification cannot be entirely excluded [61]; however, ACS-NSQIP uses rigorous quality control measures. In addition, given the retrospective nature of the study, residual selection bias was possible. The lack of external validation represented another limitation; therefore, future studies are warranted to further validate and confirm the effectiveness of CELCSS as a postoperative composite outcome. In particular, external validation is needed before recommending CELCSS for broad use in clinical trials. The percentage of missing values among CELCSS components was a limitation, although missingness rates of 50% or less have been shown to only marginally deviate from original datasets [32]. In addition, there were no hospital-specific or surgeon-specific variables. Survival data were limited to the 30-day postoperative period because no long-term outcomes were available in NSQIP.

Conclusion

CELCSS may serve as a useful tool that can be easily and consistently applied across different centers to assess short-term surgical outcomes among patients undergoing simultaneous resection of CC and CRLM. Further evidence on this complex and increasingly used procedure is necessary, and the CELCSS endpoint may prove valuable for the design of new clinical trials aimed at understanding the optimal utilization of this surgical approach.

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Declaration of competing interest

The authors declare no competing interests.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gassur.2025.102262.

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