An investigation of the relationships between postoperative pain trajectories and outcomes after surgery for colorectal cancer

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Abstract

Background: Although animal studies have shown that pain can suppress host immunity and promote tumor metastasis, few clinical studies have evaluated the association between acute pain and long-term outcomes after cancer surgery.

Methods: Patients undergoing colorectal cancer resection at a medical center between November 2010 and December 2014 were collected. Pain intensity was recorded using a numeric rating scale at 12, 24, 36, 48, 72, 96, and 120 hours postoperatively. Group-based modeling of longitudinal pain scores was used to categorize pain trajectories. Recurrence-free survival and overall survival were analyzed using Cox proportional hazards models.

Results: A total of 2401 patients with 13931 pain score observations were analyzed. The trajectory model identified three groupings of inpatient postsurgical pain, including 70.3% with mild pain dropping to low (group 1), 20.0% with moderate/severe pain dropping to mild (group 2), and 9.7% with moderate pain rebounding to severe (group 3). Univariate models showed that pain trajectories were significantly associated with recurrence-free survival (group 2 vs 1: hazard ratio [HR], 1.23; 95% CI, 1.02-1.47 and group 3 vs 1: HR, 1.63; 95% CI, 1.30-2.04) and overall survival (group 2 vs 1: HR, 1.36; 95% CI, 1.05-1.77 and group 3 vs 1: HR, 1.81; 95% CI, 1.31-2.51). However, the associations disappeared after adjusting for other significant risk factors.

Conclusion: Abnormal pain resolution identified by pain trajectory analysis and resulting from complex interactions among disease progression, surgery, and analgesia may be considered as an indicator of an inferior prognosis following colorectal cancer resection.

Keywords: Cancer; Colorectal cancer; Pain; Pain, Postoperative; Recurrence

1. INTRODUCTION

Pain, a strong stimulant of the stress response, has been shown to suppress host immunity and possibly promote tumor metastasis in animal studies.[1] Management of surgical pain may prevent surgery-induced decreases in host resistance against tumor spread, making pain control particularly important in cancer surgery.[1] In addition to preclinical studies, pain frequency and intensity have been demonstrated to be linked to cancer outcomes in humans, and the severity of chronic cancer-related pain has been shown to be an independent predictor of shorter survival in advanced non-small cell lung cancer and prostate cancer.[2,3] However, most previous studies have focused on chronic cancer pain, and few studies have investigated the effect of acute pain severity following cancer resection on cancer recurrence.

Although most previous studies have used simplified pain measurements at individual time points or their means to examine the association between pain and clinical outcomes, pain itself fluctuates in quantity and quality over time to reflect a complex interaction between treatment and symptoms. As postoperative pain scores are recorded at separate time points, they can vary greatly across patients throughout their hospital stay. Compared with conventional pain assessments, pain trajectory analysis can both quantify the intensity of pain and also capture changes over time to increase the precision and provide more valuable information.[4] A few studies have examined the association between types of postsurgical pain trajectories and specific clinical outcomes, including the risk of postoperative 30-day readmissions[5] and persistent pain after knee arthroplasty.[6] However, no study has evaluated the association between pain trajectories and oncologic outcomes in patients undergoing cancer surgery. We hypothesized that abnormal pain resolution identified by trajectory analysis may be associated with worse long-term outcomes after cancer surgery. Accordingly, this retrospective study aimed to characterize and explore the complex relationships among postoperative pain trajectories and their

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associations with cancer recurrence, overall survival, and other risk factors in patients following colorectal cancer resection.

2. METHODS

2.1. Setting and patient selection

After approval by the Institutional Review Board (IRB) of Taipei Veterans General Hospital, Taipei, Taiwan (IRB-TPEVGH No. 2017-12-025BC), we reviewed the medical records of all patients with stage I through IV colorectal adenocarcinoma who underwent primary tumor resection at our hospital between November 2010 and December 2014. The need for written informed consent was waived by the IRB. Patients were excluded from the analysis if they had postoperative complications (e.g., admission to intensive care units or reoperations) before discharge or < 2 postoperative pain assessments during the hospital stay. The electronic medical database has been used in the authors' previously published works.[7,8]

2.2. Acute pain management

At the center, colorectal cancer resection was performed under general anesthesia with neuromuscular blocking and inhalation agents as standard. For postoperative pain control, the patients received either intravenous opioid-based analgesia (patient-controlled or as-needed delivery) or epidural analgesia at the discretion of the patients and anesthesiologists.

Intravenous patient-controlled analgesia was administered via an ambulatory infusion pump (Gemstar Yellow, Hospira, IL, USA) to deliver morphine with a continuous infusion 0.5 to 1.0 mg/h and boluses of 1 mg with a lockout time of 6 minutes. Intravenous patient-controlled analgesia was typically continued for 48 to 72 hours after surgery and switched to oral acetaminophen or nonsteroidal anti-inflammatory drugs thereafter. If epidural analgesia was selected for pain control, an epidural catheter was implanted and its function was assessed 1 day prior to surgery. Epidural analgesia was started before surgical incision with local anesthetics (bupivacaine 0.25% or 0.5%) with or without fentanyl 1 to 2 μg/mL and continued at a rate of 5 to 10 mL/h based on the patients' hemodynamics. Similarly, epidural analgesia was typically continued for 48 to 72 hours to control postoperative pain. Patients receiving as-needed analgesia were given intravenous or oral narcotics (e.g., morphine and tramadol) or nonsteroidal anti-inflammatory drugs.

2.3. Measurement of postoperative pain

For acute surgical pain, self-reported numerical rating scale pain scores were recorded on a scale from 0 to 10, with 10 being the maximum imaginable pain, by trained specialist nurses at 8-hour intervals for 24 hours after surgery, 12-hour intervals for 4 days, and daily thereafter. In this study, we recorded the maximal numerical rating scale pain score at seven post-surgery time periods, 12, 24, 36, 48, 96, and 120 hours after surgery, respectively.

2.4. Determination of cancer recurrence and death

Recurrence-free survival was the primary endpoint and was defined as the time from the date of surgery to the date of first cancer recurrence. Cancer recurrence was defined by the presence of locoregional or metastatic deposits on imaging (plain films, computerized tomography, magnetic resonance imaging, or positron-emission tomography). Overall survival was the secondary endpoint and defined as the time from the date of surgery to the date of death. The date of death was determined based on medical records or death certificates. The current status of each patient was determined by documentation of subsequent outpatient visits or admissions, and was followed up to the end of August 2016. The survival time of those without an event of recurrence or death was defined as the corresponding censored observations.

2.5. Data collection

An electronic medical database was used to determine the patients' attributes and risk factors for cancer recurrence and mortality by specialist anesthesiologists not involved with the statistical analysis. The quality of the extracted data was verified through random sampling by the authors. Clinical covariates included demographics, pretreatment carcinoembryonic antigen (CEA) level,[9] perioperative blood transfusion,[10] perioperative use of analgesics, and cancer adjuvant therapy. Perioperative blood transfusion was defined as any transfusions of packed red blood cells within 7 days of surgery. Data of perioperative analgesics were also collected (e.g., acetaminophen, ketorolac, tenoxicam, and hydrocortisone) and defined as the analgesics given within 7 days of surgery. Adjuvant therapy in the form of chemotherapy or radiotherapy was given routinely in patients with stage III and IV disease and was defined as any therapy given within 90 days of surgery.

Pathologic features incorporated in the analysis included tumor differentiation,[11] mucinous or signet-ring histology,[12] lymphovascular invasion,[13] and perineural invasion.[14] Tumor node metastasis staging was translated into stages I to IV according to the American Joint Committee on Cancer criteria, seventh edition.[15] Tumor location was divided into right-sided (cecum to splenic flexure) or left-sided (splenic flexure to rectum).

2.6. Statistical analysis

Group-based modeling of longitudinal pain scores was used to assess pain trajectories using the Statistics Analysis System (SAS) procedure PROC TRAJ.[16] With respect to the number of trajectories, at least one slope parameter (linear, quadratic, or cubic) should be significantly different from zero, and we determined the number of trajectories by comparing the Bayesian information criterion of miscellaneous models and visual inspection of the resulting trajectories. Three pain trajectories were finally obtained. The average pain scores and SEs of the mean at seven time points are illustrated in Figure 1.

Comparisons of patient characteristics among the three groups were performed using the χ^2 test for categorical variables and either analysis of variance or Kruskal-Wallis test for continuous variables, as appropriate. The Kaplan-Meier method was used to illustrate the recurrence-free and overall survival curves of the three groups, and the log-rank test was used to compare

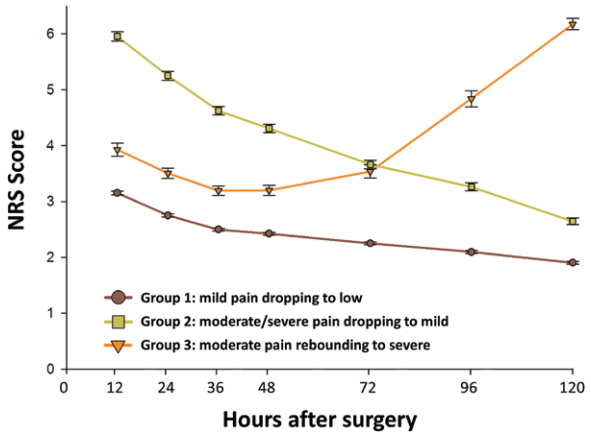

Fig. 1 Average pain scores and SEM stratified by pain trajectories. NRS, numerical rating scale.

survival distributions across pain trajectories. Univariate Cox regression analysis was used to evaluate the effects of the variables collected in the study on recurrence-free or overall survival, and significant predictors in the univariate analysis were used as candidates for stepwise model selection processes in the multivariate analysis. The entry and removal criteria of significance level were set as 0.05 and 0.1, respectively, to select factors associated with recurrence-free and overall survival in the multivariate analysis. The effect of pain trajectories on recurrence-free and overall survival was then further evaluated in the multivariate models. In addition, the effects of the collected variables on the classification of pain trajectories were also evaluated using the PROC TRAJ algorithm and expressed as odds ratios (ORs) with 95% CIs. We also used backward model selection processes to identify significant factors associated with pain trajectories in the multivariate analysis. The significance level of all hypotheses was 0.05 for a two-sided test. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

3.1. Pain trajectory groups

We identified 2401 patients with 13 931 pain score observations and a median follow-up time of 28.6 months (interquartile range, 17.5-45.5 mo) for pain trajectory grouping and subsequent trajectory-based survival analysis. Based on a pain scale from 0 to 10, low pain was defined as 0 to 2, mild pain as 2 to 4, moderate pain as 4 to 6, and severe pain as more than 6. Classifying the patients according to their inpatient pain trajectory identified three categories, including 1688 patients (70.3%) with mild pain dropping to low (group 1), 479 (20.0%) with moderate/severe pain dropping to mild (group 2), and 234 (9.7%) with moderate pain rebounding to severe (group 3) (Fig. 1).

With regards to baseline characteristics, patients in group 3 had a higher concentration of pretreatment CEA, higher proportion of right-sided tumors, longer anesthesia time, more advanced cancer, and were more likely to receive acetaminophen, ketorolac, hydrocortisone, neoadjuvant chemotherapy and/or radiotherapy, and adjuvant chemotherapy. Patients in group 2 were more likely to be younger and have perioperative blood transfusions (Table 1). With regards to pathologic features, patients in group 3 had higher proportions of poor cell differentiation and lymphovascular invasion. Patients in group 2 had a higher proportion of perineural invasion (Table 1).

3.2. Pain trajectories and recurrence-free survival

Comparisons of recurrence-free survival distribution among the three groups with distinct pain trajectories revealed a significant difference ($p < 0.001$ by the log-rank test, Fig. 2). Pain trajectories were also significantly associated with the risk of recurrence in the univariate analysis ($p < 0.001$; group 2 vs 1: hazard ratio [HR], 1.23; 95% CI, 1.02-1.47; $p = 0.028$ and group 3 vs 1: HR, 1.63; 95% CI, 1.30-2.04; $p < 0.001$). Univariate analysis identified other significant predictors of cancer recurrence, including American Society of Anesthesiologists (ASA) class ≥ 3, chronic kidney disease, pretreatment CEA level, laparoscopic surgery, blood transfusion, anesthesia time, preoperative chemotherapy, and/or radiotherapy (Table 2).

After the model selection processes, nine independent prognostic factors of cancer recurrence were identified (Table 3), including ASA class ≥ 3 (HR = 1.21), chronic kidney disease (HR = 1.29), preoperative CEA (on a base-10 logarithmic scale, HR = 1.46), blood transfusion (HR = 1.26), cancer stage (II vs I, HR = 2.98; III vs I, HR = 7.28; IV vs I, HR = 23.81), pathologic lymphovascular and perineural invasion (HR = 1.24 and 1.71, respectively), preoperative chemotherapy and/or radiotherapy (HR = 1.65), and postoperative radiotherapy (HR = 1.51) (Table 3). After adjusting for these significant risk factors of cancer recurrence, the correlation between pain trajectories and risk of recurrence became nonsignificant ($p = 0.25$; group 2 vs 1: HR, 0.92; 95% CI, 0.77-1.12 and group 3 vs 1: HR, 1.16; 95% CI, 0.92-1.46).

3.3. Pain trajectories and overall survival

A significant difference in overall survival distribution was noted among the three groups along with different pain trajectories ($p = 0.001$ by the log-rank test, Fig. 2). Pain trajectories were significantly associated with overall survival in the univariate analysis ($p = 0.001$; group 2 vs 1: HR, 1.36; 95% CI, 1.05-1.77; $p = 0.020$ and group 3 vs 1: HR, 1.81; 95% CI, 1.31-2.51; $p < 0.001$). Univariate analysis showed other significant predictors of overall survival, including age, ASA class ≥ 3, coronary arterial disease, heart failure, chronic kidney disease, pretreatment CEA level, right-sided tumor, blood transfusion, anesthesia time, hydrocortisone, preoperative chemotherapy, and/or radiotherapy (Table 2).

Multivariate regression models demonstrated a number of risk factors for mortality, including age (HR = 1.01), ASA class ≥ 3 (HR = 1.7), chronic kidney disease (HR = 1.39), higher pretreatment CEA level (HR = 1.61), blood transfusion (HR = 1.5), advanced cancer stage (II vs I, HR = 2.84; III vs I, HR = 6.79; IV vs I, HR = 28.18), tumor differentiation (moderate vs good, HR = 1.47; poor vs good, HR = 3.22), perineural invasion (HR = 1.53), and postoperative chemotherapy and radiotherapy (HR = 0.49 and 1.6, respectively) (Table 3). Similarly, the effect of pain trajectories on overall survival became nonsignificant after adjusting for other significant predictors ($p = 0.21$; group 2 vs 1: HR, 1.17; 95% CI, 0.89-1.53 and group 3 vs 1: HR, 1.31; 95% CI, 0.93-1.84).

3.4. Factors influencing pain trajectories

Compared to the patients in group 1, those in group 2 were less likely to have an older age (OR = 0.99), diabetes (OR = 0.73), and more likely to have blood transfusions (OR = 1.98), lymphovascular invasion (OR = 1.36), and preoperative chemotherapy and/or radiotherapy (OR = 1.58). Patients in group 3 were more likely to have a higher CEA level (OR = 1.31), right-sided tumor (OR = 1.54), and longer anesthesia time (OR = 1.56) (Table 4).

4. DISCUSSION

In this study, we used a pain trajectory approach to examine the associations between acute surgical pain and cancer outcomes following colorectal cancer resection. This study provides new evidence to elucidate the complex relationships between postoperative pain and cancer recurrence and death. There are several strengths to this study. First, the present analysis was performed on a much larger cohort to increase the statistical power of the results. Second, we analyzed repeated measurements of pain scores using trajectory grouping models, which not only quantified the pain intensity but also distinguished between pain intensity and pain resolution over time. Third, our models included a comprehensive collection of important clinicopathologic factors of cancer outcomes to minimize potential confounding effects.

Although pain is an expected symptom of postoperative recovery, it is often inadequately managed in clinical practice. Pain experienced by patients may reflect surgical complications and disease severity. Uncontrolled pain has a negative impact on the quality of life and can potentially lead to readmissions and persistent postsurgical pain.[5,6,17] Our trajectory grouping models demonstrated that nearly 10% of the cancer surgery patients

Table 1

Patient demographics, pathologic characteristics, and adjuvant therapies

	Group 1 (N = 1688)	Group 2 (N = 479)	Group 3 (N = 234)	*p*
Age, y	68 ± 13	66 ± 15	67 ± 14	0.042
Sex, male	1022 (60.5%)	293 (61.2%)	141 (60.3%)	0.965
ASA class ≥ 3	614 (36.4%)	180 (37.6%)	92 (39.3%)	0.644
Comorbidities				
Diabetes	414 (24.5%)	95 (19.8%)	57 (24.4%)	0.098
Coronary artery disease	168 (10.0%)	44 (9.2%)	25 (10.7%)	0.811
Heart failure	113 (6.7%)	32 (6.7%)	17 (7.3%)	0.956
Stroke	106 (6.3%)	31 (6.5%)	16 (6.8%)	0.936
Chronic kidney disease	239 (14.2%)	63 (13.2%)	29 (12.4%)	0.700
Pretreatment CEA, μg/L	3.3 (2.0-8.6)	3.5 (2.1-10.9)	4.1 (2.2-18.0)	0.010
Right-sided tumor	473 (28.0%)	153 (31.9%)	85 (36.3%)	0.015
Laparoscopic surgery	188 (11.1%)	47 (9.8%)	22 (9.4%)	0.567
Anesthesia time, min	300 (240-360)	300 (240-375)	300 (270-360)	0.002
pRBC transfusion	397 (23.5%)	164 (34.2%)	75 (32.1%)	<0.001
Pain management				
Epidural block	74 (4.4%)	10 (2.1%)	10 (4.3%)	0.068
Acetaminophen	384 (22.7%)	110 (23.0%)	84 (35.9%)	<0.001
Ketorolac	124 (7.3%)	55 (11.5%)	32 (13.7%)	<0.001
Tenoxicam	72 (4.3%)	17 (3.5%)	4 (1.7%)	0.150
Hydrocortisone	226 (13.4%)	75 (15.7%)	46 (19.7%)	0.027
AJCC stage				<0.001
Stage I	380 (22.5%)	94 (19.6%)	33 (14.1%)	
Stage II	548 (32.5%)	156 (32.6%)	65 (27.8%)	
Stage III	491 (29.1%)	125 (26.1%)	70 (29.9%)	
Stage IV	269 (15.9%)	104 (21.7%)	66 (28.2%)	
Pathologic features				
Tumor differentiation				0.013
Good	99 (5.9%)	30 (6.3%)	5 (2.1%)	
Moderate	1450 (86.2%)	403 (84.5%)	200 (85.8%)	
Poor	134 (8.0%)	44 (9.2%)	28 (12.0%)	
Mucinous histology	77 (4.6%)	27 (5.7%)	16 (6.9%)	0.252
Signet-ring histology	63 (3.7%)	23 (4.8%)	10 (4.3%)	0.547
Lymphovascular invasion	491 (29.2%)	178 (37.3%)	87 (37.3%)	<0.001
Perineural invasion	248 (14.7%)	100 (21.0%)	42 (18.0%)	0.004
Preoperative C/T ± R/T	176 (10.4%)	70 (14.6%)	37 (15.8%)	0.006
Postoperative C/T	887 (52.5%)	257 (53.7%)	152 (65.0%)	0.002
Postoperative R/T	34 (2.0%)	11 (2.3%)	9 (3.8%)	0.205

Group 1: mild pain dropping to low; group 2: moderate/severe pain dropping to mild; group 3: moderate pain rebounding to severe.

Values are presented as mean ± SD, median (interquartile range), or counts (percent). Continuous variables were analyzed using ANOVA or Kruskal-Wallis tests, as appropriate; categorical variables were analyzed using Pearson χ^2 tests.

AJCC = American Joint Committee on Cancer; ANOVA = analysis of variance; ASA = American Society of Anesthesiologists; C/T = chemotherapy; CEA = carcinoembryonic antigen; pRBC = packed red blood cell; R/T = radiotherapy.

(group 3) had persistent moderate to severe pain during the 120-hour postoperative period. Compared with the mild (group 1) and moderate pain (group 2) trajectory groups, these patients had the highest risk of cancer recurrence and mortality after bowel resection for colorectal cancer. Further analyses showed that the patients in group 3 had a higher concentration of pretreatment CEA and longer anesthesia time than those in group 1, which may imply more aggressive disease and more extensive surgical resection. With regards to clinical implications, particular attention should be paid to patients with abnormal pain resolution in pain management, cancer treatment, and surveillance.

Although the acute pain trajectories were associated with postoperative oncologic outcomes in the univariate analysis, the association disappeared after adjusting for other important clinical and pathologic predictors. This indicates that the impact of acute pain may be related to the complexity of surgery and cancer aggressiveness, and may reflect the perioperative course and disease severity rather than pain severity itself. However, pain is a continuum representing a complex interplay of underlying health status, patient perception, and treatment. Further studies with validated designs and robust statistics are necessary to elucidate the relationships between postoperative pain and oncologic outcomes after cancer resection.

Our results showed that the patients classified into the mild pain trajectory were older and had a lower proportion of lymphovascular invasion than those in the moderate pain trajectory. Older patients have been reported to either experience less pain or better pain relief from analgesics compared with their younger counterparts.[18,19] Another potential explanation is that these patients were desensitized to pain as they were an older population with higher ASA class.[20] In addition, older patients with less aggressive disease might have received more conservative resection surgery and therefore had a lower intensity of postoperative pain.

Of note, our analysis showed that diabetic patients had a lower risk of developing a moderate pain trajectory. Small-fiber neuropathy is regarded to be an early pathological change in diabetes, predominantly involving small-diameter, thinly

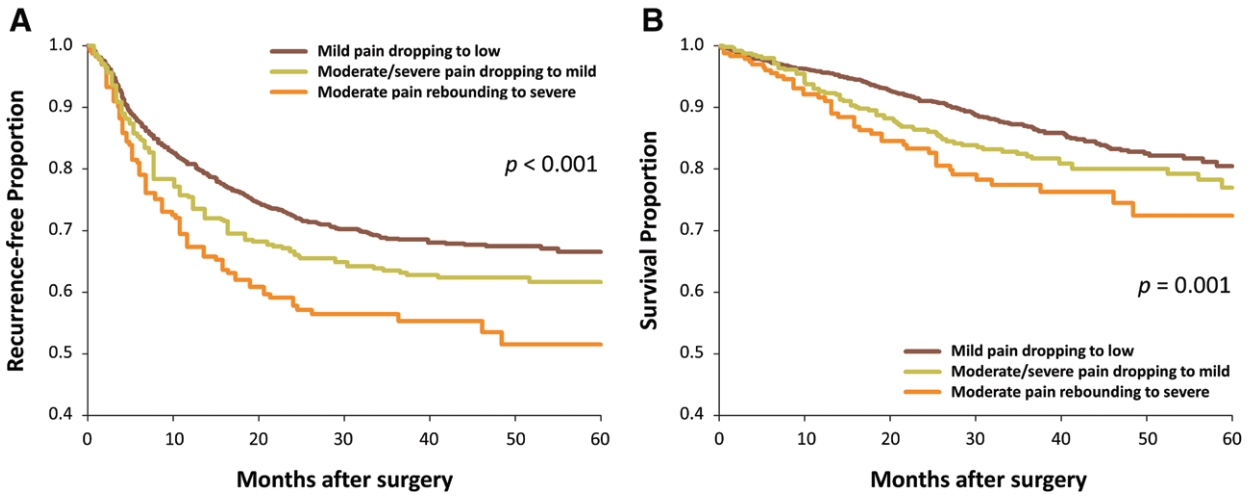

Fig. 2 Kaplan-Meier curves for recurrence-free and overall survival of three pain trajectory groups. Significant differences in (A) recurrence-free survival and (B) overall survival after surgery were found across the three pain trajectory groups by log-rank tests.

Table 2

Univariate analysis of cancer recurrence and all-cause mortality

	Cancer recurrence		All-cause mortality	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Pain trajectory groups		<0.001		0.001
Group 2 vs 1	1.23 (1.02-1.47)	0.028	1.36 (1.05-1.77)	0.020
Group 3 vs 1	1.63 (1.30-2.04)	<0.001	1.81 (1.31-2.51)	<0.001
Age	1.00 (0.99-1.00)	0.709	1.02 (1.01-1.03)	<0.001
Sex (male vs female)	0.95 (0.81-1.10)	0.481	0.96 (0.77-1.20)	0.732
ASA class ≥ 3	1.31 (1.12-1.52)	0.001	2.29 (1.83-2.85)	<0.001
Diabetes	1.03 (0.87-1.23)	0.729	1.27 (1.00-1.63)	0.054
Coronary arterial disease	1.04 (0.81-1.32)	0.778	1.41 (1.02-1.94)	0.036
Heart failure	0.92 (0.68-1.26)	0.611	1.86 (1.31-2.65)	0.001
Stroke	0.99 (0.71-1.37)	0.936	1.45 (0.95-2.19)	0.083
Chronic kidney disease	1.42 (1.16-1.73)	0.001	2.02 (1.55-2.63)	<0.001
Pretreatment CEA[a]	2.79 (2.57-3.03)	<0.001	2.79 (2.49-3.13)	<0.001
Laparoscopy surgery	0.73 (0.56-0.95)	0.020	0.72 (0.48-1.06)	0.097
Right vs left-sided tumor	1.00 (0.85-1.18)	0.985	1.40 (1.12-1.77)	0.004
pRBC transfusion	2.19 (1.88-2.55)	<0.001	3.38 (2.71-4.21)	<0.001
Anesthesia time[b]	1.84 (1.54-2.20)	<0.001	1.84 (1.42-2.39)	<0.001
Epidural block	1.06 (0.73-1.52)	0.773	0.56 (0.28-1.13)	0.108
Acetaminophen	1.08 (0.91-1.28)	0.354	1.11 (0.86-1.42)	0.434
Ketorolac	0.88 (0.67-1.15)	0.346	1.10 (0.76-1.58)	0.621
Tenoxicam	1.36 (0.98-1.90)	0.066	0.92 (0.52-1.64)	0.778
Hydrocortisone	1.07 (0.86-1.33)	0.546	1.59 (1.20-2.11)	0.001
Preoperative C/T ± R/T	2.71 (2.26-3.23)	<0.001	2.07 (1.57-2.73)	<0.001
Postoperative C/T	4.70 (3.85-5.73)	<0.001	2.08 (1.63-2.65)	<0.001
Postoperative R/T	4.05 (2.95-5.56)	<0.001	3.70 (2.38-5.76)	<0.001
Stage		<0.001		<0.001
II vs I	3.74 (2.29-6.11)	<0.001	3.85 (1.9-7.81)	<0.001
III vs I	10.76 (6.74-17.17)	<0.001	6.68 (3.36-13.29)	<0.001
IV vs I	53.15 (33.41-84.57)	<0.001	37.56 (19.2-73.49)	<0.001
Tumor differentiation		<0.001		<0.001
Moderate vs good	3.12 (1.84-5.30)	<0.001	4.75 (1.77-12.76)	0.002
Poor vs good	6.60 (3.77-11.55)	<0.001	12.67 (4.58-35.08)	<0.001
Mucinous histology	1.45 (1.08-1.97)	0.015	1.83 (1.22-2.76)	0.004
Signet-ring histology	1.82 (1.33-2.49)	<0.001	2.18 (1.42-3.33)	<0.001
Lymphovascular invasion	3.21 (2.77-3.73)	<0.001	3.08 (2.47-3.85)	<0.001
Perineural invasion	3.46 (2.95-4.05)	<0.001	2.95 (2.33-3.73)	<0.001

ASA = American Society of Anesthesiologists; C/T = chemotherapy; CEA = carcinoembryonic antigen; HR = hazard ratio; pRBC = packed red blood cell; R/T = radiotherapy.

[a]On a base-10 logarithmic scale.

[b]On a base-2 logarithmic scale.

Table 3

Multivariate analysis of cancer recurrence and all-cause mortality

Recurrence-free survival	HR (95% CI)	*p*	Overall survival	HR (95% CI)	*p*
Pain trajectory		0.248	Pain trajectory		0.214
Group 2 vs 1	0.92 (0.77-1.12)	0.411	Group 2 vs 1	1.17 (0.89-1.53)	0.257
Group 3 vs 1	1.16 (0.92-1.46)	0.213	Group 3 vs 1	1.31 (0.93-1.84)	0.118
ASA class ≥ 3	1.21 (1.03-1.42)	0.021	Age	1.01 (1.00-1.02)	0.016
Chronic kidney disease	1.29 (1.04-1.59)	0.021	ASA class ≥ 3	1.70 (1.33-2.18)	<0.001
Pretreatment CEA[a]	1.46 (1.32-1.61)	<0.001	Chronic kidney disease	1.39 (1.04-1.85)	0.025
pRBC transfusion	1.26 (1.07-1.49)	0.005	Pretreatment CEA[a]	1.61 (1.39-1.85)	<0.001
Stage		<0.001	pRBC transfusion	1.50 (1.18-1.90)	0.001
II vs I	2.98 (1.82-4.88)	<0.001	Stage		<0.001
III vs I	7.28 (4.52-11.72)	<0.001	II vs I	2.84 (1.37-5.90)	0.005
IV vs I	23.81 (14.6-38.82)	<0.001	III vs I	6.79 (3.18-14.51)	<0.001
Lymphovascular invasion	1.24 (1.05-1.48)	0.014	IV vs I	28.18 (13.02-60.99)	<0.001
Perineural invasion	1.71 (1.43-2.04)	<0.001	Tumor differentiation		<0.001
Preoperative C/T ± R/T	1.65 (1.36-2)	<0.001	Moderate vs good	1.47 (0.54-4.03)	0.455
Postoperative R/T	1.51 (1.09-2.1)	0.013	Poor vs good	3.22 (1.14-9.12)	0.028
			Perineural invasion	1.53 (1.19-1.97)	0.001
			Postoperative C/T	0.49 (0.34-0.69)	<0.001
			Postoperative R/T	1.60 (1.01-2.54)	0.043

ASA = American Society of Anesthesiologists; C/T = chemotherapy; CEA = carcinoembryonic antigen; HR = hazard ratio; pRBC = packed red blood cell; R/T = radiotherapy.
[a]On a base-10 logarithmic scale.

Table 4

Multinomial logistic regression after forward stepwise model selection

	Group 2 vs group 1		Group 3 vs group 1	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0.99 (0.98-1.00)	0.005	1.00 (0.98-1.01)	0.490
Diabetes	0.73 (0.54-0.98)	0.040	0.96 (0.67-1.37)	0.813
Pretreatment CEA[a]	0.91 (0.75-1.10)	0.333	1.31 (1.05-1.63)	0.017
Right-sided tumor	1.23 (0.95-1.60)	0.122	1.54 (1.09-2.16)	0.013
Anesthesia time[b]	1.26 (0.95-1.68)	0.111	1.56 (1.07-2.29)	0.022
pRBC transfusion	1.98 (1.51-2.61)	<0.001	1.36 (0.95-1.94)	0.097
Lymphovascular invasion	1.36 (1.05-1.75)	0.018	1.34 (0.96-1.87)	0.080
Preoperative C/T ± R/T	1.58 (1.10-2.25)	0.012	1.53 (0.96-2.43)	0.073

C/T = chemotherapy; CEA = carcinoembryonic antigen; OR = odds ratio; pRBC = packed red blood cell; R/T = radiotherapy.
[a]On a base-10 logarithmic scale.
[b]On a base-2 logarithmic scale.

myelinated Ad, and unmyelinated C-fibers.[21] In addition, previous studies have reported that patients with early diabetic neuropathy have an elevated pain threshold.[22] Further investigations are necessary to elucidate whether lower pain sensitivity in diabetic patients leads to lower perioperative requirements for analgesics.

The limitations of this study include the following: (1) it is an observational study, (2) data of narcotic use for each patient could not be obtained due to the limitations of data requisition, and (3) the confounding effect of other surgical variables and the extent of their effect on pain levels and cancer outcomes were not incorporated in the analysis.

In conclusion, our findings suggest that abnormal pain resolution identified by pain trajectory analysis and resulting from complex interactions among disease progression, surgery, and analgesia may be considered as an indicator of inferior prognosis following colorectal cancer resection. Pain trajectory analysis may provide a more comprehensive view to explore the complex relationships among pathologic findings, surgical trauma, and pain management in patients with colorectal cancer. Prospective studies are warranted to verify the associations between abnormal pain resolution and cancer outcomes and elucidate whether more intensive pain management will reduce recurrence and mortality after surgery for colorectal cancer.

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