Group-based trajectory analysis of postoperative pain and outcomes after liver cancer surgery

Wei-Nung Teng[a,b], Hsiang-Ling Wu[a,b], Ying-Hsuan Tai[c,d], Hao-Jan Lei[b,e], Mei-Yung Tsou[a,b], Kuang-Yi Chang[a,b,*]

[a]Department of Anesthesiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [c]Department of Anesthesiology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC; [d]Department of Anesthesiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [e]Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Although previous studies have shown connections between pain and worse cancer outcomes, few clinical studies have evaluated their direct association, and the current study aimed to investigate the potential association between acute pain trajectories and postoperative outcomes after liver cancer surgery.

Methods: This retrospective study was conducted in a single medical center and included patients who received liver cancer surgery between January 2010 and December 2016. Maximal pain intensity was recorded daily using a numerical rating scale during the first postoperative week. Group-based trajectory analysis was performed to classify the variations in pain scores over time. Cox and linear regression analyses were used to assess the effect of pain trajectories on recurrence-free survival, overall survival, and length of hospital stay (LOS) after surgery and to explore predictors of these outcomes.

Results: A total of 804 patients with 5396 pain score observations were analyzed within the present study. Group-based trajectory analysis categorized the changes in postoperative pain into three groups: group 1 had constantly mild pain (76.6%), group 2 had moderate/severe pain dropping to mild (10.1%), and group 3 had mild pain rebounding to moderate (13.3%). Multivariable analysis demonstrated that on average, group 3 had a 7% increase in LOS compared with the group 1 ($p = 0.02$) and no significant difference in the LOS was noted between pain trajectory groups 2 and 1 ($p = 0.93$). Pain trajectories were not associated with recurrence-free survival or overall survival after liver cancer surgery.

Conclusion: Acute pain trajectories were associated with LOS but not cancer recurrence and survival after liver cancer surgery. Group-based trajectory analysis provided a promising approach for investigating the complex relationships between variations in postoperative pain over time and clinical outcomes.

Keywords: Cancer recurrence; Group-based trajectory analysis; Liver cancer; Overall survival; Postoperative pain

1. INTRODUCTION

Postoperative pain has been proposed as an indicator for prognosis after cancer surgery[1] as inadequately treated postoperative pain is associated with the activation of stress responses, the sympathetic nervous system, postoperative complications,[2,3] more perioperative opioid use,[4] and an increased risk of developing persistent postoperative pain.[5,6] Well-managed postoperative pain control with multimodal analgesia after liver cancer surgery has been shown to reduce inflammation and postoperative nausea and vomiting, enhance the return of bowel function and reduce morbidity, and thus subsequently reduce the length of hospital stay (LOS) and medical costs.[7] However, most previous studies[8] have focused on chronic pain after cancer surgery, few have ever focused on the potential impact of variations in acute postoperative pain over time on clinical outcomes after surgery for miscellaneous cancers.

For convenience, in clinical settings, postoperative pain is often assessed using simplified pain measurements like the numerical rating scale (NRS). Pain trajectory analysis explores the variations in pain observations over time and provides more comprehensive information than individual pain measurements.[9] As the associations between pain management and changes in pain states after surgery are complex interactions, analysis of pain trajectories may be a better tool than individual pain measurements for examining the associations between changes in pain observations over time and clinical outcomes, such as postoperative readmission,[10] persistent pain,[11] cancer prognosis,[12] and so on. To the best of our knowledge, few studies have investigated the association between pain trajectories and clinical outcomes after cancer surgery[12] and we conducted this retrospective study to fill this gap in the literature. We used group-based trajectory analysis to classify postoperative pain measurements and to investigate their connections with cancer recurrence, overall survival (OS) and LOS in patients undergoing liver cancer surgery. We hypothesized that abnormal pain resolution identified after trajectory analysis was associated with a longer LOS and worse prognosis after surgery for liver cancer. Other risk factors for cancer recurrence and mortality were also evaluated to reduce

*Address correspondence. Dr. Kuang-Yi Chang, Department of Anesthesiology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: kychang@vghtpe.gov.tw (K.-Y. Chang).

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their potential confounding effects on further elucidation of the complex relationships between acute pain trajectories and clinical outcomes after liver cancer surgery.

2. METHODS

2.1. Patient selection

The current study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (IRB-TPEVGH no. 2017-12-025BC). We carefully reviewed the medical records of all patients with stage I-III hepatocellular carcinoma who underwent primary tumor resection at our hospital between January 2010 and December 2016. The exclusion criteria were as follows: severe postoperative complications (eg, admission to intensive care units or reoperation) before discharge and <3 postoperative pain assessments during their hospital stay. For full details on the data collection refer to our previous publications using this electronic medical database.[13,14]

2.2. Postoperative pain management

In general, liver cancer resection was performed under general anesthesia with inhalation agents and neuromuscular blocking. At the discretion of the patient after surgery, patients received either intravenous patient-controlled/as-needed analgesia with morphine or epidural analgesia for pain control. Intravenous patient-controlled analgesia was administered via an infusion pump (Gemstar™ Yellow; Hospira, Lake Forest, IL) to deliver morphine with a continuous infusion of 0.5 to 1.0 mg/h and boluses of 1 mg with a lockout time of 6 minutes; this was typically continued for 48 to 72 hours after surgery. If epidural analgesia was selected for postoperative pain control, an epidural catheter was implanted, and its correct functioning was confirmed one day before surgery. Epidural anesthesia with local anesthetics (bupivacaine 0.25% or 0.5%) was started before the surgical incision and continued at a rate of 5 to 10 mL/h based on the patients' hemodynamics in combination with general anesthesia. After surgery, epidural analgesia was continued for 48 to 72 hours for pain control. Intravenous or oral narcotics (eg, morphine and tramadol) or nonsteroidal anti-inflammatory drugs were used for postoperative pain management after completion of the patient-controlled analgesic course.

2.3. Pain measurements, data collection, and endpoints

Self-reported NRS pain scores were recorded by the nurses at least once per day after surgery. A scale of 0 to 10 was used, with 10 being the maximum imaginable pain. In the current study, maximum daily NRS pain scores during the first postoperative week were collected and used in the subsequent analyses. Patient attributes and risk factors for cancer recurrence and mortality were collected through review of electronic medical charts by anesthesiologists not involved in the statistical analysis. The authors conducted random sampling of the extracted data to ensure its quality. For full details on the collected clinical variables and pathological features refer to our previous publications.[13,14]

The primary endpoint was recurrence-free survival, which was defined as the time from the date of surgery to the date of first cancer recurrence. Cancer recurrence was identified as the presence of locoregional or metastatic deposits on imaging (plain films, computerized tomography, magnetic resonance imaging, or positron-emission tomography), which was confirmed by radiologists and general surgeons. If possible, the presence of recurrent disease was confirmed by biopsy and histological examinations. The secondary endpoints were LOS after surgery and OS, which was defined as the time from the date of surgery to the date of death. The date of death was determined based on the medical records or death certificate. For those without cancer recurrence or death, their survival time was regarded as the corresponding censored observations. Each patient was followed up until death or to the end of September 2018, whichever came first.

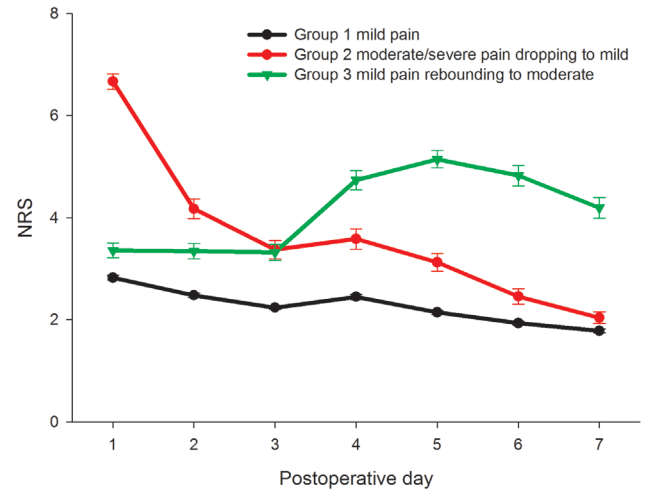

Fig. 1 Maximal daily pain scores during the first postoperative week stratified by pain trajectories. Pain score observations in distinct trajectory groups are presented as mean with its standard error. NRS = numerical rating scale.

2.4. Statistical analysis

We used group-based trajectory analysis to categorize the variations in postoperative pain scores over time using an SAS procedure PROC TRAJ.[12,15] The number of trajectories was determined by comparing the Bayesian information criteria of miscellaneous models with the aid of visual inspection of the resulting trajectories. Three pain trajectories were ultimately obtained, and their mean daily pain scores during the first postoperative week are illustrated in Fig. 1.

Comparisons of patient attributes among the three trajectory groups were conducted using chi-square analysis and one-way analysis of variance for categorical and continuous variables, respectively. The Kaplan-Meier method was used to depict recurrence-free and OS for the three groups, and the log-rank test was performed to compare the survival distributions across distinct pain trajectories. Univariate Cox and linear regression analyses were performed to evaluate the effects of the collected variables on recurrence-free or OS and the log-transformed length of hospital stay after surgery, respectively. Multivariable analysis with a stepwise model selection strategy with entry and exit significance criteria of 0.05 and 0.1, respectively, was used to identify independent predictors of recurrence-free or OS and LOS after surgery.

Moreover, 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 (OR) with 95% confidence intervals. Backward model selection processes were used to determine significant predictors of the pain trajectory groupings in the multivariable analysis. A p-value of 0.05 was considered significant for any two-sided test. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

3. RESULTS

3.1. Postoperative pain trajectory analysis

There were a total of 804 patients included in the analysis with a median LOS of 11 days (interquartile range: 9-13) and a median

Table 1

Comparisons of patient characteristics among distinct postoperative pain trajectory groups

	Group 1 (n = 616)	Group 2 (n = 81)	Group 3 (n = 107)	*p*
Age, y	62 (12)	61 (12)	62 (13)	0.502
Sex, male	459 (75%)	68 (84%)	74 (69%)	0.066
ASA ≥3	216 (35%)	22 (27%)	35 (33%)	0.353
Diabetes mellitus	174 (28%)	14 (17%)	31 (29%)	0.104
Chronic kidney disease	49 (8%)	8 (10%)	12 (11%)	0.490
Liver cirrhosis	269 (44%)	37 (46%)	54 (51%)	0.420
Child-Pugh class: B or C	11 (2%)	0 (0%)	4 (4%)	0.141
Preoperative blood tests				
Hemoglobin, g/dL	13.3 (1.7)	13.7 (1.9)	13.2 (1.9)	0.113
Platelet count, 10^3/μL	176 (77)	167 (64)	175 (86)	0.664
International normalized ratio	1.06 (0.08)	1.07 (0.08)	1.07 (0.07)	0.492
Serum creatinine; μmol/L	1.02 (0.95)	1.27 (1.94)	0.90 (0.36)	0.050
Albumin ≤3.5 g/dL	57 (9%)	6 (7%)	14 (13%)	0.362
Total bilirubin ≥1.0 mg/dL	145 (24%)	12 (15%)	28 (26%)	0.152
AST >40 IU/L	247 (40%)	40 (49%)	44 (41%)	0.280
ALT >40 IU/L	266 (43%)	35 (43%)	46 (43%)	0.997
Alpha-fetoprotein >20 ng/mL	288 (48%)	36 (46%)	62 (58%)	0.116
Cancer characteristics				
Tumour diameter >5 cm	217 (35%)	24 (30%)	48 (45%)	0.073
Multiple nodules	118 (19%)	24 (30%)	25 (23%)	0.071
Poor or undifferentiated histology	251 (41%)	30 (37%)	38 (36%)	0.521
Microvascular invasion	441 (72%)	63 (78%)	77 (72%)	0.503
Extracapsular invasion	147 (24%)	32 (40%)	29 (27%)	0.010
Positive surgical margin	46 (8%)	5 (6%)	8 (8%)	0.914
Preoperative TACE/RFA/PEI	56 (9%)	12 (15%)	6 (6%)	0.095
Operative variables				
>2 segments resected	210 (34%)	30 (37%)	51 (48%)	0.026
Laparoscopic or robotic surgery	71 (12%)	11 (14%)	4 (4%)	0.037
Blood loss, mL	891 (1405)	909 (1523)	1389 (1975)	0.008
Perioperative transfusion	236 (38%)	28 (35%)	57 (53%)	0.008
Epidural analgesia	123 (20%)	26 (32%)	36 (34%)	0.001
Anesthesia time; min	356 (124)	375 (115)	381 (118)	0.075
Surgery before 2014	323 (52%)	53 (65%)	76 (71%)	<0.001
Length of hospital stay, d	11.7 (5.3)	11.4 (3.8)	13.3 (5.7)	0.010

Value are mean (SD) or count (proportion).

ALT = alanine aminotransferase; ASA = ASA physical status; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; IPTW = inverse probability treatment weighting; pRBC = packed red blood cell; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

follow-up time of 38 months (interquartile range: 21.8-63.7). Three kinds of postoperative pain trajectories were identified after group-based trajectory analysis of the 5396 pain score measurements from the first postoperative week, including 616 patients (76.6%) with mild pain (group 1), 81 patients (10.1%) with moderate/severe pain dropping to mild (group 2), and 107 (13.3%) patients with mild pain rebounding to moderate (group 3) (Fig. 1).

Table 1 compares the baseline characteristics among the three groups. Note that the patients in group 3 had a higher incidence of surgery before 2014, resection of >2 segments and perioperative transfusion, fewer laparoscopic surgeries, more intraoperative blood loss and longer LOS. Patients in group 2 were more likely to have extracapsular invasion and those in group 3 received less epidural analgesia.

3.2. Pain trajectories and recurrence-free survival

No significant association was observed between the pain trajectories and recurrence-free survival in the univariate analysis (p = 0.32; Fig. 2A). After the multivariable analysis with model selection, eight independent risk factors for cancer recurrence were identified (Table 2), including perioperative transfusion (hazard ratio [HR] = 1.65), liver cirrhosis (HR = 1.39), abnormal total bilirubin (HR = 1.29), aspartate transaminase level (HR = 1.5), alpha-fetoprotein level (HR = 1.52), a resected tumor diameter >5 cm (HR = 1.3), multiple nodules (HR = 1.67), and poor or undifferentiated histology (HR = 1.42). After adjusting for these significant predictors of cancer recurrence, the correlation between pain trajectories and recurrence risk remained non-significant (group 2 vs 1: HR = 0.96, 95% CI: 0.7–1.31, p = 0.79; group 3 vs 1: HR = 1.07, 95% CI: 0.81–1.41, p = 0.64).

3.3. Pain trajectories and OS

Pain trajectories were not significantly associated with OS in the univariate analysis (p = 0.86, Fig. 2B). Multivariable regression analysis after model selection identified eight predictors of all-cause mortality, including perioperative transfusion (HR = 2.21), liver cirrhosis (HR = 1.73), Child-Pugh class of B or C (HR = 2.49), diabetes (HR = 1.49), abnormal total bilirubin level (HR = 1.81), alpha-fetoprotein level (HR = 1.66), resected tumor diameter >5 cm (HR = 2.32), and poor or undifferentiated histology (HR = 1.51) (Table 2). Note that the effect of pain trajectories on the OS remained nonsignificant after adjusting for these significant risk factors of all-cause mortality (group 2 vs 1: HR = 1.6, 95% CI: 0.93–2.76, p = 0.09; group 3 vs 1: HR = 0.73, 95% CI: 0.42–1.26, p = 0.25).

3.4. Pain trajectories and the LOS after surgery

In the multiple linear regression analysis, we identified 12 predictors of LOS after the stepwise model selection processes (Table 3). Note that receipt of laparoscopic or robotic surgery was the only negative predictor of LOS (p = 0.002), and on average, those who underwent laparoscopic or robotic surgery tended to have a 10% decrease in LOS. Compared with pain trajectory group 1, patients in group 3 had an average 7% longer LOS (p = 0.02) following control of all other significant predictors. There was no significant difference in the LOS between pain trajectory groups 2 and 1 (p = 0.93).

3.5. Influential factors on pain trajectories

Compared with patients in group 1, those in group 2 tended to be younger (OR = 0.97) and have higher hemoglobin (OR = 1.34), higher serum creatinine levels (OR = 1.35), and a lower probability of abnormal total bilirubin (OR = 0.17). They were also inclined to have a higher incidence of extracapsular invasion (OR = 2.27), less blood loss (OR = 0.76, on base 2 logarithmic transformation), and longer anesthesia time (OR = 2.73, on base 2 logarithmic transformation) (Table 4). Patients in group 3 were less likely to receive preoperative intervention therapy (OR = 0.36) or to receive surgery before 2014 (OR = 0.39). However, they were more likely to receive epidural analgesia (OR = 1.82), perioperative transfusion (OR = 1.89), and >2 segment tumor resection (OR = 1.75) (Table 4).

4. DISCUSSION

In the current study, group-based trajectory analysis was performed to examine the association between acute pain trajectories and outcomes after liver cancer surgery. Although we did not demonstrate any significant association between acute pain trajectories and cancer recurrence or mortality, several interesting findings were noted after the analysis. First, in our study, more than three quarters of patients receiving liver cancer surgery had adequate postoperative pain control which was reflected by the mild pain trajectory (group 1).

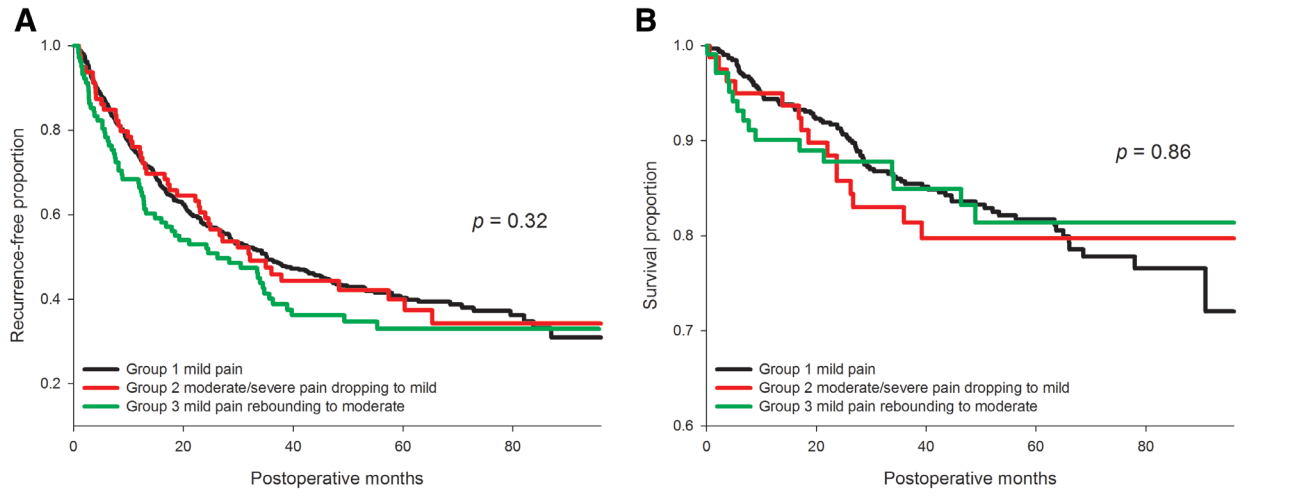

Fig. 2 Kaplan-Meier curves for recurrence-free and overall survival of three pain trajectory groups. No significant difference was noted among the three postoperative pain trajectory groups. A, Recurrence-free proportion: $p = 0.32$. B, Survival proportion: $p = 0.86$.

Second, it was not as easy to control pain immediately after surgery in about 10% of patients and we identified several risk factors for this subgroup, including both patient and surgical attributes. Despite the fact that patients in this subgroup did not have worse outcomes than those with adequate pain control during the first postoperative week, more effort should be made to control the initial pain after surgery to improve the quality of pain management and overall satisfaction in patients with risk factors for difficulty in initial pain control.

Third, we also found that some patients had a rebounding pain trajectory after the third postoperative day, which deserves further investigation. Note that rebounding pain trajectory was an independent predictor of longer LOS after surgery and strategies should be applied to reduce rebounding pain for patients at risk. For example, the transition of pain management from epidural analgesia to other analgesics should be further optimized and more aggressive pain management should be considered in those who have any sign of rebounding pain or its risk factors, to reduce the undesired effects of rebounding postoperative pain on clinical outcomes after liver cancer surgery.

Liver resection for hepatocellular carcinoma should be considered for patients with nonmetastatic disease and normal underlying liver function, or those with compensated cirrhosis and no evidence of portal hypertension.[16] Cancer recurrence after resection significantly reduces long-term survival. Despite careful patient selection and surgery, overall recurrence is high with 5-year recurrence rates ranging from 18% to 72%.[17,18] Tabrizian et al[19] demonstrated that variables independently associated with survival following recurrence included time from primary resection to recurrence, alpha fetoprotein >100 ng/mL at recurrence, recurrent tumor >3 cm, Barcelona Clinic Liver Cancer stage at recurrence, and type of treatment administered for the recurrence. We identified eight independent risks of cancer recurrence, including perioperative transfusion, liver cirrhosis, abnormal

Table 2

Multivariable analysis of cancer recurrence and all-cause mortality after surgery for liver cancer

	HR (95% CI)	p
Cancer recurrence		
Pain trajectories		0.847
Group 2 vs group 1	0.96 (0.70-1.31)	0.787
Group 3 vs group 1	1.07 (0.81-1.41)	0.641
Perioperative transfusion	1.65 (1.34-2.03)	<0.001
Cirrhosis	1.39 (1.13-1.71)	0.002
Total bilirubin ≥1.0 mg/dL	1.29 (1.02 -1.63)	0.033
AST >40 IU/L	1.50 (1.23-1.84)	<0.001
Alpha-fetoprotein >20 ng/mL	1.52 (1.24-1.87)	<0.001
Tumor diameter >5 cm	1.30 (1.04-1.63)	0.020
Multiple nodules	1.67 (1.34-2.09)	<0.001
Poor or undifferentiated histology	1.42 (1.16-1.74)	0.001
All-cause mortality		
Pain trajectories		0.093
Group 2 vs group 1	1.60 (0.93-2.76)	0.091
Group 3 vs group 1	0.73 (0.42-1.26)	0.253
Perioperative transfusion	2.21 (1.50-3.24)	<0.001
Cirrhosis	1.73 (1.17-2.56)	0.006
Child-Pugh class: B or C	2.49 (1.35-4.59)	0.003
Diabetes mellitus	1.49 (1.01-2.20)	0.046
Total bilirubin ≥1.0 mg/dL	1.81 (1.22-2.70)	0.004
Alpha-fetoprotein >20 ng/mL	1.66 (1.11-2.47)	0.013
Tumor diameter >5 cm	2.32 (1.57-3.43)	<0.001
Poor or undifferentiated histology	1.51 (1.03-2.20)	0.033

AST = aspartate aminotransferase; CI = confidence interval; HR = hazard ratio.

Table 3

Predictors of length of hospital stay after surgery for liver cancer

	β	SE	Std β	p
Pain trajectories				
Group 2 vs group 1	0.003	0.034	0.003	0.933
Group 3 vs group 1	0.071	0.030	0.078	0.018
Blood loss[a]	0.027	0.009	0.134	0.002
ASA ≥ 3	0.079	0.023	0.121	0.001
Laparoscopic or robotic surgery	-0.104	0.034	-0.103	0.002
Cirrhosis	0.053	0.021	0.085	0.010
Multiple nodules	0.083	0.025	0.109	0.001
Perioperative transfusion	0.088	0.027	0.139	0.001
Child-Pugh class: B or C	0.193	0.062	0.102	0.002
Diabetes mellitus	0.051	0.023	0.073	0.028
>2 segments resected	0.055	0.022	0.086	0.015
Age	0.002	0.001	0.091	0.009
ALT >40 IU/L	0.048	0.021	0.076	0.021

β = regression coefficients; std β = standardized regression coefficients; ALT = alanine aminotransferase; ASA = ASA physical status; group1 = mild pain; group 2 = moderate/severe pain dropping to mild; group 3 = mild pain rebounding to moderate.
[a]On base-2 logarithmic scale.

Table 4

Multinomial logistic regression after backward stepwise model selection

	Group 2 vs group 1			Group 3 vs group 1		
	OR	95% CI	*p*	OR	95% CI	*p*
Anesthesia time[a]	2.73	1.24-6.02	0.013	1.20	0.64-2.24	0.570
Extracapsular invasion	2.27	1.20-4.30	0.012	1.10	0.65-1.85	0.726
Serum creatinine	1.35	1.11-1.65	0.003	0.70	0.36-1.38	0.305
Hemoglobin	1.34	1.11-1.62	0.002	1.05	0.91-1.20	0.507
Age	0.97	0.95-1.00	0.032	1.00	0.98-1.02	0.961
Blood loss[a]	0.76	0.58-0.99	0.046	1.01	0.81-1.25	0.954
Total bilirubin ≥1.0 mg/dL	0.17	0.04-0.73	0.018	1.53	0.91-2.59	0.112
Perioperative transfusion	1.75	0.75-4.06	0.194	1.89	1.00-3.55	0.049
Preoperative TACE/RFA/PEI	1.55	0.60-3.99	0.364	0.36	0.13-0.96	0.042
Epidural analgesia	1.22	0.58-2.55	0.598	1.82	1.09-3.05	0.023
>2 segments resected	0.95	0.48-1.87	0.885	1.75	1.08-2.85	0.024
Surgery before 2014	0.58	0.30-1.13	0.109	0.39	0.23-0.66	0.001

CI = confidence interval; OR = odds ratio; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.
[a]On base-2 logarithmic scale.

total bilirubin, aspartate transaminase level, alpha-fetoprotein level, resected tumor diameter >5 cm, multiple nodules, and poor or undifferentiated histology. These were taken into consideration in our study and did not affect the outcomes of liver resection after analysis of the pain trajectory. It may indicate that the pain control method did not play as important a roll in cancer metastasis as in other cancers, such as colorectal cancer.

Opioid receptors are implicated in cancer progression and long-term patient outcomes in many cancers, such as ovarian cancer,[20] colorectal cancer, and lung cancer. However, this correlation remains controversial in certain cancers, such as breast cancer.[21,22] Although in animal studies, the μ-opioid receptor has been shown to suppress metastatic tumors, opioids and their association with liver metastasis survival have not been clearly established in human studies. Our findings that pain trajectory did not affect cancer-free survival could support the theory that metastasis mechanisms in liver cancer are complex and cannot be explained by the anesthetic or pain management strategy alone.

Patients with initial mild postoperative pain that rebounded to moderate had the following characteristics: higher incidence of surgery occurring before 2014, resection of >2 segments and perioperative transfusion, less laparoscopic surgery, more intraoperative blood loss, and longer LOS. Also, multiple linear regression analysis showed that laparoscopic or robotic surgery was the only negative predictor of LOS in our study. This is supported by recent findings that minimally invasive surgery decreases operative mortality, LOS, blood transfusions, and postoperative pain.[23] The change in pain trajectory may be associated with improvement in surgical technique. Postoperative pain management strategies should be planned according to surgical techniques that aim to give better immediate postoperative pain control during complex or multisegmental tumor resections. In addition, in recent years, multimodal analgesia has replaced intravenous patient-controlled analgesia in our hospital. This may also be a contributing factor to the changes in pain trajectory observed after the year 2014.

There were some limitations to the present study. First, it was an observational study and the effects of unobserved variables on endpoints could not be further assessed. Second, the amount of analgesic used by each patient could not be obtained due to difficulties in this data requisition. Third, potential interactions between predictors on clinical outcomes of interest were not further evaluated for the sake of model simplification. Fourth, postoperative complications, such as intestinal obstruction, anastomosis, leakage, bleeding, were not available in the database, which could have affected the outcomes. Further analysis on the associations between potential risk factors, postoperative complications, and cancer outcomes should be considered in the future.

In conclusion, acute pain trajectories were associated with LOS but were not associated with cancer recurrence or survival after liver cancer surgery. Analysis of postoperative pain trajectories provides valuable information and a comprehensive view of how to investigate the complicated relationships between variations in pain observations over time and clinical outcomes after liver cancer surgery to further explore the potential underlying mechanisms. Group-based trajectory analysis is a promising approach for investigating the complex relationships between variations in postoperative pain over time and clinical outcomes.

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