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Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study

Running title: CRC surgery with liver disease

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Abstract

Objectives: Colorectal carcinoma (CRC) patients with pre-existing chronic liver disease (CLD) had a significantly higher 30-day mortality after CRC surgery compared to healthy controls. This study investigated the factors associated with postoperative complications and in-hospital mortality in CRC patients with co-existing CLD who underwent colorectal surgery.

Design: A retrospective obaservational population-based study.

Setting: The data was from the National Inpatient Sample (NIS) database, a part of the Healthcare Cost and Utilization Project (HCUP).

Participants: This study analyzed a total of 7,463 inpatients with CRC who underwent colorectal surgery at admission.

Primary and secondary outcome measures: The primary endpoint of this study was the prevalence of postoperative complications, and the secondary endpoint was in-hospital mortality.

Results: In the CLD group, 36.27% of patients had chronic hepatitis C, 28.36% had non-alcoholic fatty liver disease, and 31.19% had other types of chronic liver diseases. Length of hospital stay was significantly associated with postoperative complications (aOR= 1.13, 95% CI= 1.12-1.15, $p < 0.001$). CRC inpatients with CLD had a significantly higher risk of in-hospital mortality compared to patients without CLD (aOR= 1.98, 95% CI= 1.39-2.82, $p < 0.001$). Length of hospital stay was also significantly associated with in-hospital mortality (aOR= 1.06, 95% CI= 1.04-1.08, $p < 0.001$). However, inpatients with hyperlipidemia had a significantly lower risk of mortality (aOR= 0.46, 95% CI= 0.28-0.75, $p = 0.002$) compared to inpatients without hyperlipidemia.

Conclusions: Status of the chronic liver disease in our population-based study make it possible to correlate peri- or post-operative complications and mortality in CRC patients, and can help improve clinical management and outcomes in these patients.

Keywords: Colorectal cancer, short-term morbidity, mortality, chronic liver disease, National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP).

Strengths and limitations of this study

- Data for this study were collected from a large, comprehensive, and national representative database.
- A large multi-ethnic population sample allowed us to explore the racial/ethnic heterogeneity
- The cross-sectional design of this study can only demonstrate association, therefore, causality could not be determined.

Introduction

Colorectal cancer (CRC) is the most common gastrointestinal malignancy, and the second leading cause of cancer-related deaths in developed countries, accounting for 51,690 deaths in 2012.[1, 2] The 5-year survival rates range from 90% for cancers detected at the localized stage, 70% for regional tumors, and 10% for distant metastatic tumors.[3] The major risk factors of CRC include age and hereditary factors, the presence of inflammatory bowel disease, and environmental factors such as nutritional practices, physical activity/obesity, cigarette smoking, and alcohol consumption.[4] The implementation of population-based screening for average-risk, asymptomatic individuals beginning at 50 years of age has resulted in a significant decrease in CRC incidence among individuals > 50 years old. However, there has been an increase in CRC incidence and mortality among individuals < 50 years old, for whom screening is limited, and who typically present at a late stage of the disease.[5] CRC patients who present at an early stage usually receive curative surgical resection, whereas patients who present with metastatic disease receive palliative systemic chemotherapy or treatment with novel biologic agents.[6]

CRC has been reported to result from an accumulation of genetic changes in key regulatory genes/signaling pathways including the RAS/MAPK pathway involving the KRAS, NRAS and BRAF genes, and the Wnt and PI3K pathways.[7] However, there is a growing awareness that epigenetic changes such as microsatellite instability, histone modifications, DNA methylation, and chromatin remodeling may play an important role in CRC initiation and progression.[8]

Chronic liver disease (CLD) represents a major health concern worldwide and accounts for approximately 1 million deaths per year.[9] The major risk factors for CLD include chronic viral hepatitis infection, chronic exposure to toxins (including excessive alcohol consumption), and autoimmune injury, which all contribute towards progression of hepatic

fibrosis and development of cirrhosis via the production and deposition of extracellular matrix components.[10] CLD also includes liver damage mediated by lipid accumulation in hepatocytes. The spectrum of obesity-related liver disease such as NAFLD (non-alcoholic fatty liver disease) can range from non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis, and end in cirrhosis.[11]

Patients with liver disease who had CRC frequently require surgery and anesthesia, and are at increased risk of perioperative complications and postoperative morbidity and mortality. This could be due to complications associated with liver disease, including hepatic encephalopathy, ascites, sepsis, and hemorrhage.[12] Patients with mild to moderate chronic liver disease without cirrhosis usually tolerate surgery well, whereas acute liver failure (previously termed fulminant hepatic failure) and acute viral or alcoholic hepatitis are considered contraindications to elective surgery.[13] Additionally, it has been reported that the location of the surgical procedure is an important risk factor for postoperative liver failure in patients with the pre-existing liver disease. Cardiac surgery, abdominal surgery, and hepatic resection are all associated with higher rates of perioperative complications, and higher rates of morbidity and mortality compared to more peripheral surgery, presumably due to greater reductions in hepatic blood flow.[13, 14]

A recent meta-analysis of 50 studies reported that patients with CLD had a significantly higher risk of CRC, which persisted after liver transplantation, compared to the general population.[15] CRC patients with the pre-existing liver disease were shown to have a significantly higher 30-day mortality after CRC surgery compared to CRC patients with non-cirrhotic liver disease and healthy controls.[16] Other data showed that colectomy of any kind was associated with a significant risk of postoperative morbidity and mortality in cirrhotic patients,[17] and this was thought to be related to increased intraoperative and early postoperative bleeding.[18] Additionally, although fatty liver has been shown to be an important

risk factor of CRC,[19] the presence of NAFLD is thought to play a protective role in the overall survival of CRC patients.[20]

The aim of our present study was to identify risk factors for postoperative complications and mortality in CRC patients with co-existing CLD who underwent colorectal surgery. Our clinical data were sourced from a national and comprehensive database, which made it possible to minimize discrepancies and biases.

Methods

Data source

Our data were sourced from the National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project (HCUP), samples approximately 20% of discharges from all HCUP-participating community hospitals, and is the largest publicly available inpatient database in the United States [www.hcup-us.ahrq.gov/nisoverview.jsp]. The NIS is representative of approximately 95% of the US population (http://www.cdc.gov/nchs/nhanes/). All of the HCUP-NIS data are de-identified and analysis of the data does not require IRB approval or informed consent by all subjects.

Study population

This study extracted data of inpatients diagnosed with primary CRC based on specific International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (153, 154), who underwent surgical intervention at admission. Surgical interventions included open and partial or subtotal colectomy (ICD-9-CM: 45.7), pull-through resection of rectum (ICD-9-CM: 48.40, 48.41, 48.43, 48.49, abdominoperineal resection of rectum / complete proctectomy (ICD-9-CM: 48.50, 48.52, 48.59), and other resections of rectum / partial proctectomy / rectosigmoidectomy (ICD-9-CM: 48.6x). Patients with missing data for

demographics, patients diagnosed with liver cirrhosis, and patients with co-existing other primary malignancies were excluded.

Study Variables

The primary endpoint of this study was the prevalence of post-operative complications, including post-operative infection (ICD-9-CM=998.5), post-operative shock (ICD-9-CM=998.0), post-operative bleeding (ICD-9-CM=998.1), disruption of wound (ICD-9-CM=998.3), non-healing surgical wound (ICD-9-CM=998.83), nervous system complications (ICD-9-CM=997.0x), cardiac arrest/heart failure (ICD-9-CM=997.1), phlebitis/thrombophlebitis (ICD-9-CM=997.2), respiratory complications (ICD-9-CM=997.3x), digestive system complications (ICD-9-CM=997.4). urinary complications (ICD-9-CM=997.5), vascular complications (ICD-9-CM=997.7x), and unspecified complications (ICD-9-CM=998.9). The secondary endpoint was in-hospital mortality, which reflected the severity of the disease.

The independent variables included the presence of chronic liver disease. Although there were several etiologies of chronic liver disease, we only focused on specific etiologies found in higher percentages in our study population, such as chronic hepatitis B (ICD-9-CM=070.22, 070.32), chronic hepatitis C (ICD-9-CM=070.44, 070.54, 070.7x), non-alcoholic fatty liver disease (ICD-9-CM=571.8, 571.9), and other minor causes.

The relative variables obtained for each record included patient demographics (age, gender, race/ethnicity), socioeconomic status (household income), severity of CRC (locoregional involvement, distant metastasis), co-morbidity (hyperlipidemia, obesity), place of hospitalization, type of admission (elective, non-elective), and length of hospital stay.

Socioeconomic Status – household income

This categorical variable provides a quartile classification of the estimated median household income of residents in the patient's ZIP Code. The quartiles are identified by values of 1 to 4, indicating the poorest to wealthiest populations. These values are derived from ZIP Code-demographic data obtained from Claritas. Since these estimates are updated annually, the value ranges for these categories vary by year.

Comorbidities

For matching criteria between case and control groups, a number of co-morbid conditions were included, such as diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, Alzheimer's disease and other cognitive impairment, AIDS, alcohol abuse, chronic blood loss anemia, chronic pulmonary disease, coagulopathy, drug abuse, hypothyroidism, other neurological disorders, peripheral vascular disorders, pulmonary circulation disorders, renal failure, valvular diseases, and weight loss.

For relative variables, two comorbid conditions (hyperlipidemia and obesity) were selected to be incorporated into analysis. These two conditions were inter-correlated and were selected considering the difficulty of operation in obese patients, which could cause a series of postoperative complications.

Statistical analysis

Simple matching was used to match inpatients who had chronic liver diseases with those who did not have chronic liver diseases by age, gender, the severity of CRC, and comorbidities. Selected cases were matched with controls by 1:4 matching. Continuous variables were expressed as mean ± standard deviation, and categorical data were shown as counts and percentages. Conditional logistic regression method was performed after matching, and a univariate logistic regression model was performed to determine the independent risk

factors of postoperative complications or mortality. Multiple logistic regression analysis was performed on variables with an unadjusted effect and a p-value < 0.05 on univariate logistic regression analysis. Statistical significance was defined by a p-value < 0.05. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and clinical characteristics

Analysis of the HCUP-NIS database for the period 2005-2014 showed that 152,625 inpatients diagnosed with CRC had undergone surgical treatment. After excluding patients with liver cirrhosis, patients with co-existing other primary malignancies, and patients with missing data for age and gender, a total of 129,958 inpatients were enrolled in this study. The study population comprised 1,555 patients with CLD (case group) and 128,403 patients without CLD (control group). Due to the small sample size of the case group, simple matching was used to balance the case and control groups. After matching, a total of 7,463 inpatients were enrolled in the final study population. Of these patients, 5,908 patients (79.16%) had no CLD and 1,555 patients (20.84%) had CLD. A majority of patients in the CLD group had chronic hepatitis C (n = 564, 36.27%), while 441 patients (28.36%) had the non-alcoholic fatty liver disease, and 485 patients (31.19%) patients had other types of chronic liver diseases.

Baseline demographics and clinical characteristics of study patients are described in Table 1. The mean age of the inpatients was 62.53 years old, and the mean length of hospital stay was 8.96 days. A majority of the inpatients (57.39%) was male, and 60.78% were white. A total of 1993 patients (26.71%) were classified in the first quartile of median household income, and almost half the patients (49.99%) were operated upon in urban teaching hospitals.

Analysis of the whole study population showed that 1,633 inpatients (21.88%) had post-operative complications, the most frequent of which was digestive system complications (n = 675, 41.33%). A total of 1839 patients (24.64%) had hyperlipidemia, and 907 patients (12.15%) were obese. Length of hospital stay was 8.61 ± 6.49 days for non-CLD patients and 10.26 ± 9.46 for CLD patients. In-hospital mortality was recorded for 162 inpatients (2.17%).

Associating factors for postoperative complications in CRC inpatients with underlying CLD

Univariate and multivariate logistic regression analyses were performed to assess risk factors significantly associated with postoperative complications (Table 2). Although univariate analysis showed that hyperlipidemia and length of hospital stay were both significant associating factors of postoperative complications, length of hospital stay was the only variable significantly associated with postoperative complications by multivariate analysis (aOR= 1.13, 95% CI= 1.12-1.15, $p < 0.001$). The presence of underlying CLD was not significantly associated with the occurrence of postoperative complications (aOR=0.91, 95% CI= 0.78-1.05, p=0.192).

Associating factors for in-hospital mortality in CRC inpatients with underlying CLD

Univariate and multivariate logistic regression analyses were performed to assess risk factors significantly associated with in-hospital mortality (Table 3). Compared with patients without CLD, inpatients who had CLD had a significantly higher risk of in-hospital mortality events (aOR= 1.98, 95% CI= 1.39-2.82, $p < 0.001$). Patients in Quartile 2 of median household income had a significantly higher risk of in-hospital mortality by multivariate analysis. Multivariate analysis also showed that the length of hospital stay was significantly associated with in-hospital mortality events (aOR= 1.06, 95% CI= 1.04-1.08, $p < 0.001$).

However, inpatients with hyperlipidemia had a significantly lower risk of mortality (aOR= 0.46, 95% CI= 0.28-0.75, p = 0.002) compared to inpatients without hyperlipidemia.

Discussion

This study investigated factors significantly associated with postoperative complications and in-hospital mortality in CRC patients with co-existing CLD who underwent colorectal surgery. Approximately 20% of our study population comprised patients with CLD. Our data showed that patients with CLD had a significantly longer duration of hospital stay compared to patients without CLD. Duration of hospital stay was significantly associated with the prevalence of postoperative complications as well as the occurrence of in-hospital mortality. Additionally, inpatients with hyperlipidemia had a significantly lower association with in-hospital mortality compared to inpatients without hyperlipidemia.

Data for this study were extracted from the HCUP-NIS database, which is the largest publicly available collection of longitudinal hospital care clinical data in the United States beginning in 1988. We were, therefore, able to perform analysis of trends over time and make national estimates of health care utilization, access, charges, quality, and outcomes. The NIS sampling frame has grown from 8 States in 1988, to 22 States in 1998, to 46 States in 2011, and currently, covers 97% of the U.S. population.

Studies evaluating operative risk in patients with liver disease found that operative risk was correlated with severity of the underlying liver disease and the nature of the surgical procedure. The increased perioperative risk among patients with the underlying liver disease could be due to impairment of hepatic functions such as drug metabolism, detoxification of endogenous or exogenous toxins, and production of plasma proteins.[13] Assessment of Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) score, in

combination with careful pre- and post-operative monitoring has been shown to be crucial for improving outcomes.[13, 21, 22] Additionally, some investigators have described the development of risk indices to distinguish low-risk and high-risk subgroups for predicting postoperative mortality in cirrhotic and CRC patients.[17, 23]

Patients with CLD who undergo CRC surgery have previously been shown to have a significantly higher risk of postoperative mortality compared to patients without CLD. [17, 24, 25, 26] Data from a previous population-based study showed that CLD patients had a 6.5-fold higher risk of mortality after colorectal surgery, as well as significantly higher rates of postoperative complications compared to non-CLD patients.[27] These data suggested that identification of risk factors associated with postoperative complications and mortality in these patients could be critical to improving the clinical outcome.

The majority of CLD patients in our study had chronic hepatitis C infection, followed by NAFLD. Our data were consistent with previous studies showing that patients with chronic hepatitis C and NAFLD had a significantly higher incidence of colorectal adenomas and advanced neoplasms compared to healthy controls.[19, 28, 29] Interestingly, our data showed that the presence of underlying CLD was not significantly associated with the rate of postoperative complications, although it was significantly associated with postoperative mortality.

Our data showing that CRC patients with CLD had a significantly longer hospital stay compared to patients without CLD, could possibly be due to a higher rate of postoperative complications and in-hospital mortality in these patients, which was evident in our multivariate regression analysis. Previous results showed that although mortality rates were higher in patients who were emergently admitted compared to patients with elective admission, there was no significant difference in the adjusted relative risk of mortality between the two groups.[16] Our data showed that the type of admission (emergent vs. elective)

was not significantly associated with either the risk of postoperative complications or risk of mortality among inpatients with CRC who had co-existing CLD.

It has been reported that a low socio-economic status was significantly associated with a high incidence of CRC, regardless of individual-level CRC risk factors.[30] Our multivariate analysis showed that patients in Quartile 2 of median household income had a significantly higher risk of in-hospital mortality compared to patients in Quartiles 3 and 4, suggesting that low socioeconomic status (SES) was significantly associated with a higher risk of in-hospital mortality in CRC patients with CLD. This could be a reflection of poorer access to, and lower utilization of health care services among patients with low SES.

Our data showed that the presence of hyperlipidemia was significantly less associated with postoperative in-hospital mortality. Hyperlipidemia is known to be associated with increased risk of CVD events and increased all-cause mortality. Our present findings could be due to the fact that patients with a diagnosis of hyperlipidemia were prescribed statins, and had a good compliance. Statin monotherapy has previously been shown to exert a protective effect and decreasing the rate of colorectal cancer mortality.[31] Statin use has been shown to be an independent predictor of longer cancer-specific survival, and overall survival in patients with curatively resected CRC.[32] Additionally, since the levels of adiponectin and leptin are significantly decreased and increased, respectively, in NAFLD and CRC patients,[33, 34] it will be interesting to evaluate whether changes in adiponectin/leptin ratios in these patients are associated with clinical outcomes.

Based on our data source, the major strengths of our study are 1) the sample size is large enough to determine fairly precise prevalence measures at the national level, 2) a large multi-ethnic population sample which allowed us to explore the racial/ethnic heterogeneity, 3) the analysis was conducted in a nationally representative sample; therefore, our results may be generalized to the entire U.S. adult population. The major limitations of this study were 1) this

was a cross-sectional analysis, and the unit of this database was the individual medical record. Our study, therefore, could not make any inferences regarding causality, 2) it is possible that the number of hospital discharges recorded could include an undetermined number of repeat hospital stays for the same patient, 3) NIS is a US inpatient data (including representative proportions of people of different ethnicity) and should be validated in other countries. To the best of our knowledge, this is the first population-based, cross-sectional study of hospitalized patients evaluating the factors associated with postoperative complications and mortality in CRC patients with co-existing CLD.

Conclusion

Our study showed that the postoperative complications among CRC patients with underlying CLD was positively associated with length of hospital stay, but was not associated with the presence of CLD. The presence of CLD and duration of hospital stay were positively associated with the occurrence of in-hospital mortality, whereas the presence of hyperlipidemia was a protective factor. The associating factors identified in our population-based study make it possible to correlate peri- or post-operative complications and mortality in CRC patients with underlying CLD, and can help to improve clinical management and outcomes in this group of CRC patients.

Data Sharing Statement

All data can be available in the text.

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Conflict of interest

The authors declare no conflict of interest.

Statement of Author Contribution

Ko-Chao Lee: Conception and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; guarantor of integrity of the entire study; definition of intellectual content; Administrative, technical or material support; Supervision

Kuan-Chih Chung: Conception and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; guarantor of integrity of the entire study; definition of intellectual content; Administrative, technical or material support; Supervision

Hong-Hwa Chen: Acquisition of data; Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; Administrative, technical or material support

Kung-Chuan Cheng: Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; clinical studies

Kuen-Lin Wu: Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; clinical studies

Chien-Chang Lu: Analysis and interpretation of data; Critical revision of the manuscript; literature research; clinical studies

All authors have read and approved the submitted version.

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Table 1. Baseline demographic and clinical characteristics of study population

	Total sample N = 7463	Chronic liver diseases		p-value
		No N = 5908	Yes N = 1555	
Type of chronic liver diseases				
None	5908 (79.16)	5908 (100.00)	0 (0.00)	
Chronic hepatitis B	65 (0.87)	0 (0.00)	65 (4.18)	
Chronic hepatitis C	564 (7.56)	0 (0.00)	564 (36.27)	
Non-alcoholic fatty liver disease	441 (5.91)	0 (0.00)	441 (28.36)	
Other types	485 (6.50)	0 (0.00)	485 (31.19)	
Postoperative complications				0.228
No	5830 (78.12)	4633 (78.42)	1197 (76.98)	
Yes	1633 (21.88)	1275 (21.58)	358 (23.02)	
Postoperative infection	360 (22.05)	276 (21.65)	84 (23.46)	
Postoperative shock	23 (1.41)	15 (1.18)	8 (2.23)	
Postoperative bleeding	149 (9.12)	104 (8.16)	45 (12.57)	
Disruption of wound	73 (4.47)	55 (4.31)	18 (5.03)	
Non-healing surgical wound	4 (0.24)	4 (0.31)	0 (0.00)	
Nervous system complications	17 (1.04)	16 (1.25)	1 (0.28)	
Cardiac arrest/heart failure	125 (7.65)	102 (8.00)	23 (6.42)	
Phlebitis/thrombophlebitis	5 (0.31)	3 (0.24)	2 (0.56)	
Respiratory complications	141 (8.63)	121 (9.49)	20 (5.59)	
Digestive system complications	675 (41.33)	529 (41.49)	146 (40.78)	
Urinary complications	60 (3.67)	49 (3.84)	11 (3.07)	
Unspecified complications	1 (0.06)	1 (0.08)	0 (0.00)	
In-Hospital Mortality				< 0.001
No	7301 (97.83)	5806 (98.28)	1495 (96.14)	
Yes	162 (2.17)	102 (1.73)	60 (3.86)	
Age				0.984
Mean ± SD	62.53 ± 12.17	62.53 ± 12.16	62.52 ± 12.17	
Gender				0.708
Male	4283 (57.39)	3384 (57.28)	899 (57.81)	
Female	3180 (42.61)	2524 (42.72)	656 (42.19)	
Race				< 0.001
White	4536 (60.78)	3570 (60.43)	966 (62.12)	
Black	810 (10.85)	614 (10.39)	196 (12.60)	
Hispanic	359 (4.81)	266 (4.50)	93 (5.98)	
Asian or Pacific Islander	154 (2.06)	108 (1.83)	46 (2.96)	
Native American	24 (0.32)	19 (0.32)	5 (0.32)	

Other/Missing	1580 (21.17)	1331 (22.53)	249 (16.01)	
Median household income				< 0.001
Quartile 1	1993 (26.71)	1564 (26.47)	429 (27.59)	
Quartile 2	1902 (25.49)	1489 (25.20)	413 (26.56)	
Quartile 3	1757 (23.54)	1386 (23.46)	371 (23.86)	
Quartile 4	1646 (22.06)	1354 (22.92)	292 (18.78)	
Others	165 (2.21)	115 (1.95)	50 (3.22)	
Location of hospital				< 0.001
Rural	984 (13.19)	833 (14.10)	151 (9.71)	
Urban non-teaching	2711 (36.33)	2152 (36.43)	559 (35.95)	
Urban teaching	3731 (49.99)	2894 (48.98)	837 (53.83)	
Others	37 (0.50)	29 (0.49)	8 (0.51)	
Types of admission				0.006
Non-elective	2323 (31.13)	1789 (30.28)	534 (34.34)	
Elective	5122 (68.63)	4103 (69.45)	1019 (65.53)	
Others	18 (0.24)	16 (0.27)	2 (0.13)	
Severity of CRC				0.987
None	4889 (65.51)	3868 (65.47)	1021 (65.66)	
Lymph node metastasis	1823 (24.43)	1444 (24.44)	379 (24.37)	
Distant metastasis	751 (10.06)	596 (10.09)	155 (9.97)	
Length of hospital stay (day)				< 0.001
Mean ± SD	8.96 ± 7.24	8.61 ± 6.49	10.26 ± 9.46	
Hyperlipidemia				< 0.001
No	5624 (75.36)	4382 (74.17)	1242 (79.87)	
Yes	1839 (24.64)	1526 (25.83)	313 (20.13)	
Obesity				0.827
No	6556 (87.85)	5187 (87.80)	1369 (88.04)	
Yes	907 (12.15)	721 (12.20)	186 (11.96)	

Abbreviation: CRC, colorectal cancer.

Table 2. Univariate and multivariate logistic regression analyses to identify factors associated with postoperative complications among inpatients diagnosed with colorectal cancer

	Univariate		Multivariate	
	OR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	1.08 (0.94, 1.23)	0.292	0.91 (0.78, 1.05)	0.192
Race				
White	reference			
Black	1.01 (0.83, 1.23)	0.842		
Hispanic	1.03 (0.79, 1.35)	0.767		
Asian or Pacific islander	0.85 (0.54, 1.34)	0.486		
Native American	1.10 (0.42, 2.92)	0.792		
Other/Missing	0.95 (0.81, 1.10)	0.686		
Median household income				
Quartile 1	reference			
Quartile 2	1.16 (0.99, 1.36)	0.074		
Quartile 3	0.93 (0.79, 1.10)	0.127		
Quartile 4	1.02 (0.86, 1.21)	0.878		
Others	1.06 (0.71, 1.59)	0.867		
Location of hospital				
Rural	reference			
Urban non-teaching	1.09 (0.90, 1.32)	0.996		
Urban teaching	1.04 (0.87, 1.25)	0.647		
Others	1.25 (0.57, 2.75)	0.642		
Types of admission				
Non-elective	reference			
Elective	0.95 (0.83, 1.08)	0.937		
Others	0.85 (0.24, 3.03)	0.835		
Length of hospital stay	**1.13 (1.12, 1.14)**	**<0.001**	**1.13 (1.12, 1.15)**	**<0.001**
Hyperlipidemia				
No	reference		reference	
Yes	**0.77 (0.67, 0.89)**	**<0.001**	0.97 (0.83, 1.12)	0.671
Obesity				
No	reference			
Yes	1.09 (0.91, 1.30)	0.353		

$P < 0.05$ were shown in boldface.

Table 3. Univariate and multivariate logistic regression analyses to identify factors associated with in-hospital mortality among inpatients diagnosed with colorectal cancer.

	Univariate		Multivariate	
	OR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	**2.33 (1.68, 3.23)**	**<0.001**	**1.98 (1.39, 2.82)**	**<0.001**
Race				
White	reference			
Black	1.31 (0.76, 2.27)	0.992		
Hispanic	0.93 (0.42, 2.06)	0.992		
Asian or Pacific Islander	NA	NA		
Native American	NA	NA		
Other/Missing	0.86 (0.55, 1.35)	0.992		
Median household income				
Quartile 1	reference		reference	
Quartile 2	1.28 (0.83, 1.96)	0.114	**1.45 (0.92, 2.29)**	**0.03**
Quartile 3	**0.58 (0.35, 0.99)**	**0.016**	0.67 (0.39, 1.16)	0.092
Quartile 4	0.68 (0.40, 1.15)	0.083	0.69 (0.39, 1.22)	0.128
Others	1.72 (0.59, 4.96)	0.178	1.31 (0.40, 4.29)	0.534
Location of hospital				
Rural	reference			
Urban non-teaching	0.65 (0.40, 1.04)	0.146		
Urban teaching	0.59 (0.37, 0.94)	0.074		
Others	2.87 (0.29, 28.13)	0.233		
Types of admission				
Non-elective	reference			
Elective	0.37 (0.26, 0.52)	0.984		
Others	NA	NA		
Length of hospital stay	**1.07 (1.05, 1.09)**	**<0.001**	**1.06 (1.04, 1.08)**	**<0.001**
Hyperlipidemia				
No	reference		reference	
Yes	**0.39 (0.25, 0.63)**	**<0.001**	**0.46 (0.28, 0.75)**	**0.002**
Obesity				
No	reference			
Yes	0.56 (0.29, 1.08)	0.084		

$P < 0.05$ were shown in boldface.
Abbreviation: NA, not applicable

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Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study

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Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study

Running title: CRC surgery with liver disease

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Abstract

Objectives: Colorectal carcinoma (CRC) patients with pre-existing chronic liver disease (CLD) had a significantly higher 30-day mortality after CRC surgery compared to healthy controls. This study investigated the factors associated with postoperative complications and in-hospital mortality in CRC patients with co-existing CLD (excluding cirrhosis) who underwent colorectal surgery.

Design: A retrospective observational population-based study.

Setting: Data were sourced from the National Inpatient Sample (NIS) database, a part of the Healthcare Cost and Utilization Project (HCUP).

Participants: This study analyzed a total of 7,463 inpatients with CRC who underwent colorectal surgery at admission between 2005 and 2014.

Primary and secondary outcome measures: The primary endpoint of this study was the prevalence of postoperative complications, and the secondary endpoint was in-hospital mortality.

Results: In the CLD group, 36.27% of patients had chronic hepatitis C, 28.36% had non-alcoholic fatty liver disease, and 31.19% had other types of chronic liver diseases. Length of hospital stay was significantly associated with postoperative infection (aOR= 1.13, 95% CI= 1.11-1.15, $p < 0.001$), postoperative bleeding (aOR= 1.02, 95% CI= 1.01-1.04, $p = 0.013$), respiratory complications (aOR= 1.04, 95% CI= 1.02-1.07, $p < 0.001$), and digestive complications (aOR= 1.05, 95% CI= 1.04-1.06, $p < 0.00$). Presence of CLD was significantly associated with higher risk of postoperative bleeding (aOR= 1.64, 95% CI= 1.15-2.34, $p = 0.007$). Presence of CLD (aOR= 1.98, 95% CI= 1.39-2.82, $p < 0.001$), and length of hospital stay (aOR= 1.06, 95% CI= 1.04-1.08, $p < 0.001$) were significantly associated with higher risk of in-hospital mortality. However, hyperlipidemia was associated with a significantly lower risk of mortality (aOR= 0.46, 95% CI= 0.28-0.75, $p = 0.002$).

Conclusions: Identification of factors associated with postoperative complications, and mortality in CRC patients with underlying CLD can help to improve clinical management and outcomes in this group of CRC patients.

Keywords: Colorectal cancer, short-term morbidity, mortality, chronic liver disease, National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP).

Strengths and limitations of this study

- Data for this study were collected from a large, comprehensive, and national representative database.
- A large multi-ethnic population sample allowed us to explore the racial/ethnic heterogeneity
- The cross-sectional design of this study can only demonstrate association, therefore, causality could not be determined.

Introduction

Colorectal cancer (CRC) is the most common gastrointestinal malignancy, and the second leading cause of cancer-related deaths in developed countries, accounting for 51,690 deaths in the United States in 2012.[1, 2] The 5-year survival rates range from 90% for cancers detected at the localized stage, 70% for regional tumors, and 10% for distant metastatic tumors.[3] The major risk factors of CRC include age and hereditary factors, the presence of inflammatory bowel disease, and environmental factors such as nutritional practices, physical activity/obesity, cigarette smoking, and alcohol consumption.[4]The implementation of population-based screening for average-risk, asymptomatic individuals beginning at 50 years of age has resulted in a significant decrease in CRC incidence among individuals > 50 years old. CRC patients who present at an early stage usually receive curative surgical resection, whereas patients who present with metastatic disease receive palliative systemic chemotherapy or treatment with novel biologic agents.[5]

Chronic liver disease (CLD) represents a major health concern and accounts for approximately 1 million deaths per year worldwide.[6]The major risk factors for CLD include chronic viral hepatitis infection, chronic exposure to toxins (including excessive alcohol consumption), and autoimmune injury, which all contribute towards progression of hepatic fibrosis and development of cirrhosis via the production and deposition of extracellular matrix components.[7]CLD also includes liver damage mediated by lipid accumulation in hepatocytes. The spectrum of obesity-related liver disease such as NAFLD (non-alcoholic fatty liver disease) can range from non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis, and end in cirrhosis.[8]

Patients with liver disease who had CRC frequently required surgery and anesthesia, and were shown to have an increased risk of perioperative complications and postoperative morbidity and mortality. This could be due to complications associated with liver disease,

including hepatic encephalopathy, ascites, sepsis, and hemorrhage.[9]Patients with mild to moderate chronic liver disease without cirrhosis usually tolerate surgery well, whereas acute liver failure (previously termed fulminant hepatic failure) and acute viral or alcoholic hepatitis are considered contraindications to elective surgery.[10]Additionally, it has been reported that the location of the surgical procedure is an important risk factor for postoperative liver failure in patients withpre-existing liver disease. Cardiac surgery, abdominal surgery, and hepatic resection are all associated with higher rates of perioperative complications, and higher rates of morbidity and mortality compared to more peripheral surgery, presumably due to greater reductions in hepatic blood flow.[10, 11]

A recent meta-analysis of 50 studies reported that patients with CLD had a significantly higher risk of CRC, which persisted after liver transplantation, compared to the general population.[12]CRC patients with pre-existing liver disease were shown to have a significantly higher 30-day mortality after CRC surgery compared to CRC patients with non-cirrhotic liver disease and healthy controls.[13] Other data showed that colectomy of any kind was associated with a significant risk of postoperative morbidity and mortality in cirrhotic patients,[14] and this was thought to be related to increased intraoperative and early postoperative bleeding.[15]Additionally, although fatty liver has been shown to be an important risk factor of CRC,[16] the presence of NAFLD is thought to play a protective role in the overall survival of CRC patients.[17]

The aim of our present study was to identify risk factors associated with postoperative complications and mortality in CRC patients with co-existing CLD who underwent colorectal surgery. Our clinical data were sourced from a national and comprehensive database, which made it possible to minimize discrepancies and biases.

Methods

Data source

In this population-based, cross-sectional study, data were sourced from the National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project (HCUP). The NIS database samples approximately 20% of discharges from all HCUP-participating community hospitals, and is the largest publicly available inpatient database in the United States[www.hcup-us.ahrq.gov/nisoverview.jsp]. The NIS is representative of approximately 95% of the US population(http://www.cdc.gov/nchs/nhanes/). All of the HCUP-NIS data are de-identified and analysis of the data does not require IRB approval or informed consent by all subjects.

Study population

This study extracted data of inpatients diagnosed with primary CRC based on specific International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (153, 154), who underwent surgical intervention at admission. Surgical interventions included open and partial or subtotal colectomy (ICD-9-CM: 45.7), pull-through resection of rectum (ICD-9-CM: 48.40, 48.41, 48.43, 48.49, abdominoperineal resection of rectum / complete proctectomy (ICD-9-CM: 48.50, 48.52, 48.59), and other resections of rectum / partial proctectomy / rectosigmoidectomy (ICD-9-CM: 48.6x). Patients with missing data for demographics, patients diagnosed with liver cirrhosis, and patients with co-existing other primary malignancies were excluded.

Study Variables

The primary endpoint of this study was the prevalence of post-operative complications, including post-operative infection (ICD-9-CM=998.5), post-operative shock (ICD-9-

CM=998.0), post-operative bleeding (ICD-9-CM=998.1), disruption of wound (ICD-9-CM=998.3), non-healing surgical wound (ICD-9-CM=998.83), nervous system complications (ICD-9-CM=997.0x), cardiac arrest/heart failure (ICD-9-CM=997.1), phlebitis/thrombophlebitis (ICD-9-CM=997.2), respiratory complications (ICD-9-CM=997.3x), digestive system complications (ICD-9-CM=997.4). urinary complications (ICD-9-CM=997.5), vascular complications (ICD-9-CM=997.7x), and unspecified complications (ICD-9-CM=998.9). The secondary endpoint was in-hospital mortality, which reflected the severity of the disease.

The independent variables included the presence of chronic liver disease. Although there were several etiologies of chronic liver disease, we only focused on specific etiologies found in higher percentages in our study population, such as chronic hepatitis B (ICD-9-CM=070.22, 070.32), chronic hepatitis C (ICD-9-CM=070.44, 070.54, 070.7x), non-alcoholic fatty liver disease (ICD-9-CM=571.8, 571.9), and other minor causes.

The relative variables obtained for each record included patient demographics (age, gender, race/ethnicity), socioeconomic status (household income), severity of CRC (locoregional involvement, distant metastasis), co-morbidity (hyperlipidemia, obesity), place of hospitalization, type of admission (elective, non-elective), and length of hospital stay.

Socioeconomic Status – household income

This categorical variable provides a quartile classification of the estimated median household income of residents in the patient's ZIP Code. The quartiles are identified by values of 1 to 4, indicating the poorest to wealthiest populations. These values are derived from ZIP Code-demographic data obtained from Claritas. Since these estimates are updated annually, the value ranges for these categories vary by year.

Comorbidities

For matching criteria between case and control groups, a number of co-morbid conditions were included, such as diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, Alzheimer's disease and other cognitive impairment, AIDS, alcohol abuse, chronic blood loss anemia, chronic pulmonary disease, coagulopathy, drug abuse, hypothyroidism, other neurological disorders, peripheral vascular disorders, pulmonary circulation disorders, renal failure, valvular diseases, and weight loss.

For relative variables, two comorbid conditions (hyperlipidemia and obesity) were selected to be incorporated into analysis. These two conditions were inter-correlated and were selected considering the difficulty of operation in obese patients, which could cause a series of postoperative complications.

Statistical analysis

Simple matching was used to match inpatients who had chronic liver diseases with those who did not have chronic liver diseases by age, gender, the severity of CRC, and comorbidities. Selected cases were matched with controls by 1:4 matching. Continuous variables were expressed as mean± standard deviation, and categorical data were shown as counts and percentages. Conditional logistic regression method was performed after matching, and a univariate logistic regression model was performed to determine the independent risk factors of postoperative complications or mortality. Multiple logistic regression analysis was performed on variables with an unadjusted effect and a p-value < 0.05 on univariate logistic regression analysis. Statistical significance was defined by a p-value < 0.05. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and clinical characteristics

Analysis of the HCUP-NIS database for the period 2005-2014 showed that 152,625 inpatients diagnosed with CRC had undergonesurgical treatment. After excluding patients with liver cirrhosis, patients with co-existing other primary malignancies, and patients with missing data for age and gender, a total of 129,958 inpatients were enrolled in this study. The study population comprised 1,555 patients with CLD (case group) and 128,403 patients without CLD (control group). Due to the small sample size of the case group, simple matching was used to balance the case and control groups. After matching, a total of 7,463 inpatients were enrolled in the final study population. Of these patients, 5,908 patients (79.16%) had no CLD and 1,555 patients (20.84%) had CLD. A majority of patients in the CLD group had chronic hepatitis C (n = 564, 36.27%), while 441 patients (28.36%) had non-alcoholic fatty liver disease, and 485 patients (31.19%) patients had other types of chronic liver diseases.

Baseline demographics and clinical characteristics of study patients are described in Table 1. The mean age of the inpatients was 62.53 years old, and the mean length of hospital stay was 8.96 days. A majority of the inpatients (57.39%) was male, and 60.78% were white. A total of 1993 patients (26.71%) was classified in the first quartile of median household income, and almost half the patients (49.99%) were operated upon in urban teaching hospitals.

Analysis of the whole study population showed that 1,633 inpatients (21.88%) had post-operative complications, the most frequent of which was digestive system complications (n = 675, 41.33%). A total of 1839 patients (24.64%) had hyperlipidemia, and 907 patients (12.15%)were obese. Length of hospital stay was 8.61 $\pm$ 6.49 days for non-CLD patients and 10.26 $\pm$ 9.46 for CLD patients. In-hospital mortality was recorded for 162 inpatients (2.17%).

Factors associated with postoperative complications in CRC patients with underlying CLD

Univariate and multivariate logistic regression analyses were performed to assess risk factors significantly associated with postoperative complications (Table 2). Although univariate analysis showed that hyperlipidemia and length of hospital stay were both significantly associated with risk of postoperative complications, the length of hospital stay was the only variable significantly associated with risk of post-operative complications by multivariate analysis (aOR= 1.13, 95% CI= 1.12-1.15, p < 0.001). The presence of underlying CLD was not significantly associated with the occurrence of overall postoperative complications (aOR=0.91, 95% CI= 0.78-1.05, p=0.192).

We subsequently used logistic regression analysis to identify factors associated with specific postoperative complications which occurred in > 5% of patients (postoperative infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications, and digestive system complications; Table 3-1, Table 3-2, and Table 4). Univariate analysis showed that 1) presence of hyperlipidemia, and length of hospital stay were significantly associated with postoperative infection (all P<0.010; Table 3-1); 2) presence of CLD, and length of hospital stay were significantly associated with postoperative infection, and postoperative bleeding (all P<0.010; Table 3-1); 3) presence of CLD, treatment at an urban teaching hospital, and length of hospital stay were significantly associated with respiratory complications (all P ≤ 0.048, Table 3-2); 4) black race and length of hospital stay were both significantly associated with digestive system complications (P<0.05; Table 3-2). None of the factors analyzed was significantly associated with cardiac arrest/heart failure (all P ≥ 0.05, Table 3-1).

Our multivariate analysis showed that 1) length of hospital stay was the only factor significantly associated with postoperative infection (aOR= 1.13, 95% CI= 1.11-1.15, p <

0.001) (Table 4); 2) presence of CLD(aOR= 1.64, 95% CI= 1.15-2.34, p = 0.007), and length of hospital stay (aOR= 1.02, 95% CI= 1.01-1.04, p = 0.013)were both significantly associated with postoperative bleeding; 3) patients with CLD, and patients treated at an urban teaching hospital had a lower risk of respiratory complications (CLD: aOR= 0.58, 95% CI= 0.36-0.95, p = 0.029; Urban teaching hospital: aOR= 0.44, 95% CI= 0.26-0.75, p = 0.002, respectively), while length of hospital stay was positively associated with respiratory complications (aOR= 1.04, 95% CI= 1.02-1.07, p < 0.001); 4) length of hospital stay was the only variable significantly associated with digestive system complications (aOR= 1.05, 95% CI= 1.04-1.06, p < 0.001; Table 4).

Factors **associated with in-hospital mortality in CRC inpatients with underlying CLD**

Univariate and multivariate logistic regression analyses were performed to assess risk factors significantly associated with in-hospital mortality (Table 5). Compared with patients without CLD, inpatients who had CLD had a significantly higher risk of in-hospital mortality events (aOR= 2.05, 95% CI= 1.43-2.94, p < 0.001). Multivariate analysis also showed that the length of hospital stay was significantly associated with in-hospital mortality events (aOR= 1.06, 95% CI= 1.04-1.08, p < 0.001). However, patients with elective admission (aOR= 0.50, 95% CI= 0.34-0.73, p < 0.001) and inpatients with hyperlipidemia had a significantly lower risk of mortality (aOR= 0.46, 95% CI= 0.28-0.75, p = 0.002) compared to inpatients without hyperlipidemia and inpatients without elective admission, respectively.

Discussion

This study investigated factors significantly associated with risk of postoperative complications and in-hospital mortality in CRC patients with co-existing CLD who underwent colorectal surgery. Our data showed that 20.84% of our study population comprised patients with CLD. Patients with CLD had a significantly longer duration of hospital stay compared to patients without CLD. Length of hospital stay was significantly associated with risk of postoperative infection, postoperative bleeding, respiratory complications, and digestive complications among CRC patients with underlying CLD. The presence of CLD was significantly associated with a higher risk of postoperative bleeding, and a lower risk of respiratory complications. The presence of CLD and duration of hospital stay were significantly associated with a higher risk of in-hospital mortality, whereas the presence of hyperlipidemia was associated with a lower risk of in-hospital mortality.

Data for this study were extracted from the HCUP-NIS database, which is the largest publicly available collection of longitudinal hospital care clinical data in the United States beginning in 1988. We were, therefore, able to perform analysis of trends over time and make national estimates of health care utilization, access, charges, quality, and outcomes. The NIS sampling frame has grown from 8 States in 1988, to 22 States in 1998, to 46 States in 2011, and currently, covers 97% of the U.S. population.

Studies evaluating operative risk in patients with liver disease found that operative risk was correlated with severity of the underlying liver disease and the nature of the surgical procedure. The increased perioperative risk among patients with underlying liver disease could be due to impairment of hepatic functions such as drug metabolism, detoxification of endogenous or exogenous toxins, and production of plasma proteins.[10]Assessment of Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) score, in

combination with careful pre- and post-operative monitoring has been shown to be crucial for improving outcomes.[10, 18, 19] Additionally, some investigators have described the development of risk indices to distinguish low-risk and high-risk subgroups for predicting postoperative mortality in cirrhotic and CRC patients.[14, 20]

Patients with CLD who undergo CRC surgery have previously been shown to have a significantly higher risk of postoperative mortality compared to patients without CLD.[14, 21, 22, 23] Data from a previous population-based study showed that CLD patients had a 6.5-fold higher risk of mortality after colorectal surgery, as well as significantly higher rates of postoperative complications compared to non-CLD patients.[24] These data were consistent with our results which showed that presence of CLD was associated with a higher risk of in-hospital mortality, and suggested that identification of risk factors associated with postoperative complications and mortality in these patients could be critical to improving the clinical outcome.

Our data showed that CRC patients with CLD had a significantly longer hospital stay compared to patients without CLD. This could possibly be due to a higher rate of specific postoperative complications. This was evident in our multivariate regression analysis, which showed that the presence of CLD was associated with a higher risk of postoperative bleeding. Although our data showed that the presence of CLD was associated with a lower risk of respiratory complications, we only evaluated surgery-related respiratory complications, and not the most common CLD-related pulmonary complications such as hepatopulmonary syndrome, porto-pulmonary hypertension, and hepatic hydrothorax[25].

The majority of CLD patients in our study had chronic hepatitis C infection, followed by NAFLD. Our data were consistent with previous studies showing that patients with chronic hepatitis C and NAFLD had a significantly higher incidence of colorectal adenomas and advanced neoplasms compared to healthy controls.[16, 26, 27]

Previous results showed that although mortality rates were higher in patients who were emergently admitted compared to patients with elective admission, there was no significant difference in the adjusted relative risk of mortality between the two groups.[13] Our data showed that the type of admission (emergent vs. elective) was not significantly associated with the risk of postoperative complications, but was associated with risk of mortality among inpatients with CRC who had co-existing CLD.

It has been reported that a low socio-economic status was significantly associated with a high incidence of CRC, regardless of individual-level CRC risk factors.[28] Our multivariate analysis showed that patients in Quartile 2 of median household income had a significantly higher risk of in-hospital mortality compared to patients in Quartiles 3 and 4, suggesting that low socioeconomic status (SES) was significantly associated with a higher risk of in-hospital mortality in CRC patients with CLD. This could be a reflection of poorer access to, and lower utilization of health care services among patients with low SES.

Our data showed that hyperlipidemia was associated with a significantly lower risk of postoperative in-hospital mortality. Hyperlipidemia is known to be associated with increased risk of CVD events and increased all-cause mortality. Our present findings could be due to the fact that patients with a diagnosis of hyperlipidemia were prescribed statins, and had a good compliance. Statin monotherapy has previously been shown to exert a protective effect and decreasing the rate of colorectal cancer mortality.[29] Statin use has been shown to be an independent predictor of longer cancer-specific survival, and overall survival in patients with curatively resected CRC.[30] Additionally, since the levels of adiponectin and leptin are significantly decreased and increased, respectively, in NAFLD and CRC patients,[31, 32] it will be interesting to evaluate whether changes in adiponectin/leptin ratios in these patients are associated with clinical outcomes.

Based on our data source, the major strengths of our study are 1) the sample size is large enough to determine fairly precise prevalence measures at the national level, 2) a large multi-ethnic population sample which allowed us to explore the racial/ethnic heterogeneity, 3) the analysis was conducted in a nationally representative sample; therefore, our results may be generalized to the entire U.S. adult population. The major limitations of this study were 1) this was a cross-sectional analysis, and the unit of this database was the individual medical record. Our study, therefore, could not make any inferences regarding causality, 2) it is possible that the number of hospital discharges recorded could include an undetermined number of repeat hospital stays for the same patient, 3) NIS is a US inpatient data (including representative proportions of people of different ethnicity) and should be validated in other countries, 4) our study used ICD-9 codes to characterize the disease, co-morbidities, and interventions. Validation of ICD-9 codes using parameters such as patient charts, or a combination of patient claims along with Part B Medicare claims is important during the course of epidemiological studies performed using administrative databases such as SEER.[33, 34] To the best of our knowledge, this is the first population-based, cross-sectional study of hospitalized patients evaluating the factors associated with postoperative complications and mortality in CRC patients with co-existing CLD.

Conclusion

Our study showed that length of hospital stay was significantly associated with postoperative infection, postoperative bleeding, respiratory complications, and digestive complications among CRC patients with underlying CLD. The presence of CLD was significantly associated with a higher risk of postoperative bleeding, and a lower risk of respiratory complications. Our data suggested that postoperative bleeding should be closely monitored in CRC patients with CLD, since it may result in a higher risk of in-hospital

mortality in these patients. The presence of CLD and duration of hospital stay were significantly associated with a higher risk of in-hospital mortality, whereas the presence of hyperlipidemia was a protective factor.

Identification of factors associated with peri- or postoperative complications, and mortality in CRC patients with underlying CLD, can help to improve clinical management and outcomes in this group of CRC patients.

Data Sharing Statement

All data can be accessed from the National Inpatient Sample Database.

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Conflict of interest

The authors declare no conflict of interest.

Statement of Author Contribution

Ko-Chao Lee: Conception and design;Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; guarantor of integrity of the entire study; definition of intellectual content; Administrative, technical or material support; Supervision

Kuan-Chih Chung: Conception and design;Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; guarantor of integrity of the entire study; definition of intellectual content; Administrative, technical or material support; Supervision

Hong-Hwa Chen: Acquisition of data; Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; Administrative, technical or material support

Kung-Chuan Cheng: Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; clinical studies

Kuen-Lin Wu: Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; clinical studies

Chien-Chang Lu: Analysis and interpretation of data; Critical revision of the manuscript; literature research; clinical studies

All authors have read and approved the submitted version.

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Table 1. Baseline demographic and clinical characteristics of study population

	Total sample N = 7463	Chronic liver diseases		p-value
		No N = 5908	Yes N = 1555	
Type of chronic liver diseases				
None	5908 (79.16)	5908 (100.00)	0 (0.00)	
Chronic hepatitis B	65 (0.87)	0 (0.00)	65 (4.18)	
Chronic hepatitis C	564 (7.56)	0 (0.00)	564 (36.27)	
Non-alcoholic fatty liver disease	441 (5.91)	0 (0.00)	441 (28.36)	
Other types	485 (6.50)	0 (0.00)	485 (31.19)	
Postoperative complications				0.228
No	5830 (78.12)	4633 (78.42)	1197 (76.98)	
Yes	1633 (21.88)	1275 (21.58)	358 (23.02)	
Postoperative infection	360 (22.05)	276 (21.65)	84 (23.46)	
Postoperative shock	23 (1.41)	15 (1.18)	8 (2.23)	
Postoperative bleeding	149 (9.12)	104 (8.16)	45 (12.57)	
Disruption of wound	73 (4.47)	55 (4.31)	18 (5.03)	
Non-healing surgical wound	4 (0.24)	4 (0.31)	0 (0.00)	
Nervous system complications	17 (1.04)	16 (1.25)	1 (0.28)	
Cardiac arrest/heart failure	125 (7.65)	102 (8.00)	23 (6.42)	
Phlebitis/thrombophlebitis	5 (0.31)	3 (0.24)	2 (0.56)	
Respiratory complications	141 (8.63)	121 (9.49)	20 (5.59)	
Digestive system complications	675 (41.33)	529 (41.49)	146 (40.78)	
Urinary complications	60 (3.67)	49 (3.84)	11 (3.07)	
Unspecified complications	1 (0.06)	1 (0.08)	0 (0.00)	
In-Hospital Mortality				< 0.001
No	7301 (97.83)	5806 (98.28)	1495 (96.14)	
Yes	162 (2.17)	102 (1.73)	60 (3.86)	
Age				0.984
Mean ± SD	62.53 ± 12.17	62.53 ± 12.16	62.52 ± 12.17	
Gender				0.708
Male	4283 (57.39)	3384 (57.28)	899 (57.81)	
Female	3180 (42.61)	2524 (42.72)	656 (42.19)	
Race				< 0.001
White	4536 (60.78)	3570 (60.43)	966 (62.12)	
Black	810 (10.85)	614 (10.39)	196 (12.60)	
Hispanic	359 (4.81)	266 (4.50)	93 (5.98)	
Asian or Pacific Islander	154 (2.06)	108 (1.83)	46 (2.96)	
Native American	24 (0.32)	19 (0.32)	5 (0.32)	

Other/Missing	1580 (21.17)	1331 (22.53)	249 (16.01)	
Median household income				< 0.001
Quartile 1	1993 (26.71)	1564 (26.47)	429 (27.59)	
Quartile 2	1902 (25.49)	1489 (25.20)	413 (26.56)	
Quartile 3	1757 (23.54)	1386 (23.46)	371 (23.86)	
Quartile 4	1646 (22.06)	1354 (22.92)	292 (18.78)	
Others	165 (2.21)	115 (1.95)	50 (3.22)	
Location of hospital				< 0.001
Rural	984 (13.19)	833 (14.10)	151 (9.71)	
Urban non-teaching	2711 (36.33)	2152 (36.43)	559 (35.95)	
Urban teaching	3731 (49.99)	2894 (48.98)	837 (53.83)	
Others	37 (0.50)	29 (0.49)	8 (0.51)	
Types of admission				0.006
Non-elective	2323 (31.13)	1789 (30.28)	534 (34.34)	
Elective	5122 (68.63)	4103 (69.45)	1019 (65.53)	
Others	18 (0.24)	16 (0.27)	2 (0.13)	
Severity of CRC				0.987
None	4889 (65.51)	3868 (65.47)	1021 (65.66)	
Lymph node metastasis	1823 (24.43)	1444 (24.44)	379 (24.37)	
Distant metastasis	751 (10.06)	596 (10.09)	155 (9.97)	
Length of hospital stay (day)				< 0.001
Mean ± SD	8.96 ± 7.24	8.61 ± 6.49	10.26 ± 9.46	
Hyperlipidemia				< 0.001
No	5624 (75.36)	4382 (74.17)	1242 (79.87)	
Yes	1839 (24.64)	1526 (25.83)	313 (20.13)	
Obesity				0.827
No	6556 (87.85)	5187 (87.80)	1369 (88.04)	
Yes	907 (12.15)	721 (12.20)	186 (11.96)	

Abbreviation: CRC, colorectal cancer.

Table 2. Univariate and multivariate logistic regression analyses to identify factors associated with postoperative complications among inpatients diagnosed with colorectal cancer

	Univariate		Multivariate	
	OR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	1.08 (0.94, 1.23)	0.292	0.91 (0.78, 1.05)	0.192
Race				
White	reference			
Black	1.01 (0.83, 1.23)	0.905		
Hispanic	1.03 (0.79, 1.35)	0.827		
Asian or Pacific islander	0.85 (0.54, 1.34)	0.494		
Native American	1.10 (0.42, 2.92)	0.845		
Other/Missing	0.95 (0.81, 1.10)	0.456		
Median household income				
Quartile 1	reference			
Quartile 2	1.16 (0.99, 1.36)	0.075		
Quartile 3	0.93 (0.79, 1.10)	0.389		
Quartile 4	1.02 (0.86, 1.21)	0.827		
Others	1.06 (0.71, 1.59)	0.785		
Location of hospital				
Rural	reference			
Urban non-teaching	1.09 (0.90, 1.32)	0.355		
Urban teaching	1.04 (0.87, 1.25)	0.667		
Others	1.25 (0.57, 2.75)	0.572		
Types of admission				
Non-elective	reference			
Elective	0.95 (0.83, 1.08)	0.397		
Others	0.85 (0.24, 3.03)	0.802		
Length of hospital stay	**1.13 (1.12, 1.14)**	**<0.001**	**1.13 (1.12, 1.15)**	**<0.001**
Hyperlipidemia				
No	reference		reference	
Yes	**0.77 (0.67, 0.89)**	**<0.001**	0.97 (0.83, 1.12)	0.671
Obesity				
No	reference			
Yes	1.09 (0.91, 1.30)	0.353		

P< 0.05 were shown in boldface.

Table 3-1. Univariate logistic regression analyses to identify risk factors for specific postoperative complications among inpatients diagnosed with colorectal cancer

	Postoperative infection		Postoperative bleeding		Cardiac arrest/heart failure	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Chronic liver diseases						
No	reference		reference		reference	
Yes	1.16 (0.90, 1.49)	0.255	**1.67 (1.17, 2.38)**	**0.005**	0.82 (0.51, 1.31)	0.404
Race						
White	reference		reference		reference	
Black	0.93 (0.64, 1.35)	0.691	0.72 (0.38, 1.34)	0.301	0.86 (0.43, 1.72)	0.664
Hispanic	1.30 (0.81, 2.08)	0.273	0.94 (0.43, 2.06)	0.867	1.39 (0.62, 3.11)	0.428
Asian or Pacific islander	0.96 (0.43, 2.16)	0.924	0.32 (0.04, 2.39)	0.265	1.95 (0.55, 6.92)	0.301
Native American	2.65 (0.66, 10.63)	0.169	NA	NA	1.68 (0.20, 13.93)	0.630
Other/Missing	0.93 (0.70, 1.25)	0.636	0.96 (0.62, 1.48)	0.858	0.79 (0.48, 1.29)	0.314
Median household income						
Quartile 1	reference		reference		reference	
Quartile 2	0.96 (0.71, 1.29)	0.763	1.41 (0.90, 2.19)	0.133	1.32 (0.77, 2.25)	0.314
Quartile 3	0.94 (0.69, 1.28)	0.691	0.74 (0.44, 1.25)	0.260	1.40 (0.81, 2.43)	0.225
Quartile 4	0.78 (0.56, 1.09)	0.141	0.87 (0.52, 1.45)	0.597	1.23 (0.70, 2.16)	0.479
Others	0.73 (0.30, 1.76)	0.488	0.92 (0.26, 3.21)	0.898	1.82 (0.59, 5.57)	0.296
Location of hospital						
Rural	reference		reference		reference	
Urban non-teaching	1.23 (0.82, 1.84)	0.320	0.94 (0.53, 1.67)	0.833	1.04 (0.57, 1.90)	0.888
Urban teaching	1.45 (0.99, 2.14)	0.058	1.06 (0.61, 1.84)	0.828	1.08 (0.60, 1.96)	0.797
Others	0.52 (0.07, 4.07)	0.536	NA	NA	3.16 (0.60, 16.64)	0.175
Types of admission						
Non-elective	reference		reference		reference	
Elective	0.90 (0.71, 1.15)	0.405	1.21 (0.82, 1.78)	0.341	1.01 (0.67, 1.53)	0.959
Others	1.33 (0.16, 11.06)	0.791	NA	NA	NA	NA
Length of hospital stay	**1.13 (1.11, 1.15)**	**<0.001**	**1.03 (1.01, 1.05)**	**0.010**	1.01 (0.98, 1.04)	0.434
Hyperlipidemia						
No	reference		reference		reference	
Yes	**0.64 (0.48, 0.85)**	**0.002**	0.88 (0.59, 1.32)	0.544	0.75 (0.49, 1.15)	0.191
Obesity						
No	reference		reference		reference	
Yes	1.30 (0.95, 1.78)	0.098	0.69 (0.38, 1.25)	0.218	1.12 (0.62, 2.02)	0.709

P< 0.05 were shown in boldface.

Abbreviation: NA, not available

Table 3-2. Univariate logistic regression analyses to identify risk factors for specific postoperative complications among inpatients diagnosed with colorectal cancer

	Respiratory complications		Digestive system complications	
	OR (95% CI)	p value	OR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	**0.62 (0.38, 1.00)**	**0.048**	1.04 (0.86, 1.26)	0.697
Race				
White	reference		reference	
Black	0.60 (0.30, 1.18)	0.139	**1.32 (1.02, 1.72)**	**0.034**
Hispanic	0.61 (0.23, 1.59)	0.312	0.70 (0.45, 1.08)	0.106
Asian or Pacific islander	NA	NA	1.14 (0.63, 2.08)	0.668
Native American	NA	NA	0.47 (0.06, 3.67)	0.474
Other/Missing	1.06 (0.69, 1.63)	0.776	0.99 (0.81, 1.23)	0.957
Median household income				
Quartile 1	reference		reference	
Quartile 2	1.15 (0.71, 1.86)	0.577	1.05 (0.83, 1.32)	0.706
Quartile 3	0.84 (0.50, 1.39)	0.492	1.00 (0.78, 1.27)	0.990
Quartile 4	1.05 (0.63, 1.74)	0.857	1.21 (0.96, 1.54)	0.112
Others	0.96 (0.27, 3.44)	0.953	1.24 (0.71, 2.18)	0.454
Location of hospital				
Rural	reference		reference	
Urban non-teaching	0.91 (0.55, 1.48)	0.694	1.08 (0.82, 1.40)	0.588
Urban teaching	**0.46 (0.27, 0.76)**	**0.003**	0.95 (0.73, 1.24)	0.710
Others	NA	NA	2.16 (0.82, 5.69)	0.120
Types of admission				
Non-elective	reference		reference	
Elective	1.06 (0.72, 1.56)	0.777	1.01 (0.84, 1.22)	0.879
Others	NA	NA	0.98 (0.21, 4.46)	0.977
Length of hospital stay	**1.04 (1.02, 1.06)**	**0.001**	**1.05 (1.04, 1.06)**	**< 0.001**
Hyperlipidemia				
No	reference		reference	
Yes	0.74 (0.48, 1.15)	0.183	1.01 (0.83, 1.22)	0.948
Obesity				
No	reference		reference	
Yes	1.24 (0.72, 2.14)	0.441	1.14 (0.88, 1.48)	0.328

P< 0.05 were shown in boldface.

Abbreviation:NA, not available

Table 4. Multivariate logistic regression analyses to identify risk factors forspecific postoperative complications among inpatients diagnosed with colorectal cancer

	Postoperative infection		Postoperative bleeding		Respiratory complications		Digestive system complications	
	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases								
No	reference		reference		reference		reference	
Yes	0.90 (0.67, 1.20)	0.459	**1.64 (1.15, 2.34)**	**0.007**	**0.58 (0.36, 0.95)**	**0.029**	0.97 (0.80, 1.18)	0.768
Race								
White							reference	
Black							1.26 (0.97, 1.65)	0.081
Hispanic							0.65 (0.41, 1.01)	0.056
Asian or Pacific islander							1.17 (0.64, 2.14)	0.600
Native American							0.52 (0.07, 4.05)	0.534
Other/Missing								
Median household income								
Quartile 1								
Quartile 2								
Quartile 3								
Quartile 4								
Others								
Location of hospital								
Rural					reference			
Urban non-teaching					0.89 (0.54, 1.46)	0.640		
Urban teaching					**0.44 (0.26, 0.75)**	**0.002**		
Others					NA	NA		
Types of admission								

Non-elective								
Elective								
Others								
Length of hospital stay	**1.13 (1.11, 1.15)**	**<0.001**	**1.02 (1.01, 1.04)**	**0.013**	**1.04 (1.02, 1.07)**	**< 0.001**	**1.05 (1.04, 1.06)**	**< 0.001**
Hyperlipidemia								
No	reference							
Yes	0.81 (0.59, 1.12)	0.202						
Obesity								
No								
Yes								

P< 0.05 were shown in boldface.
Abbreviation:NA, not available

Table 5. Univariate and multivariate logistic regression analyses to identifyfactors associated with in-hospital mortality among inpatients diagnosed with colorectal cancer.

	Univariate		Multivariate	
	OR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	**2.33 (1.68, 3.23)**	**<0.001**	**2.05 (1.43, 2.94)**	**<0.001**
Race				
White	reference			
Black	1.31 (0.76, 2.27)	0.332		
Hispanic	0.93 (0.42, 2.06)	0.864		
Asian or Pacific Islander	NA	NA		
Native American	NA	NA		
Other/Missing	0.86 (0.55, 1.35)	0.512		
Median household income				
Quartile 1	reference		reference	
Quartile 2	1.28 (0.83, 1.96)	0.268	1.51(0.95, 2.40)	0.083
Quartile 3	**0.58 (0.35, 0.99)**	**0.046**	0.71(0.41, 1.26)	0.247
Quartile 4	0.68 (0.40, 1.15)	0.152	0.77(0.42, 1.39)	0.384
Others	1.72 (0.59, 4.96)	0.320	1.17(0.35, 3.83)	0.800
Location of hospital				
Rural	reference		reference	
Urban non-teaching	0.65 (0.40, 1.04)	0.073	0.63 (0.37, 1.08)	0.094
Urban teaching	**0.59 (0.37, 0.94)**	**0.025**	0.63 (0.37, 1.06)	0.084
Others	2.87 (0.29, 28.13)	0.365	4.54 (0.43, 48.16)	0.209
Types of admission				
Non-elective	reference		reference	
Elective	**0.37 (0.26, 0.52)**	**<0.001**	**0.50 (0.34, 0.73)**	**<0.001**
Others	NA	NA	NA	NA
Length of hospital stay	**1.07 (1.05, 1.09)**	**<0.001**	**1.06 (1.04, 1.08)**	**<0.001**

Hyperlipidemia				
No	reference		reference	
Yes	**0.39 (0.25, 0.63)**	**<0.001**	**0.46 (0.28, 0.75)**	**0.002**
Obesity				
No	reference			
Yes	0.56 (0.29, 1.08)	0.084		

P< 0.05 were shown in boldface.
Abbreviation: NA, not applicable

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study

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Keywords:	Colorectal cancer, short-term morbidity, mortality, chronic liver disease, National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP)

Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study

Running title: CRC surgery with liver disease

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Abstract

Objectives: Colorectal carcinoma (CRC) patients with pre-existing chronic liver disease (CLD) had a significantly higher 30-day mortality after CRC surgery compared to healthy controls. This study investigated the factors associated with postoperative complications and in-hospital mortality in CRC patients with co-existing CLD (excluding cirrhosis) who underwent colorectal surgery.

Design: A retrospective observational population-based study.

Setting: Data were sourced from the National Inpatient Sample (NIS) database, a part of the Healthcare Cost and Utilization Project (HCUP).

Participants: This study analyzed 7,463 inpatients with CRC who underwent colorectal surgery at admission between 2005 and 2014.

Primary and secondary outcome measures: The primary endpoint of this study was the prevalence of postoperative complications, and the secondary endpoint was in-hospital mortality.

Results: In the CLD group, 36.27% of patients had chronic hepatitis C, 28.36% had non-alcoholic fatty liver disease, and 31.19% had other types of chronic liver diseases. The median hospital stay was 7.0 (5.0, 10.0) days in patients with no postoperative complications versus 17.0 (10.0, 26.0) days, 8.0 (6.0, 12.0) days, 8.0 (6.0, 17.0) days, 9.0 (8.0, 14.0) days, and 10.5 (7.0, 17.0) days for patients with postoperative infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications, and digestive complications, respectively (all $p < 0.05$). Presence of CLD was significantly associated with higher risk of postoperative bleeding(aOR= 1.64, 95% CI= 1.15-2.34, $p = 0.007$). Presence of CLD (aOR= 1.98, 95% CI= 1.39-2.82, $p < 0.001$), and length of hospital stay(aOR= 1.06, 95% CI= 1.04-1.08, $p < 0.001$) were significantly associated with higher risk of in-hospital mortality. However, hyperlipidemia was associated with a significantly lower risk of mortality (aOR= 0.46, 95%

CI= 0.28-0.75, p = 0.002).

Conclusions: Postoperative complications prolonged the length of hospital stay. Presence of CLD and hyperlipidemia were important factors impacting postoperative complications and in-hospital mortality in CRC patients with underlying CLD.

Keywords: Colorectal cancer, short-term morbidity, mortality, chronic liver disease, National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP).

Strengths and limitations of this study

- Data for this study were collected from a large, comprehensive, and national representative database.
- A large multi-ethnic population sample allowed us to explore the racial/ethnic heterogeneity
- The cross-sectional design of this study can only demonstrate association, therefore, causality could not be determined.

Introduction

Colorectal cancer (CRC) is the most common gastrointestinal malignancy, and the second leading cause of cancer-related deaths in developed countries, accounting for 51,690 deaths in the United States in 2012.[1, 2] The 5-year survival rates range from 90% for cancers detected at the localized stage, 70% for regional tumors, and 10% for distant metastatic tumors.[3] The major risk factors of CRC include age and hereditary factors, the presence of inflammatory bowel disease, and environmental factors such as nutritional practices, physical activity/obesity, cigarette smoking, and alcohol consumption.[4]The implementation of population-based screening for average-risk, asymptomatic individuals beginning at 50 years of age has resulted in a significant decrease in CRC incidence among individuals > 50 years old. CRC patients who present at an early stage usually receive curative surgical resection, whereas patients who present with metastatic disease receive palliative systemic chemotherapy or treatment with novel biologic agents.[5]

Chronic liver disease (CLD) represents a major health concern and accounts for approximately 1 million deaths per year worldwide.[6]The major risk factors for CLD include chronic viral hepatitis infection, chronic exposure to toxins (including excessive alcohol consumption), and autoimmune injury, which all contribute towards progression of hepatic fibrosis and development of cirrhosis via the production and deposition of extracellular matrix components.[7]CLD also includes liver damage mediated by lipid accumulation in hepatocytes. The spectrum of obesity-related liver disease such as NAFLD (non-alcoholic fatty liver disease) can range from non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis, and end in cirrhosis.[8]

Patients with liver disease who had CRC frequently required surgery and anesthesia, and were shown to have an increased risk of perioperative complications and postoperative morbidity and mortality. This could be due to complications associated with liver disease,

including hepatic encephalopathy, ascites, sepsis, and hemorrhage.[9]Patients with mild to moderate chronic liver disease without cirrhosis usually tolerate surgery well, whereas acute liver failure (previously termed fulminant hepatic failure) and acute viral or alcoholic hepatitis are considered contraindications to elective surgery.[10]Additionally, it has been reported that the location of the surgical procedure is an important risk factor for postoperative liver failure in patients with pre-existing liver disease. Cardiac surgery, abdominal surgery, and hepatic resection are all associated with higher rates of perioperative complications, and higher rates of morbidity and mortality compared to more peripheral surgery, presumably due to greater reductions in hepatic blood flow.[10, 11]

A recent meta-analysis of 50 studies reported that patients with CLD had a significantly higher risk of CRC, which persisted after liver transplantation, compared to the general population.[12]CRC patients with pre-existing liver disease were shown to have a significantly higher 30-day mortality after CRC surgery compared to CRC patients with non-cirrhotic liver disease and healthy controls.[13] Other data showed that colectomy of any kind was associated with a significant risk of postoperative morbidity and mortality in cirrhotic patients,[14] and this was thought to be related to increased intraoperative and early postoperative bleeding.[15]Additionally, although fatty liver has been shown to be an important risk factor of CRC,[16] the presence of NAFLD is thought to play a protective role in the overall survival of CRC patients.[17]

The aim of our present study was to identify risk factors associated with postoperative complications and mortality in CRC patients with co-existing CLD who underwent colorectal surgery. Our clinical data were sourced from a national and comprehensive database, which made it possible to minimize discrepancies and biases.

Methods

Data source

In this population-based, cross-sectional study, data were sourced from the National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project (HCUP). The NIS database samples approximately 20% of discharges from all HCUP-participating community hospitals, and is the largest publicly available inpatient database in the United States [www.hcup-us.ahrq.gov/nisoverview.jsp]. The NIS is representative of approximately 95% of the US population (http://www.cdc.gov/nchs/nhanes/). All of the HCUP-NIS data are de-identified and analysis of the data does not require IRB approval or informed consent by all subjects.

Study population

This study extracted data of inpatients diagnosed with primary CRC based on specific International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (153, 154), who underwent surgical intervention at admission. Surgical interventions included open and partial or subtotal colectomy (ICD-9-CM: 45.7), pull-through resection of rectum (ICD-9-CM: 48.40, 48.41, 48.43, 48.49, abdominoperineal resection of rectum / complete proctectomy (ICD-9-CM: 48.50, 48.52, 48.59), and other resections of rectum / partial proctectomy / rectosigmoidectomy (ICD-9-CM: 48.6x). Patients with missing data for demographics, patients diagnosed with liver cirrhosis, and patients with co-existing other primary malignancies were excluded.

Study Variables

The primary endpoint of this study was the prevalence of post-operative complications, including post-operative infection (ICD-9-CM=998.5), post-operative shock (ICD-9-

CM=998.0), post-operative bleeding (ICD-9-CM=998.1), disruption of wound (ICD-9-CM=998.3), non-healing surgical wound (ICD-9-CM=998.83), nervous system complications (ICD-9-CM=997.0x), cardiac arrest/heart failure (ICD-9-CM=997.1), phlebitis/thrombophlebitis (ICD-9-CM=997.2), respiratory complications (ICD-9-CM=997.3x), digestive system complications (ICD-9-CM=997.4), urinary complications (ICD-9-CM=997.5), vascular complications (ICD-9-CM=997.7x), and unspecified complications (ICD-9-CM=998.9). The secondary endpoint was in-hospital mortality, which reflected the severity of the disease.

The independent variables included the presence of chronic liver disease. Although there were several etiologies of chronic liver disease, we only focused on specific etiologies found in higher percentages in our study population, such as chronic hepatitis B (ICD-9-CM=070.22, 070.32), chronic hepatitis C (ICD-9-CM=070.44, 070.54, 070.7x), non-alcoholic fatty liver disease (ICD-9-CM=571.8, 571.9), and other minor causes.

The relative variables obtained for each record included patient demographics (age, gender, race/ethnicity), socioeconomic status (household income), severity of CRC (locoregional involvement, distant metastasis), co-morbidity (hyperlipidemia, obesity), place of hospitalization, type of admission (elective, non-elective), and length of hospital stay.

Socioeconomic Status – household income

This categorical variable provides a quartile classification of the estimated median household income of residents in the patient's ZIP Code. The quartiles are identified by values of 1 to 4, indicating the poorest to wealthiest populations. These values are derived from ZIP Code-demographic data obtained from Claritas. Since these estimates are updated annually, the value ranges for these categories vary by year.

Comorbidities

For matching criteria between case and control groups, a number of co-morbid conditions were included, such as diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, Alzheimer's disease and other cognitive impairment, AIDS, alcohol abuse, chronic blood loss anemia, chronic pulmonary disease, coagulopathy, drug abuse, hypothyroidism, other neurological disorders, peripheral vascular disorders, pulmonary circulation disorders, renal failure, valvular diseases, and weight loss.

For relative variables, two comorbid conditions (hyperlipidemia and obesity) were selected to be incorporated into analysis. These two conditions were inter-correlated and were selected considering the difficulty of operation in obese patients, which could cause a series of postoperative complications.

Patient and Public Involvement

Since the present study utilized the NIS database that is the largest publicly available inpatient health care database in the United States, no patient and public involvement in the present study.

Statistical analysis

Simple matching was used to match inpatients who had chronic liver diseases with those who did not have chronic liver diseases by age, gender, the severity of CRC, and comorbidities. Selected cases were matched with controls by 1:4 matching. Continuous variables were expressed as mean± standard deviation, and categorical data were shown as counts and percentages. Conditional logistic regression method was performed after matching, and a univariate logistic regression model was performed to determine the independent risk factors of postoperative complications or mortality. Multiple logistic regression analysis was

performed on variables with an unadjusted effect and a p-value < 0.05 on univariate logistic regression analysis. Statistical significance was defined by a p-value < 0.05. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and clinical characteristics

Analysis of the HCUP-NIS database for the period 2005-2014 showed that 152,625 inpatients diagnosed with CRC had undergonesurgical treatment. After excluding patients with liver cirrhosis, patients with co-existing other primary malignancies, and patients with missing data for age and gender, a total of 129,958 inpatients were enrolled in this study. The study population comprised 1,555 patients with CLD (case group) and 128,403 patients without CLD (control group). Due to the small sample size of the case group, simple matching was used to balance the case and control groups. After matching, a total of 7,463 inpatients were enrolled in the final study population. Of these patients, 5,908 patients (79.16%) had no CLD and 1,555 patients (20.84%) had CLD. A majority of patients in the CLD group had chronic hepatitis C (n = 564, 36.27%), while 441 patients (28.36%) had non-alcoholic fatty liver disease, and 485 patients (31.19%) patients had other types of chronic liver diseases.

Baseline demographics and clinical characteristics of study patients are described in Table 1. The mean age of the inpatients was 62.53 years old, and the mean length of hospital stay was 8.96 days. A majority of the inpatients (57.39%) was male, and 60.78% were white. A total of 1993 patients (26.71%) was classified in the first quartile of median household income, and almost half the patients (49.99%) were operated upon in urban teaching hospitals.

Analysis of the whole study population showed that 1,633 inpatients (21.88%) had post-

operative complications, the most frequent of which was digestive system complications (n = 675, 41.33%). A total of 1839 patients (24.64%) had hyperlipidemia, and 907 patients (12.15%) were obese. Length of hospital stay was 8.61 ± 6.49 days for non-CLD patients and 10.26 ± 9.46 for CLD patients. In-hospital mortality was recorded for 162 inpatients (2.17%).

Factors associated with postoperative complications in CRC patients with underlying CLD

Univariate and multivariate logistic regression analyses were performed to assess risk factors significantly associated with postoperative complications (Table 2). Although univariate analysis showed that hyperlipidemia and length of hospital stay were both significantly associated with risk of postoperative complications, the length of hospital stay was the only variable significantly associated with risk of post-operative complications by multivariate analysis (aOR= 1.13, 95% CI= 1.12-1.15, $p < 0.001$). The presence of underlying CLD was not significantly associated with the occurrence of overall postoperative complications (aOR=0.91, 95% CI= 0.78-1.05, p=0.192).

We subsequently used logistic regression analysis to identify factors associated with specific postoperative complications which occurred in > 5% of patients (postoperative infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications, and digestive system complications; Table 3-1, Table 3-2, and Table 4). Univariate analysis showed that 1) presence of hyperlipidemia, and length of hospital stay were significantly associated with postoperative infection (all P<0.010; Table 3-1); 2) presence of CLD, and length of hospital stay were significantly associated with postoperative infection, and postoperative bleeding (all P<0.010; Table 3-1); 3) presence of CLD, treatment at an urban teaching hospital, and length of hospital stay were significantly associated with respiratory complications (all $P \leq 0.048$, Table 3-2); 4) black race and length of hospital stay were both

significantly associated with digestive system complications (P<0.05; Table 3-2). None of the factors analyzed was significantly associated with cardiac arrest/heart failure (all P ≥ 0.05, Table 3-1).

Our multivariate analysis showed that 1) length of hospital stay was the only factor significantly associated with postoperative infection (aOR= 1.13, 95% CI= 1.11-1.15, p < 0.001) (Table 4); 2) presence of CLD (aOR= 1.64, 95% CI= 1.15-2.34, p = 0.007), and length of hospital stay (aOR= 1.02, 95% CI= 1.01-1.04, p = 0.013) were both significantly associated with postoperative bleeding; 3) patients with CLD, and patients treated at an urban teaching hospital had a lower risk of respiratory complications (CLD: aOR= 0.58, 95% CI= 0.36-0.95, p = 0.029; Urban teaching hospital: aOR= 0.44, 95% CI= 0.26-0.75, p = 0.002, respectively), while length of hospital stay was positively associated with respiratory complications (aOR= 1.04, 95% CI= 1.02-1.07, p < 0.001); 4) length of hospital stay was the only variable significantly associated with digestive system complications (aOR= 1.05, 95% CI= 1.04-1.06, p < 0.001; Table 4).

Factors associated with in-hospital mortality in CRC inpatients with underlying CLD

Univariate and multivariate logistic regression analyses were performed to assess risk factors significantly associated with in-hospital mortality (Table 5). Compared with patients without CLD, inpatients who had CLD had a significantly higher risk of in-hospital mortality events (aOR= 2.05, 95% CI= 1.43-2.94, p < 0.001). Multivariate analysis also showed that the length of hospital stay was significantly associated with in-hospital mortality events (aOR= 1.06, 95% CI= 1.04-1.08, p < 0.001). However, patients with elective admission (aOR= 0.50, 95% CI= 0.34-0.73, p < 0.001) and inpatients with hyperlipidemia had a significantly lower risk of mortality (aOR= 0.46, 95% CI= 0.28-0.75, p = 0.002) compared to inpatients without hyperlipidemia and inpatients without elective admission, respectively.

Postoperative complications were associated with length of hospital stay among CRC patients with underlying CLD

Since our multivariate analysis suggested that the length of hospital stay was correlated with different postoperative complications, we analyzed the length of hospital stay in patients with and without postoperative complications (Table 6). Patients who did not have postoperative complications had a median hospital stay of 7.0 (5.0, 10.0) days. In contrast, the length of hospital stay was 17.0 (10.0, 26.0) days, 8.0 (6.0, 12.0) days, 8.0 (6.0, 17.0) days, 9.0 (8.0, 14.0) days, and 10.5 (7.0, 17.0) days for patients with postoperative infection ($p< 0.001$), postoperative bleeding ($p= 0.009$), cardiac arrest/heart failure ($p= 0.047$), respiratory complications ($p= 0.007$), and digestive complications, respectively ($p< 0.001$).

Discussion

This study investigated factors significantly associated with risk of postoperative complications and in-hospital mortality in CRC patients with co-existing CLD who underwent colorectal surgery. Our data showed that 20.84% of our study population comprised patients with CLD. Patients with CLD had a significantly longer duration of hospital stay compared to patients without CLD. Patients with postoperative infection, postoperative bleeding, respiratory complications, and digestive complications had a significantly longer hospital stay compared to patients without postoperative complications. The presence of CLD was significantly associated with a higher risk of postoperative bleeding, and a lower risk of respiratory complications. The presence of CLD and duration of hospital stay were significantly associated with a higher risk of in-hospital mortality, whereas the presence of hyperlipidemia was associated with a lower risk of in-hospital mortality.

Data for this study were extracted from the HCUP-NIS database, which is the largest publicly available collection of longitudinal hospital care clinical data in the United States beginning in 1988. We were, therefore, able to perform analysis of trends over time and make national estimates of health care utilization, access, charges, quality, and outcomes. The NIS sampling frame has grown from 8 States in 1988, to 22 States in 1998, to 46 States in 2011, and currently, covers 97% of the U.S. population.

Studies evaluating operative risk in patients with liver disease found that operative risk was correlated with severity of the underlying liver disease and the nature of the surgical procedure. The increased perioperative risk among patients with underlying liver disease could be due to impairment of hepatic functions such as drug metabolism, detoxification of endogenous or exogenous toxins, and production of plasma proteins.[10] Assessment of Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) score, in combination with careful pre- and post-operative monitoring has been shown to be crucial for improving outcomes.[10, 18, 19] Additionally, some investigators have described the development of risk indices to distinguish low-risk and high-risk subgroups for predicting postoperative mortality in cirrhotic and CRC patients.[14, 20]

Patients with CLD who undergo CRC surgery have previously been shown to have a significantly higher risk of postoperative mortality compared to patients without CLD.[14, 21, 22, 23] Data from a previous population-based study showed that CLD patients had a 6.5-fold higher risk of mortality after colorectal surgery, as well as significantly higher rates of postoperative complications compared to non-CLD patients.[24] These data were consistent with our results which showed that presence of CLD was associated with a higher risk of in-hospital mortality, and suggested that identification of risk factors associated with postoperative complications and mortality in these patients could be critical to improving the clinical outcome.

Our data showed that CRC patients with CLD had a significantly longer hospital stay compared to patients without CLD. This could possibly be due to a higher rate of specific postoperative complications. This was evident in our multivariate regression analysis, which showed that the presence of CLD was associated with a higher risk of postoperative bleeding. Although our data showed that the presence of CLD was associated with a lower risk of respiratory complications, we only evaluated surgery-related respiratory complications, and

not the most common CLD-related pulmonary complications such as hepatopulmonary syndrome, porto-pulmonary hypertension, and hepatic hydrothorax[25]. We also analyzed the correlation between length of hospital stay and incidence of postoperative complications. Our data indicated that patients with postoperative complications (including postoperative infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications, and digestive complications had a significantly longer duration of hospital stay compared to patients without postoperative complications.

The majority of CLD patients in our study had chronic hepatitis C infection, followed by NAFLD. Our data were consistent with previous studies showing that patients with chronic hepatitis C and NAFLD had a significantly higher incidence of colorectal adenomas and advanced neoplasms compared to healthy controls.[16, 26, 27]

Previous results showed that although mortality rates were higher in patients who were emergently admitted compared to patients with elective admission, there was no significant difference in the adjusted relative risk of mortality between the two groups.[13] Our data showed that the type of admission (emergent vs. elective) was not significantly associated with the risk of postoperative complications, but was associated with risk of mortality among inpatients with CRC who had co-existing CLD.

It has been reported that a low socio-economic status was significantly associated with a high incidence of CRC, regardless of individual-level CRC risk factors.[28] Our multivariate analysis showed that patients in Quartile 2 of median household income had a significantly higher risk of in-hospital mortality compared to patients in Quartiles 3 and 4, suggesting that low socioeconomic status (SES) was significantly associated with a higher risk of in-hospital mortality in CRC patients with CLD. This could be a reflection of poorer access to, and lower utilization of health care services among patients with low SES.

Our data showed that hyperlipidemia was associated with a significantly lower risk of postoperative in-hospital mortality. Hyperlipidemia is known to be associated with increased risk of CVD events and increased all-cause mortality. Our present findings could be due to the fact that patients with a diagnosis of hyperlipidemia were prescribed statins, and had a good compliance. Statin monotherapy has previously been shown to exert a protective effect and decreasing the rate of colorectal cancer mortality.[29] Statin use has been shown to be an independent predictor of longer cancer-specific survival, and overall survival in patients with curatively resected CRC.[30] Additionally, since the levels of adiponectin and leptin are significantly decreased and increased, respectively, in NAFLD and CRC patients,[31, 32] it will be interesting to evaluate whether changes in adiponectin/leptin ratios in these patients are associated with clinical outcomes.

Based on our data source, the major strengths of our study are 1) the sample size is large enough to determine fairly precise prevalence measures at the national level, 2) a large multi-ethnic population sample which allowed us to explore the racial/ethnic heterogeneity, 3) the analysis was conducted in a nationally representative sample; therefore, our results may be generalized to the entire U.S. adult population. The major limitations of this study were 1) this was a cross-sectional analysis, and the unit of this database was the individual medical record. Our study, therefore, could not make any inferences regarding causality, 2) it is possible that the number of hospital discharges recorded could include an undetermined number of repeat hospital stays for the same patient, 3) NIS is a US inpatient data (including representative proportions of people of different ethnicity) and should be validated in other countries, 4) our study used ICD-9 codes to characterize the disease, co-morbidities, and interventions. Validation of ICD-9 codes using parameters such as patient charts, or a combination of patient claims along with Part B Medicare claims is important during the course of epidemiological studies performed using administrative databases such as SEER.[33, 34]To the best of our

knowledge, this is the first population-based, cross-sectional study of hospitalized patients evaluating the factors associated with postoperative complications and mortality in CRC patients with co-existing CLD.

Conclusion

Our study showed thatpostoperative infection, postoperative bleeding, respiratory complications, and digestive complications all significantly prolonged the duration of hospital stay among CRC patients with underlying CLD. The presence of CLD was significantly associated with a higher risk of postoperative bleeding, and a lower risk of respiratory complications. Our data suggested that postoperative bleeding should be closely monitored in CRC patients with CLD, since it may result in a higher risk of in-hospital mortality in these patients. The presence of CLD and duration of hospital stay were significantly associated with a higher risk of in-hospital mortality, whereas the presence of hyperlipidemia was a protective factor.

Identification of factors associated with peri- or postoperative complications, and mortality in CRC patients with underlying CLD, can help to improve clinical management and outcomes in this group of CRC patients.

Data Sharing Statement

All data can be accessed from the National Inpatient Sample Database.
NIS releases for data years 1988 through 2015 are available for purchase online through the Online HCUP Central Distributor. All HCUP data users, including data purchasers and collaborators, must complete the online HCUP Data Use Agreement Training Tool, and must read and sign the Data Use Agreement for Nationwide Databases. Questions about purchasing databases can be directed to the HCUP Central Distributor:

Email: HCUPDistributor@AHRQ.gov

Telephone: (866) 556-4287 (toll free)

Fax: (866) 792-5313 (toll free)

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Conflict of interest

The authors declare no conflict of interest.

Statement of Author Contribution

Ko-Chao Lee: Conception and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; guarantor of integrity of the entire study; definition of intellectual content; Administrative, technical or material support; Supervision

Kuan-Chih Chung: Conception and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript; guarantor of integrity of the entire study; definition of intellectual content; Administrative, technical or material support; Supervision

Hong-Hwa Chen: Acquisition of data; Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; Administrative, technical or material support

Kung-Chuan Cheng: Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; clinical studies

Kuen-Lin Wu: Analysis and interpretation of data; Critical revision of the manuscript; statistical analysis; clinical studies

Chien-Chang Lu: Analysis and interpretation of data; Critical revision of the manuscript; literature research; clinical studies

All authors have read and approved the submitted version.

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Table 1. Baseline demographic and clinical characteristics of study population

	Total sample N = 7463	Chronic liver diseases		p-value
		No N = 5908	Yes N = 1555	
Type of chronic liver diseases				
None	5908 (79.16)	5908 (100.00)	0 (0.00)	
Chronic hepatitis B	65 (0.87)	0 (0.00)	65 (4.18)	
Chronic hepatitis C	564 (7.56)	0 (0.00)	564 (36.27)	
Non-alcoholic fatty liver disease	441 (5.91)	0 (0.00)	441 (28.36)	
Other types	485 (6.50)	0 (0.00)	485 (31.19)	
Postoperative complications				0.228
No	5830 (78.12)	4633 (78.42)	1197 (76.98)	
Yes	1633 (21.88)	1275 (21.58)	358 (23.02)	
Postoperative infection	360 (22.05)	276 (21.65)	84 (23.46)	
Postoperative shock	23 (1.41)	15 (1.18)	8 (2.23)	
Postoperative bleeding	149 (9.12)	104 (8.16)	45 (12.57)	
Disruption of wound	73 (4.47)	55 (4.31)	18 (5.03)	
Non-healing surgical wound	4 (0.24)	4 (0.31)	0 (0.00)	
Nervous system complications	17 (1.04)	16 (1.25)	1 (0.28)	
Cardiac arrest/heart failure	125 (7.65)	102 (8.00)	23 (6.42)	
Phlebitis/thrombophlebitis	5 (0.31)	3 (0.24)	2 (0.56)	
Respiratory complications	141 (8.63)	121 (9.49)	20 (5.59)	
Digestive system complications	675 (41.33)	529 (41.49)	146 (40.78)	
Urinary complications	60 (3.67)	49 (3.84)	11 (3.07)	
Unspecified complications	1 (0.06)	1 (0.08)	0 (0.00)	
In-Hospital Mortality				< 0.001
No	7301 (97.83)	5806 (98.28)	1495 (96.14)	
Yes	162 (2.17)	102 (1.73)	60 (3.86)	
Age				0.984
Mean ± SD	62.53 ± 12.17	62.53 ± 12.16	62.52 ± 12.17	
Gender				0.708
Male	4283 (57.39)	3384 (57.28)	899 (57.81)	
Female	3180 (42.61)	2524 (42.72)	656 (42.19)	
Race				< 0.001
White	4536 (60.78)	3570 (60.43)	966 (62.12)	
Black	810 (10.85)	614 (10.39)	196 (12.60)	
Hispanic	359 (4.81)	266 (4.50)	93 (5.98)	
Asian or Pacific Islander	154 (2.06)	108 (1.83)	46 (2.96)	
Native American	24 (0.32)	19 (0.32)	5 (0.32)	

Other/Missing	1580 (21.17)	1331 (22.53)	249 (16.01)	
Median household income				< 0.001
Quartile 1	1993 (26.71)	1564 (26.47)	429 (27.59)	
Quartile 2	1902 (25.49)	1489 (25.20)	413 (26.56)	
Quartile 3	1757 (23.54)	1386 (23.46)	371 (23.86)	
Quartile 4	1646 (22.06)	1354 (22.92)	292 (18.78)	
Others	165 (2.21)	115 (1.95)	50 (3.22)	
Location of hospital				< 0.001
Rural	984 (13.19)	833 (14.10)	151 (9.71)	
Urban non-teaching	2711 (36.33)	2152 (36.43)	559 (35.95)	
Urban teaching	3731 (49.99)	2894 (48.98)	837 (53.83)	
Others	37 (0.50)	29 (0.49)	8 (0.51)	
Types of admission				0.006
Non-elective	2323 (31.13)	1789 (30.28)	534 (34.34)	
Elective	5122 (68.63)	4103 (69.45)	1019 (65.53)	
Others	18 (0.24)	16 (0.27)	2 (0.13)	
Severity of CRC				0.987
None	4889 (65.51)	3868 (65.47)	1021 (65.66)	
Lymph node metastasis	1823 (24.43)	1444 (24.44)	379 (24.37)	
Distant metastasis	751 (10.06)	596 (10.09)	155 (9.97)	
Length of hospital stay (day)				< 0.001
Mean ± SD	8.96 ± 7.24	8.61 ± 6.49	10.26 ± 9.46	
Hyperlipidemia				< 0.001
No	5624 (75.36)	4382 (74.17)	1242 (79.87)	
Yes	1839 (24.64)	1526 (25.83)	313 (20.13)	
Obesity				0.827
No	6556 (87.85)	5187 (87.80)	1369 (88.04)	
Yes	907 (12.15)	721 (12.20)	186 (11.96)	

Abbreviation: CRC, colorectal cancer.

Table 2. Univariate and multivariate logistic regression analyses to identify factors associated with postoperative complications among inpatients diagnosed with colorectal cancer

	Univariate		Multivariate	
	OR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	1.08 (0.94, 1.23)	0.292	0.91 (0.78, 1.05)	0.192
Race				
White	reference			
Black	1.01 (0.83, 1.23)	0.905		
Hispanic	1.03 (0.79, 1.35)	0.827		
Asian or Pacific islander	0.85 (0.54, 1.34)	0.494		
Native American	1.10 (0.42, 2.92)	0.845		
Other/Missing	0.95 (0.81, 1.10)	0.456		
Median household income				
Quartile 1	reference			
Quartile 2	1.16 (0.99, 1.36)	0.075		
Quartile 3	0.93 (0.79, 1.10)	0.389		
Quartile 4	1.02 (0.86, 1.21)	0.827		
Others	1.06 (0.71, 1.59)	0.785		
Location of hospital				
Rural	reference			
Urban non-teaching	1.09 (0.90, 1.32)	0.355		
Urban teaching	1.04 (0.87, 1.25)	0.667		
Others	1.25 (0.57, 2.75)	0.572		
Types of admission				
Non-elective	reference			
Elective	0.95 (0.83, 1.08)	0.397		
Others	0.85 (0.24, 3.03)	0.802		
Length of hospital stay	**1.13 (1.12, 1.14)**	**<0.001**	**1.13 (1.12, 1.15)**	**<0.001**
Hyperlipidemia				
No	reference		reference	
Yes	**0.77 (0.67, 0.89)**	**<0.001**	0.97 (0.83, 1.12)	0.671
Obesity				
No	reference			
Yes	1.09 (0.91, 1.30)	0.353		

P< 0.05 were shown in boldface.

Table 3-1. Univariate logistic regression analyses to identify risk factors for specific postoperative complications among inpatients diagnosed with colorectal cancer

	Postoperative infection		Postoperative bleeding		Cardiac arrest/heart failure	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Chronic liver diseases						
No	reference		reference		reference	
Yes	1.16 (0.90, 1.49)	0.255	**1.67 (1.17, 2.38)**	**0.005**	0.82 (0.51, 1.31)	0.404
Race						
White	reference		reference		reference	
Black	0.93 (0.64, 1.35)	0.691	0.72 (0.38, 1.34)	0.301	0.86 (0.43, 1.72)	0.664
Hispanic	1.30 (0.81, 2.08)	0.273	0.94 (0.43, 2.06)	0.867	1.39 (0.62, 3.11)	0.428
Asian or Pacific islander	0.96 (0.43, 2.16)	0.924	0.32 (0.04, 2.39)	0.265	1.95 (0.55, 6.92)	0.301
Native American	2.65 (0.66, 10.63)	0.169	NA	NA	1.68 (0.20, 13.93)	0.630
Other/Missing	0.93 (0.70, 1.25)	0.636	0.96 (0.62, 1.48)	0.858	0.79 (0.48, 1.29)	0.314
Median household income						
Quartile 1	reference		reference		reference	
Quartile 2	0.96 (0.71, 1.29)	0.763	1.41 (0.90, 2.19)	0.133	1.32 (0.77, 2.25)	0.314
Quartile 3	0.94 (0.69, 1.28)	0.691	0.74 (0.44, 1.25)	0.260	1.40 (0.81, 2.43)	0.225
Quartile 4	0.78 (0.56, 1.09)	0.141	0.87 (0.52, 1.45)	0.597	1.23 (0.70, 2.16)	0.479
Others	0.73 (0.30, 1.76)	0.488	0.92 (0.26, 3.21)	0.898	1.82 (0.59, 5.57)	0.296
Location of hospital						
Rural	reference		reference		reference	
Urban non-teaching	1.23 (0.82, 1.84)	0.320	0.94 (0.53, 1.67)	0.833	1.04 (0.57, 1.90)	0.888
Urban teaching	1.45 (0.99, 2.14)	0.058	1.06 (0.61, 1.84)	0.828	1.08 (0.60, 1.96)	0.797
Others	0.52 (0.07, 4.07)	0.536	NA	NA	3.16 (0.60, 16.64)	0.175
Types of admission						
Non-elective	reference		reference		reference	
Elective	0.90 (0.71, 1.15)	0.405	1.21 (0.82, 1.78)	0.341	1.01 (0.67, 1.53)	0.959
Others	1.33 (0.16, 11.06)	0.791	NA	NA	NA	NA
Length of hospital stay	**1.13 (1.11, 1.15)**	**<0.001**	**1.03 (1.01, 1.05)**	**0.010**	1.01 (0.98, 1.04)	0.434
Hyperlipidemia						
No	reference		reference		reference	
Yes	**0.64 (0.48, 0.85)**	**0.002**	0.88 (0.59, 1.32)	0.544	0.75 (0.49, 1.15)	0.191
Obesity						
No	reference		reference		reference	
Yes	1.30 (0.95, 1.78)	0.098	0.69 (0.38, 1.25)	0.218	1.12 (0.62, 2.02)	0.709

P< 0.05 were shown in boldface.

Abbreviation: NA, not available

Table 3-2. Univariate logistic regression analyses to identify risk factors for specific postoperative complications among inpatients diagnosed with colorectal cancer

	Respiratory complications		Digestive system complications	
	OR (95% CI)	p value	OR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	**0.62 (0.38, 1.00)**	**0.048**	1.04 (0.86, 1.26)	0.697
Race				
White	reference		reference	
Black	0.60 (0.30, 1.18)	0.139	**1.32 (1.02, 1.72)**	**0.034**
Hispanic	0.61 (0.23, 1.59)	0.312	0.70 (0.45, 1.08)	0.106
Asian or Pacific islander	NA	NA	1.14 (0.63, 2.08)	0.668
Native American	NA	NA	0.47 (0.06, 3.67)	0.474
Other/Missing	1.06 (0.69, 1.63)	0.776	0.99 (0.81, 1.23)	0.957
Median household income				
Quartile 1	reference		reference	
Quartile 2	1.15 (0.71, 1.86)	0.577	1.05 (0.83, 1.32)	0.706
Quartile 3	0.84 (0.50, 1.39)	0.492	1.00 (0.78, 1.27)	0.990
Quartile 4	1.05 (0.63, 1.74)	0.857	1.21 (0.96, 1.54)	0.112
Others	0.96 (0.27, 3.44)	0.953	1.24 (0.71, 2.18)	0.454
Location of hospital				
Rural	reference		reference	
Urban non-teaching	0.91 (0.55, 1.48)	0.694	1.08 (0.82, 1.40)	0.588
Urban teaching	**0.46 (0.27, 0.76)**	**0.003**	0.95 (0.73, 1.24)	0.710
Others	NA	NA	2.16 (0.82, 5.69)	0.120
Types of admission				
Non-elective	reference		reference	
Elective	1.06 (0.72, 1.56)	0.777	1.01 (0.84, 1.22)	0.879
Others	NA	NA	0.98 (0.21, 4.46)	0.977
Length of hospital stay	**1.04 (1.02, 1.06)**	**0.001**	**1.05 (1.04, 1.06)**	**< 0.001**
Hyperlipidemia				
No	reference		reference	
Yes	0.74 (0.48, 1.15)	0.183	1.01 (0.83, 1.22)	0.948
Obesity				
No	reference		reference	
Yes	1.24 (0.72, 2.14)	0.441	1.14 (0.88, 1.48)	0.328

P< 0.05 were shown in boldface.

Abbreviation:NA, not available

Table 4. Multivariate logistic regression analyses to identify risk factors forspecific postoperative complications among inpatients diagnosed with colorectal cancer

	Postoperative infection		Postoperative bleeding		Respiratory complications		Digestive system complications	
	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases								
No	reference		reference		reference		reference	
Yes	0.90 (0.67, 1.20)	0.459	**1.64 (1.15, 2.34)**	**0.007**	**0.58 (0.36, 0.95)**	**0.029**	0.97 (0.80, 1.18)	0.768
Race								
White							reference	
Black							1.26 (0.97, 1.65)	0.081
Hispanic							0.65 (0.41, 1.01)	0.056
Asian or Pacific islander							1.17 (0.64, 2.14)	0.600
Native American							0.52 (0.07, 4.05)	0.534
Other/Missing								
Median household income								
Quartile 1								
Quartile 2								
Quartile 3								
Quartile 4								
Others								
Location of hospital								
Rural					reference			
Urban non-teaching					0.89 (0.54, 1.46)	0.640		
Urban teaching					**0.44 (0.26, 0.75)**	**0.002**		
Others					NA	NA		
Types of admission								

Non-elective								
Elective								
Others								
Length of hospital stay	**1.13 (1.11, 1.15)**	**<0.001**	**1.02 (1.01, 1.04)**	**0.013**	**1.04 (1.02, 1.07)**	**< 0.001**	**1.05 (1.04, 1.06)**	**< 0.001**
Hyperlipidemia								
No	reference							
Yes	0.81 (0.59, 1.12)	0.202						
Obesity								
No								
Yes								

P< 0.05 were shown in boldface.
Abbreviation:NA, not available

Table 5. Univariate and multivariate logistic regression analyses to identifyfactors associated with in-hospital mortality among inpatients diagnosed with colorectal cancer.

	Univariate		Multivariate	
	OR (95% CI)	p value	aOR (95% CI)	p value
Chronic liver diseases				
No	reference		reference	
Yes	**2.33 (1.68, 3.23)**	**<0.001**	**2.05 (1.43, 2.94)**	**<0.001**
Race				
White	reference			
Black	1.31 (0.76, 2.27)	0.332		
Hispanic	0.93 (0.42, 2.06)	0.864		
Asian or Pacific Islander	NA	NA		
Native American	NA	NA		
Other/Missing	0.86 (0.55, 1.35)	0.512		
Median household income				
Quartile 1	reference		reference	
Quartile 2	1.28 (0.83, 1.96)	0.268	1.51(0.95, 2.40)	0.083
Quartile 3	**0.58 (0.35, 0.99)**	**0.046**	0.71(0.41, 1.26)	0.247
Quartile 4	0.68 (0.40, 1.15)	0.152	0.77(0.42, 1.39)	0.384
Others	1.72 (0.59, 4.96)	0.320	1.17(0.35, 3.83)	0.800
Location of hospital				
Rural	reference		reference	
Urban non-teaching	0.65 (0.40, 1.04)	0.073	0.63 (0.37, 1.08)	0.094
Urban teaching	**0.59 (0.37, 0.94)**	**0.025**	0.63 (0.37, 1.06)	0.084
Others	2.87 (0.29, 28.13)	0.365	4.54 (0.43, 48.16)	0.209
Types of admission				
Non-elective	reference		reference	
Elective	**0.37 (0.26, 0.52)**	**<0.001**	**0.50 (0.34, 0.73)**	**<0.001**
Others	NA	NA	NA	NA
Length of hospital stay	**1.07 (1.05, 1.09)**	**<0.001**	**1.06 (1.04, 1.08)**	**<0.001**

Hyperlipidemia				
No	reference		reference	
Yes	**0.39 (0.25, 0.63)**	**<0.001**	**0.46 (0.28, 0.75)**	**0.002**
Obesity				
No	reference			
Yes	0.56 (0.29, 1.08)	0.084		

P< 0.05 were shown in boldface.
Abbreviation: NA, not applicable

Table 6. Difference between postoperative complication and length of hospital stay in CRC patients with CLD (n = 1,555)

	Length of hospital stay	
	Median (IQR)	p-value
Postoperative complications		<0.001
No	7.0 (5.0, 10.0)	
Yes	11.5 (5.0, 10.0)	
Postoperative infection		<0.001
No	7.0 (5.0, 10.0)	
Yes	17.0 (10.0, 26.0)	
Postoperative bleeding		0.009
No	7.0 (5.0, 10.0)	
Yes	8.0 (6.0, 12.0)	
Cardiac arrest/heart failure		0.047
No	7.0 (5.0, 10.0)	
Yes	8.0 (6.0, 17.0)	
Respiratory complications		0.007
No	7.0 (5.0, 10.0)	
Yes	9.0 (8.0, 14.0)	

Digestive system complications		<0.001
No	7.0 (5.0, 10.0)	
Yes	10.5 (7.0, 17.0)	