# Colonic Continuity After Splenic Flexure Resection: Does the Orientation of the Anastomosis Matter? A Retrospective Cohort Study

*Ann. Ital. Chir.*, 2026 97, 6: 1120–1126
https://doi.org/10.62713/aic.4318

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AIM: Splenic flexure resection (SFR) is a technically demanding procedure due to the region's complex vascular anatomy and limited colonic mobility. The orientation of the colonic anastomosis—either isoperistaltic or anisoperistaltic—represents a critical yet understudied technical factor that may influence operative complexity and postoperative recovery. This study aimed to compare short-term outcomes between these two anastomotic configurations.

METHODS: We conducted a retrospective cohort study at a tertiary colorectal center, including consecutive patients who underwent elective SFR for colon cancer between January 2023 and December 2024 (n = 53). Patients were stratified according to the orientation of the side-to-side anastomosis: isoperistaltic (ISO, n = 32) or anisoperistaltic (ANISO, n = 21). Demographic, oncologic, surgical, and postoperative variables were analyzed. Primary endpoints were operative time, gastrointestinal recovery (time to first flatus and first stool), and length of hospital stay. Secondary endpoints included estimated blood loss, conversion rate, 30-day complications, inflammatory markers, analgesic use, costs, and quality of life assessed using the Gastrointestinal Quality of Life Index (GIQLI).

RESULTS: Baseline demographics were largely comparable between groups, although patients in the ANISO group were significantly older (71.4 ± 6.0 vs. 67.8 ± 4.4 years; $p = 0.023$) and had a slightly lower body mass index (BMI) (25.4 ± 1.4 vs. 26.5 ± 2.3 kg/m$^2$; $p = 0.049$). Operative time was significantly shorter in the ANISO group (126.5 ± 13.8 vs. 154.8 ± 23.4 minutes; $p < 0.001$). Gastrointestinal recovery was faster following anisoperistaltic anastomosis, with earlier first flatus (31.7 ± 8.7 vs. 39.3 ± 10.2 hours; $p = 0.005$), while time to first stool did not differ significantly (51.2 ± 12.5 vs. 55.8 ± 9.0 hours; $p = 0.159$). Length of hospital stay was comparable (5.2 ± 0.8 vs. 5.6 ± 1.3 days; $p = 0.172$). Estimated blood loss was significantly lower in the ANISO group (34.6 ± 17.0 vs. 47.6 ± 13.6 mL; $p = 0.006$). Conversion rate and postoperative complications were comparable between groups ($p = 1.000$ and $p = 0.743$ respectively). No differences were observed in inflammatory markers, analgesic use, or costs. GIQLI scores at 30 days were similar between groups (126.9 ± 11.0 vs. 123.0 ± 8.1; $p = 0.166$).

CONCLUSIONS: Anisoperistaltic anastomosis following splenic flexure resection is safe and effective and is associated with shorter operative time and faster postoperative gastrointestinal recovery without compromising short-term outcomes. The choice of anastomotic orientation may be influenced by intraoperative anatomical conditions and technical factors.

**Keywords:** splenic flexure resection; isoperistaltic; anisoperistaltic; gastrointestinal function; quality of life

## Introduction

Splenic flexure resection is widely regarded as one of the most technically challenging procedures in colorectal surgery. Its anatomical location, variable vascular supply, and limited colonic mobility contribute to operative complexity and increased technical demands [1–3]. Positioned at the junction of the distal transverse and proximal descending colon, the splenic flexure represents an embryologic transition zone between the midgut and hindgut. As a result, it receives a dual blood supply from the terminal branch of the middle colic artery (superior mesenteric artery) and the left colic artery (inferior mesenteric artery), rendering it a classic watershed area vulnerable to ischemia during extensive mobilization or vascular ligation [4].

Although splenic flexure tumors account for only 2–8% of colorectal malignancies [5,6], resection of this segment may also be required for non-oncologic indications, including ischemic colitis, complicated diverticulitis, or iatrogenic in-

*Submitted: 25 August 2025 Revised: 14 October 2025 Accepted: 28 October 2025 Published: 27 May 2026*
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*Editor: Aldo Rocca*

jury. From an oncologic perspective, the optimal extent of resection and lymphadenectomy remains debated, particularly with respect to achieving adequate nodal clearance and negative margins [6]. While segmental resections were historically considered acceptable, more recent trends favor extended resections, such as left hemicolectomy or subtotal colectomy, to ensure oncologic radicality and facilitate safer reconstruction [7].

Unlike right or sigmoid colectomy, splenic flexure resection lacks a universally accepted operative standard, resulting in substantial heterogeneity in surgical approach, extent of resection, and reconstructive strategy [7].

A pivotal yet often underappreciated technical consideration in splenic flexure resection is the orientation of the side-to-side anastomosis, namely whether it is configured in an isoperistaltic or anisoperistaltic fashion. Isoperistaltic anastomosis aligns the proximal and distal bowel segments in the same direction of peristaltic flow and is traditionally considered more physiological. In contrast, anisoperistaltic anastomosis orients the bowel segments in opposing directions and is frequently adopted when anatomical constraints—such as limited reach or excessive tension—preclude isoperistaltic alignment. Despite theoretical concerns regarding physiological motility, several studies suggest that anisoperistaltic anastomoses may achieve comparable functional outcomes, particularly when a tension-free and well-perfused reconstruction is ensured [8–10].

The choice of anastomotic orientation is typically dictated by intraoperative factors, including mesenteric length, vascular reach, and the need to minimize tension or torsion. Achieving an isoperistaltic configuration often requires extensive mobilization of the descending colon, careful preservation of the marginal artery of Drummond, and meticulous handling of the mesocolon to maintain perfusion and alignment [1–3]. Conversely, anisoperistaltic orientation may offer a technically simpler solution when colonic mobility is limited, particularly in the setting of high inferior mesenteric artery ligation or a fixed descending colon [3,6].

The literature addressing optimal anastomotic orientation after splenic flexure resection is sparse and largely extrapolated from studies involving other colonic segments or upper gastrointestinal procedures [8–11]. Data from analogous operations suggest that peristaltic alignment may influence anastomotic integrity, transit time, and functional outcomes, including bowel regularity and quality of life [9,12]. However, colonic motility—particularly in the left colon—is slower, segmental, and governed by complex neuromuscular patterns, making the clinical relevance of anastomotic orientation in this setting uncertain.

Within the framework of enhanced recovery after surgery (ERAS) protocols, which prioritize early functional recovery and discharge readiness [13], anastomotic orientation represents a potentially modifiable factor influencing postoperative outcomes. Beyond anastomotic safety, this includes patient-centered endpoints such as bowel function and quality of life.

This study aimed to compare perioperative outcomes and gastrointestinal recovery between isoperistaltic and anisoperistaltic anastomotic configurations following splenic flexure resection.

## Methods

*Study Design and Participants*

This retrospective cohort study was conducted at a tertiary colorectal center (Desio Hospital). Consecutive patients undergoing elective splenic flexure resection for colon cancer between January 2023 and December 2024 were included. The study protocol was approved by the Institutional Review Board of the Comitato Etico Milano Area 3 (Approval Number: 2950520245) and conducted in accordance with the Declaration of Helsinki. Since this retrospective study involved no patient-identifiable information and ensured complete anonymization, the Institutional Review Board of the Comitato Etico Milano Area 3 waived the requirement for informed consent.

The study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [14].

*Patient Selection*

Patients were eligible for inclusion if they met the following criteria:

- Age $\geq$18 years.
- Elective splenic flexure resection with primary colonic anastomosis.
- Documented side-to-side anastomotic orientation (isoperistaltic or anisoperistaltic) in the operative report.

The following exclusion criteria were applied:

- Emergency surgery (e.g., perforation, obstruction).
- Construction of a diverting stoma.
- Missing or incomplete perioperative data.

*Surgical Technique*

All surgeries were performed by experienced colorectal surgeons using either an open or laparoscopic approach, based on individual case assessment.

The extent of resection, segmental colectomy, left hemicolectomy, or extended colectomy was tailored to the underlying pathology and oncologic considerations. Standardized lateral-to-medial mobilization of the splenic flexure was performed in all cases.

Patients were stratified into two groups according to the orientation of the anastomosis:

- Isoperistaltic (ISO) group: side-to-side anastomosis with aligned peristaltic direction of both bowel segments.
- Anisoperistaltic (ANISO) group: side-to-side anastomosis with opposing peristaltic direction.

The choice between isoperistaltic and anisoperistaltic side-to-side anastomosis was not protocolized and was made in-

traoperatively to achieve a tension-free, well-perfused reconstruction. The decision was primarily influenced by: (1) mesenteric reach/length after splenic flexure mobilization; (2) vascular ligation level of the Inferior Mesenteric Artery (high vs. low) and handling of the middle colic branches; (3) preservation/continuity of the marginal artery; (4) descending colon mobility and need for additional medial-to-lateral mobilization; (5) subjective anastomotic tension or torsion risk on a trial approximation; and (6) perfusion assessment according to the operating surgeon (with or without indocyanine-green fluorescence, when available). When isoperistaltic alignment required excessive mobilization or resulted in perceived tension, an anisoperistaltic configuration was preferred to prioritize perfusion and low tension.

*Perioperative Management*

All patients followed a standardized ERAS-based perioperative pathway, including early ambulation on the day of surgery whenever feasible, initiation of oral intake on the evening of surgery, opioid-sparing multimodal analgesia, early urinary catheter removal, and avoidance of routine nasogastric decompression.

*Data Collection*

Data were retrospectively collected from electronic medical records and operative reports. Collected variables included:

• Demographics: sex, age, body mass index (BMI), ASA classification and comorbidities.

• Tumor Characteristics: histological grade and stage according to the American Joint Committee on Cancer (AJCC) [15].

• Surgical details: anastomotic orientation and technique (ISO vs ANISO), operative time (minutes), estimated blood loss (mL) and conversion rate (laparoscopic to open).

*Outcomes*

Primary endpoints were operative time, gastrointestinal recovery and length of hospital stay (LOS). Gastrointestinal recovery was defined as the time from the end of surgery to the first passage of flatus and the first stool. Both events were nurse-recorded in the standardized postoperative flow sheet, based on direct patient reporting during routine rounds.

Secondary endpoints included estimated blood loss, conversion, 30-day complication rate classified by Clavien–Dindo (CD) grading [16], and additional clinical indicators: inflammatory response (white blood cell [WBC] count and C-reactive protein [CRP] on postoperative day 3 [POD-3]), analgesic requirement (cumulative ketorolac during hospitalization), cost (according to adjusted government reimbursement), and quality of life.

Quality of life was assessed using the Gastrointestinal Quality of Life Index (GIQLI) at 30 days [17], a validated and widely used instrument consisting of 36 items covering gastrointestinal symptoms, physical function, emotional status, and social function. Each item is scored from 0 to 4, the total score ranges from 0 to 144 with higher scores indicating better quality of life.

*Statistical Analysis*

Statistical analyses were performed using RStudio statistical software (version 2025.05.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation and compared using the Student's *t* test, while non-normally distributed data are reported as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. Categorical variables were expressed as counts and percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. A $p$-value $< 0.05$ was considered statistically significant.

## Results

*Patient Characteristics and Group Allocation*

A total of 53 patients underwent splenic flexure resection between January 2023 and December 2024 and met the inclusion criteria. Of these, 32 patients received an isoperistaltic anastomosis and 21 received an anisoperistaltic anastomosis. Baseline demographics and tumor characteristics for the entire cohort are reported in Table 1.

No statistically significant differences were observed between the ISO and ANISO groups in terms of sex ($p$ = 0.577), ASA classification ($p$ = 0.553), diabetes ($p$ = 1.000), cardiovascular disease ($p$ = 1.000), Chronic Obstructive Pulmonary Disease (COPD) ($p$ = 1.000), tumor grade ($p$ = 0.755), or tumor stage ($p$ = 1.000). However, patients in the ANISO group were significantly older (71.4 ± 6.0 vs. 67.8 ± 4.4 years; $p$ = 0.023) and had a slightly lower BMI (25.4 ± 1.4 vs. 26.5 ± 2.3 kg/m$^2$; $p$ = 0.049).

*Primary Outcomes*

Primary outcomes are presented in Table 2. Operative time was significantly shorter in the ANISO group (126.5 ± 13.8 vs. 154.8 ± 23.4 min, $p < 0.001$). First flatus occurred earlier (31.7 ± 8.7 vs. 39.3 ± 10.2 h, $p$ = 0.005). Time to first stool (51.2 ± 12.5 vs. 55.8 ± 9.0 h, $p$ = 0.159) and length of hospital stay (5.2 ± 0.8 vs. 5.6 ± 1.3 days, $p$ = 0.172) were comparable between groups.

*Secondary Outcomes*

Estimated blood loss was significantly lower in the ANISO group (34.6 ± 17.0 vs. 47.6 ± 13.6 mL, $p$ = 0.006). Conversion rates (4.8% vs. 6.3%, $p$ = 1.000) and complication rates (19.0% vs 25.0%, $p$ = 0.743) were comparable. No anastomotic leaks or mortalities occurred. Clavien–Dindo grade ≥III complications were rare. POD-3, WBC and CRP, ketorolac use, and costs did not differ significantly. Adjusted hospital reimbursement was also similar (6679.8 ± 2267.6

**Table 1. Baseline demographics and tumor characteristics of the study population.**

| Characteristic | ISO | ANISO | *p*-value |
|---|---|---|---|
| Total | 32 | 21 | |
| Age, years, mean ± SD | 67.8 ± 4.4 | 71.4 ± 6.0 | 0.023 |
| Sex, *n* (%) | | | 0.577 |
| Male | 17 (53.1) | 9 (42.9) | |
| Female | 15 (46.9) | 12 (57.1) | |
| BMI, kg/m$^2$, mean ± SD | 26.5 ± 2.3 | 25.4 ± 1.4 | 0.049 |
| ASA score, *n* (%) | | | 0.553 |
| I | 8 (25.0) | 2 (9.5) | |
| II | 16 (50.0) | 14 (66.7) | |
| III | 6 (18.8) | 4 (19.0) | |
| IV | 2 (6.3) | 1 (4.8) | |
| Diabetes | 5 (15.6) | 4 (19.0) | 1.000 |
| Cardiovascular disease | 6 (18.8) | 3 (14.3) | 1.000 |
| COPD | 2 (6.3) | 2 (9.5) | 1.000 |
| Tumor grade (AJCC), *n* (%) | | | 0.755 |
| G1 | 12 (37.5) | 6 (28.6) | |
| G2 | 18 (56.3) | 13 (61.9) | |
| G3 | 2 (6.3) | 2 (9.5) | |
| Tumor stage (AJCC), *n* (%) | | | 1.000 |
| I | 10 (31.3) | 7 (33.3) | |
| II | 13 (40.6) | 9 (42.9) | |
| III | 9 (28.1) | 5 (23.8) | |

BMI, body mass index; SD, standard deviation; ASA, American Society of Anesthesiologists; ISO, isoperistaltic; ANISO, anisoperistaltic; COPD, Chronic Obstructive Pulmonary Disease; AJCC, American Joint Committee on Cancer.

vs 6303.3 ± 1335.7 €, $p = 0.498$). GIQLI scores at 30 days were similar between groups (126.9 ± 11.0 vs. 123.0 ± 8.1, $p = 0.166$). Results are summarized in Table 3.

## Discussion

This retrospective study offers one of the first focused analyses comparing isoperistaltic and anisoperistaltic anastomoses following splenic flexure resection (SFR), a technically demanding procedure characterized by anatomical variability, complex vascularization, and absence of standardized operative guidelines [1,3,6]. Our findings suggest that anisoperistaltic orientation is not only technically feasible but may also confer advantages in operative efficiency and early postoperative gastrointestinal recovery without increasing morbidity.

A key finding of this study is the significantly shorter operative time observed in the anisoperistaltic group, likely attributable to reduced need for extensive medial-to-lateral mobilization and avoidance of high-tension anastomoses, particularly in the setting of high inferior mesenteric artery ligation or short mesentery [2,3,6]. In contrast, isoperistaltic alignment typically requires greater mobilization of the descending colon and careful preservation of the marginal artery of Drummond to achieve tension-free reconstruction, thereby prolonging operative time and increasing technical complexity [1,3,4]. The absolute differences observed—approximately 30 minutes in operative time is clinically meaningful in the context of perioperative care. A 30-minute reduction in operative time may reduce anesthesia exposure and operating room utilization, with potential benefits in terms of surgical efficiency.

Importantly, anisoperistaltic anastomosis was associated with significantly lower intraoperative blood loss. This finding supports the hypothesis that this configuration may facilitate a technically simpler and less demanding anastomotic strategy. This is consistent with prior anatomical studies highlighting the vulnerability of the splenic flexure as a watershed zone at the junction of the Superior Mesenteric Artery and Inferior Mesenteric Artery territories, where aggressive mobilization can compromise perfusion and increase intraoperative bleeding [1,4].

Postoperative gastrointestinal recovery was partially improved in the anisoperistaltic group, with a significantly earlier return of flatus. However, time to first stool and length of hospital stay were comparable between groups. GIQLI scores at 30 days were comparable between groups, suggesting that anastomotic configuration does not significantly influence early patient-reported outcomes [17].

These findings are particularly relevant in the context of ERAS protocols, where early restoration of gut function is a cornerstone of postoperative care and a determinant of discharge readiness [13]. Interestingly, despite improvements in operative time and early bowel function, no differences were observed in length of stay or overall postoperative recovery. This may reflect the standardized ERAS pathway applied to all patients, which can attenuate variability in postoperative trajectories and limit differences in discharge timing. Our results align with recent studies reporting comparable or partially improved functional recovery with anisoperistaltic configurations, particularly in patients undergoing right hemicolectomy or ileocolic anastomosis [8–11,18].

The assumption that isoperistaltic alignment is more "physiological" has largely been extrapolated from upper gastrointestinal and small bowel surgery. In gastrojejunostomy, isoperistaltic orientation has been associated with improved motility and reduced bile reflux [19]. Similarly, in ileocolic anastomoses, some evidence suggests that isoperistaltic orientation may influence bacterial overgrowth and regularity of bowel habits [10]. However, these dynamics may not apply to colonic segments, especially in the left colon where peristalsis is intermittent, haustral, and influenced by segmental neural and myogenic control rather than continuous propulsive activity. In fact, it is important to note that results from right-sided colectomies cannot be directly extrapolated to splenic flexure resections. Regional differences in colonic motility are well documented: the right colon is characterized by segmental mixing and slower peristaltic activity, whereas the left colon

**Table 2. Primary outcomes.**

| Primary outcomes | ISO | ANISO | *p*-value |
|---|---|---|---|
| Total | 32 | 21 | |
| Operative time, minutes, mean ± SD | 154.8 ± 23.4 | 126.5 ± 13.8 | < 0.001 |
| First flatus, hours, mean ± SD | 39.3 ± 10.2 | 31.7 ± 8.7 | 0.005 |
| First passage of stool, hours, mean ± SD | 55.8 ± 9.0 | 51.2 ± 12.5 | 0.159 |
| Length of stay, days, mean ± SD | 5.6 ± 1.3 | 5.2 ± 0.8 | 0.172 |

**Table 3. Secondary outcomes.**

| Secondary outcomes | ISO | ANISO | *p*-value |
|---|---|---|---|
| Total | 32 | 21 | |
| Estimated blood loss, mL, mean ± SD | 47.6 ± 13.6 | 34.6 ± 17.0 | 0.006 |
| Conversion rate, *n* (%) | 2 (6.3) | 1 (4.8) | 1.000 |
| 30-day complications, *n* (%) | 8 (25.0) | 4 (19.0) | 0.743 |
| Clavien-Dindo 1 | 4 (12.5) | 1 (4.8) | |
| Clavien-Dindo 2 | 3 (9.4) | 2 (9.5) | |
| Clavien-Dindo 3 | 1 (3.1) | 1 (4.8) | |
| WBC count, POD-3, $\times 10^9$/L, mean ± SD | 6.20 ± 1.44 | 6.63 ± 1.78 | 0.363 |
| C-reactive protein, POD-3, mg/L, mean ± SD | 115.2 ± 32.3 | 113.7 ± 25.1 | 0.850 |
| Ketorolac use during hospitalization, mg, mean ± SD | 148.7 ± 47.4 | 163.7 ± 29.7 | 0.164 |
| Cost, adjusted government reimbursement, €, mean ± SD | 6303.3 ± 1335.7 | 6679.8 ± 2267.6 | 0.498 |
| GIQLI score at 30 days after surgery, mean ± SD | 123.0 ± 8.1 | 126.9 ± 11.0 | 0.166 |

WBC, white blood cell; POD-3, postoperative day 3; GIQLI, Gastrointestinal Quality of Life Index.

and splenic flexure show more coordinated propulsive contractions. These physiological variations may influence how isoperistaltic versus anisoperistaltic configurations behave in different colonic regions, reinforcing the need for site-specific evidence rather than extrapolation from right-sided data [8,11,20].

Consistent with our findings, Matsuda *et al.* [8] demonstrated comparable short-term outcomes between isoperistaltic and anisoperistaltic colorectal anastomoses, suggesting that functional differences may be negligible in colonic surgery. A randomized trial (Isoperistaltic versus antiperistaltic ileocolic anastomosis [ISOVANTI]) also failed to identify significant differences in postoperative outcomes between the two orientations in ileocolic anastomosis [9]. These data reinforce the view that in colorectal reconstruction, especially at the splenic flexure, perfusion and tension-free alignment may be more critical than directional peristalsis.

Safety outcomes in our study were comparable between groups. Overall 30-day morbidity, including Clavien–Dindo grade ≥3 complications, was low and did not differ significantly. Notably, no anastomotic leaks or 30-day mortalities were observed in either cohort. These results are reassuring and align with previous reports showing acceptable outcomes for both configurations in colorectal surgery [7,8,10].

In addition, no significant differences were observed in postoperative inflammatory markers, including WBC count and CRP levels on postoperative day 3, suggesting that the orientation of the anastomosis does not significantly influence the systemic inflammatory response. Similarly, hospital costs were comparable between groups, indicating that the shorter operative time and length of stay associated with the anisoperistaltic configuration did not translate into significant economic differences within the current reimbursement framework.

Our findings carry several clinical implications. First, anisoperistaltic alignment should be considered a valid and often preferable option in cases where an isoperistaltic configuration is technically challenging or anatomically unfeasible. Second, the observed improvements in operative efficiency and reduced intraoperative blood loss may be particularly beneficial in elderly or frail patients, where minimizing surgical stress is critical. [13].

The retrospective design and monocentric nature introduce potential selection bias, especially since the choice of anastomotic orientation was at the discretion of the surgeon. Although most baseline characteristics were comparable between groups, significant differences in age and BMI were observed and should be taken into account when interpreting the results. Unmeasured variables such as mesenteric thickness, bowel redundancy, or vascular anatomy may have also influenced intraoperative decision-making. Additionally, our limited sample size, inherent to the rarity of splenic flexure resections, may not detect rare events such as anastomotic leaks or late strictures and limits the statistical power to detect differences in some outcomes, thereby limiting the generalizability of our findings. Moreover, we acknowledge that our study included only elective resections with primary anastomosis, while emergency cases

(e.g., obstruction, perforation) and patients requiring diverting stomas were excluded. This selection enhances internal validity but limits external generalizability. In urgent or technically complex scenarios, anastomotic orientation may behave differently, as mesenteric length, colonic distension, contamination, and hemodynamic instability can significantly influence reconstruction. Therefore, our findings should be interpreted with caution in emergency or high-risk settings, where the priority may shift from optimal orientation to rapid, safe restoration of continuity or stoma formation. Finally, long-term functional outcomes, such as continence, need for laxatives, or quality-of-life measures, were not assessed but represent important endpoints for future research.

Moving forward, larger prospective multicenter studies, with standardized intraoperative documentation and objective functional assessments, are needed to validate these findings. The development of peristalsis-neutral anastomotic strategies, prioritizing perfusion and low tension over directionality, may ultimately represent a paradigm shift in left-sided colonic reconstruction.

## Conclusions

This retrospective study suggests that anisoperistaltic anastomosis following splenic flexure resection is a safe and effective alternative to isoperistaltic configuration. While both orientations yielded comparable complication rates and oncologic outcomes, anisoperistaltic alignment was associated with shorter operative time and earlier return of bowel function.

These findings challenge the assumption that isoperistaltic orientation is inherently superior and support a pragmatic approach to anastomotic reconstruction, prioritizing perfusion and tension-free alignment over theoretical physiological considerations. Given the complex anatomy of the splenic flexure, this flexibility may enhance operative efficiency without compromising patient outcomes.

Further prospective studies are needed to validate these results and explore long-term functional outcomes. Until then, anastomotic orientation should be guided by intraoperative conditions, not dogma.

## Availability of Data and Materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

Conceptualization: JC, DM, CM, GMM. Methodology: RS, BV, GMM. Data Analysis: FR, MS, VD and AB. Writing - Original Draft: FR, AB. Writing - Review & Editing: JC, RS, DM, CM, GMM. Supervision: CM, GMM. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of the Comitato Etico Milano Area 3 (Approval Number: 2950520245). The research was conducted in line with the Declaration of Helsinki. Since this retrospective study involved no patient-identifiable information and ensured complete anonymization, the Institutional Review Board of the Comitato Etico Milano Area 3 waived the requirement for informed consent.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

Giulio Mari is serving as one of the Guest Editors of this journal. We declare that Giulio Mari had no involvement in the peer review of this article and has no access to information regarding its peer review. Other authors declare no conflict of interest.

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