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Clinical Study

Liver disease is an independent predictor of poor 30-day outcomes following surgery for degenerative disease of the cervical spine

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Abstract

BACKGROUND AND CONTEXT: The impact of underlying liver disease on surgical outcomes has been recognized in a wide variety of surgical disciplines. However, less empiric data are available about the importance of liver disease in spinal surgery.
PURPOSE: To measure the independent impact of underlying liver disease on 30-day outcomes following surgery for the degenerative cervical spine.
STUDY DESIGN: Retrospective comparative study.
PATIENT SAMPLE: A cohort of 21,207 patients undergoing elective surgery for degenerative disease of the cervical spine from the American College of Surgeons National Surgical Quality Improvement Program.
OUTCOME MEASURES: Outcome measures included mortality, hospital length of stay, and postoperative complications within 30 days of surgery.
METHODS: The NSQIP dataset was queried for patients undergoing surgery for degenerative disease of the cervical spine from 2006 to 2015. Assessment of underlying liver disease was based on aspartate aminotransferase-to-platelet ratio index and Model of End-Stage Liver Disease-Sodium scores, computed from preoperative laboratory data. The effect of liver disease on outcomes was assessed by bivariate and multivariate analyses, in comparison with 16 other preoperative and operative factors.
RESULTS: Liver disease could be assessed in 21,207 patients based on preoperative laboratory values. Mild liver disease was identified in 2.2% of patients, and advanced liver disease was identified in 1.6% of patients. The 30-day mortality rates were 1.7% and 5.1% in mild and advanced liver diseases, respectively, compared with 0.6% in patients with healthy livers. The 30-day complication rates were 11.8% and 31.5% in these patients, respectively, compared with 8.8% in patients with healthy livers. In multivariate analysis, the presence of any liver disease (mild or advanced) was independently associated with an increased risk of mortality (OR=2.00, 95% CI=1.12–3.55, p=.019), morbidity (OR=1.35, 95% CI=1.07–1.70, p=.012), and length of hospital stay longer than 7 days (OR=1.73, 95% CI=1.40–2.13, p<.001), when compared with 18 other preoperative and operative factors. Liver disease was also independently associated with perioperative respiratory

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failure (OR=1.80, 95% CI=1.21–2.68, p=.004), bleeding requiring transfusion (OR=1.43, 95% CI=1.01–2.02, p=.044), wound disruption (OR=2.82, 95% CI=1.04–7.66, p=.042), and unplanned reoperation (OR=1.49, 95% CI=1.05–2.11, p=.025).

CONCLUSIONS: Liver disease independently predicts poor perioperative outcome following surgery for degenerative disease of the cervical spine. Based on these findings, careful consideration of a patient's underlying liver function before surgery may prove valuable in surgical decision-making, preoperative patient counseling, and postoperative patient care.

Keywords: Cervical spine; Cirrhosis; Complications; Degenerative disease; Liver disease; Mortality; NSQIP

Introduction

The prevalence of liver cirrhosis among American adults has seen a well-documented rise in recent years [1,2]. Importantly, as many as two-thirds of patients with some form of underlying liver disease may be asymptomatic and unaware of their condition [1]. These same patients have been shown to exhibit poor perioperative outcomes across a wide variety of surgical interventions, including cardiac surgery [3–5], abdominal surgery [3–10], bariatric surgery [11], head and neck surgery [12,13], orthopedic surgery [14], trauma [15], and craniotomy [16]. Liver cirrhosis is a systemic disease and its effect on surgical outcomes is multifactorial. Associations of chronic liver disease that may be of particular importance to surgeons include coagulopathy, impaired wound healing, immune dysfunction, respiratory and renal dysfunction, encephalopathy, and the effects of anesthesia on hepatic blood flow [17,18].

While the impact of liver disease in surgical outcomes has been demonstrated across a wide spectrum of surgical disciplines, less empiric data are available on its importance in spinal surgery. To our knowledge, only two prior studies have linked liver disease to elevated morbidity and mortality following spinal surgery [19, 20]. We sought to measure the independent effects of liver disease on perioperative outcome in a different spine surgical population, those undergoing elective surgery for degenerative conditions of the cervical spine in a large multi-institutional cohort.

Methods

Data source

The American College of Surgeons National Surgical Quality of Improvement Program (ACS-NSQIP) is a collaboration of more than 400 medical institutions across the United States, measuring 30-day outcomes in surgical patients. The ACS-NSQIP includes information on demographics, preoperative risk factors, preoperative laboratory data, operative data, and all complications occurring within 30 days of surgery. Details of the NSQIP sampling protocol have been described in detail elsewhere [21]. Briefly, preoperative patient data is collected prior to surgery after which patients are followed prospectively for 30 days. In this period, information on all complications is recorded, whether they occurred during surgical hospitalization or after discharge. Data reported by contributing institutions are routinely audited, and previous studies have systematically validated the NSQIP dataset [22]. In this study, data were collected from the NSQIP dataset from 2006 to 2015. The University of Pennsylvania institutional review board has exempted studies using the deidentified NSQIP dataset from individual review.

Inclusion criteria

This study population includes patients undergoing surgery for degenerative spinal disease in the cervical spine. Inclusion in the study was based on both Current Procedural Terminology (CPT) codes and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. First, patients undergoing surgery from 2006 to 2015 with a primary CPT code describing arthrodesis, discectomy, corpectomy, laminotomy, foraminotomy, or facetectomy at the level of the cervical spine were identified. This yielded an initial cohort of 61,967. Subsequently, ICD-9-CM codes were screened to eliminate any patients with a primary diagnosis unrelated to degenerative cervical spinal disease. Such diagnoses included spinal trauma, neoplasm, infection, vascular malformation, or primary disease locus in the lumbar or thoracic spine. In total, 6,565 patients were eliminated on the basis of ICD-9-CM codes, leaving 55,402 patients in the study population. The 10 most common primary CPT codes and ICD-9-CM codes for the study population are given in Supplementary Tables 1 and 2.

Assessment of liver disease

Assessment of liver disease was based on aspartate aminotransferase-to-platelet ratio (APRI) and Model for End-Stage Liver Disease-Sodium (MELD-Na) score, using a method described previously [13, 16]. These scores were calculated as follows: APRI score=[(AST (IU/L)/40)/platelet count (10^9/L)]×100; MELD score=[3.8×(ln[bilirubin (mg/dL)])+11.2×(ln[INR])+9.6×(ln[creatinine (mg/dL)]) +6.43; MELD-Na score=MELD−sodium (mmol/L)−(0.025×MELD×[140−sodium (mmol/L)]) +140. A minimum value of 125 mmol/L and a maximum value of 140 mmol/L were applied to serum sodium levels. For

Table 1
Risk factors and comorbidities in patients with liver disease

		Healthy liver	Mild disease	Advanced disease	Unknown liver function*	Total	p Value	Healthy liver %	Mild disease %	Advanced disease %	Unknown liver function %	Total %
Total	–	20,404	467	336	34,195	55,402		96.2	2.2	1.6	60.7	–
Age (SD)	Age exact	56.6	56.2	59.9	54.4	55.3	<.001	12.4	12.1	10.6	12.4	12.4
	Unknown†	60	1	2	48	111		0.3	0.2	0.6	0.1	0.2
Gender	Male	10,570	309	234	17,943	29,056	<.001	51.8	66.2	69.6	52.5	52.5
	Female	9,826	158	102	16,236	26,322		48.2	33.8	30.4	47.5	47.5
	Unknown	8	0	0	16	24		0.0	0.0	0.0	0.0	0.0
Race	White	15,699	320	213	26,405	42,637	<.001	84.4	76.9	70.8	86.3	85.4
	Black	2,157	77	74	3,362	5,670		11.6	18.5	24.6	11.0	11.4
	Asian	488	10	10	714	1,222		2.6	2.4	3.3	2.3	2.4
	Native	258	9	4	114	385		1.4	2.2	1.3	0.4	0.8
	Unknown	1,802	51	35	3,600	5,488		8.8	10.9	10.4	10.5	9.9
BMI (SD)	BMI exact	29.9	29.8	28.9	29.8	29.8	.023	6.7	7.1	7.2	6.5	6.6
	Unknown	151	6	7	307	471		0.7	1.3	2.1	0.9	0.9
Smoking	Smoker	5,792	155	124	9,596	15,667	<.001	28.4	33.2	36.9	28.1	28.3
	Nonsmoker	14,612	312	212	24,599	39,735		71.6	66.8	63.1	71.9	71.7
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Diabetes	Diabetes	3,712	88	83	4,740	8,623	.009	18.2	18.8	24.7	13.9	15.6
	No diabetes	16,692	379	253	29,455	46,779		81.8	81.2	75.3	86.1	84.4
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Hypertension	Hypertension	10,319	240	222	14,811	25,592	<.001	50.6	51.4	66.1	43.3	46.2
	Normal	10,085	227	114	19,384	29,810		49.4	48.6	33.9	56.7	53.8
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Chronic steroid use	Steroids	992	19	26	989	2,026	.037	4.9	4.1	7.7	2.9	3.7
	No steroids	19,412	448	310	33,206	53,376		95.1	95.9	92.3	97.1	96.3
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Preoperative sepsis	Sepsis	330	9	50	215	604	<.001	1.6	1.9	14.9	0.6	1.1
	No sepsis	20,042	458	286	33,911	54,697		98.4	98.1	85.1	99.4	98.9
	Unknown	32	0	0	69	101		0.2	0.0	0.0	0.2	0.2
Open or infected wound	Complicated	243	8	18	147	416	<.001	1.2	1.7	5.4	0.4	0.8
	Uncomplicated	20,161	459	318	34,048	54,986		98.8	98.3	94.6	99.6	99.2
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Disseminated cancer	Cancer	225	9	20	97	351	<.001	1.1	1.9	6.0	0.3	0.6
	No cancer	20,179	458	316	34,098	55,051		98.9	98.1	94.0	99.7	99.4
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Pulmonary comorbidity	Complicated	2,090	48	63	2,646	4,847	<.001	10.2	10.3	18.8	7.7	8.7
	Uncomplicated	18,313	419	273	31,549	50,554		89.8	89.7	81.3	92.3	91.3
	Unknown	1	0	0	0	1		0.0	0.0	0.0	0.0	0.0
Bleeding comorbidity	Complicated	1,402	176	214	1,867	3,659	<.001	8.8	37.7	63.7	9.7	10.2
	Uncomplicated	14,479	291	122	17,461	32,353		91.2	62.3	36.3	90.3	89.8
	Unknown	4,523	0	0	14,867	19,390		22.2	0.0	0.0	43.5	35.0
Renal comorbidity	Complicated	137	0	24	123	284	<.001	0.7	0.0	7.1	0.4	0.5
	Uncomplicated	20,267	467	312	34,072	55,118		99.3	100.0	92.9	99.6	99.5
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0

Table 1 (*Continued*)

		Healthy liver	Mild disease	Advanced disease	Unknown liver function*	Total	p Value	Healthy liver %	Mild disease %	Advanced disease %	Unknown liver function %	Total %
Patient care setting	Outpatient	3,491	74	24	7,018	10,607	<.001	17.1	15.8	7.1	20.5	19.1
	Inpatient	16,913	393	312	27,177	44,795		82.9	84.2	92.9	79.5	80.9
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Surgical approach	Anterior	14,968	338	191	25,308	40,805	<.001	73.4	72.4	56.8	74.0	73.7
	Posterior	5,436	129	145	8,887	14,597		26.6	27.6	43.2	26.0	26.3
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Fusion or instrumentation	Yes	16,526	380	268	26,973	44,147	.83	81.0	81.4	79.8	78.9	79.7
	No	3,878	87	68	7,222	11,255		19.0	18.6	20.2	21.1	20.3
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Extent of surgery	One spinal level	7,992	181	184	12,960	21,317	<.001	39.2	38.8	54.8	37.9	38.5
	Multiple levels	12,412	286	152	21,235	34,085		60.8	61.2	45.2	62.1	61.5
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0

SD = Standard deviation.

* Patients with undetermined liver function were excluded from chi-squared statistical testing.

† Unknown percentages are expressed as a fraction of all cases (known and unknown). All other percentages are expressed as a fraction of all cases whose value is known.

serum bilirubin, INR, and serum creatinine, a minimum value of 1 was used. For serum creatinine, a maximum value of 4 mg/dL was applied for all patients on dialysis or with serum creatinine measured at 4 mg/dL or greater. Patients were considered to have some degree of liver disease with APRI $\geq$0.7. Among these patients, a MELD-Na score $<$10 represented mild disease and MELD-Na score $\geq$10 represented advanced disease, based on thresholds utilized in prior studies [13, 16]. APRI and MELD-Na scores could not be computed if aspartate aminotransferase (AST) level, platelet count, total bilirubin, serum creatinine, international normalized ratio (INR) for prothrombin time, or serum sodium were not recorded prior to surgery.

It is reasonable to assume that patients suspected of having liver disease or some other underlying abnormality were more likely to have these laboratory values taken before surgery. To measure and account for this form of selection bias, basic descriptive data were provided in this study on the population of patients in whom liver disease could not be assessed due to lack of laboratory testing, ie, patients with undetermined liver function (Table 1). However, this population was excluded from all bivariate and multivariate statistical analyses. Of the 55,402 patients meeting CPT and ICD-9-CM inclusion criteria, liver disease could not be assessed in 34,195 (61.7%) leaving a cohort of 21,207 patients that were included fully in this study.

Preoperative factors and outcomes measures

In general, preoperative factors, operative factors, and complications were defined in the study based on definitions detailed in the NSQIP participant use file (PUF), when applicable.

The following preoperative and operative factors were included in analysis: age, gender, race, body mass index (BMI), smoking within the last year, diabetes, hypertension, chronic steroid use within 30 days, preoperative sepsis within 30 days, open or infected wound at the time of surgery, disseminated cancer within one year, pulmonary comorbidity, bleeding comorbidity, renal comorbidity, patient care setting, surgical approach, extent of surgery, and spinal fusion or instrumentation during surgery. Age was categorized as over or under 65 years. Patients were considered obese with a BMI $>$30 kg/m^2 and nonobese otherwise. Patients were considered diabetic or hypertensive if they had been prescribed an antidiabetic or antihypertensive agent, respectively, for more than two weeks within 30 days of surgery or at the time of surgical evaluation. Patients were considered to have a pulmonary comorbidity if dyspnea, ventilator dependence, or history of severe COPD were reported in the medical record. Patients were considered to have a bleeding comorbidity if their platelet count was less than 150,000$\times$10^6/mL, if INR exceeded 1.2, or if any active bleeding disorder was reported in the medical record. Patients were considered to have a renal

comorbidity based on dialysis use within two weeks of surgery, serum creatinine level of 3 mg/dL within 24 hours of surgery, or elevated blood urea nitrogen (based on hospital reference range) within 24 hours of surgery. Patient care setting was classified as inpatient or outpatient. Surgical approach was classified as anterior or posterior, based on primary CPT code. Extent of surgery was classified as involving only one or greater than one vertebral level, based on CPT codes. Spinal fusion or instrumentation during surgery was also assessed based on primary CPT code. All other preoperative and operative factors were assessed based on reporting in the medical record.

Primary outcome measures were 30-day morbidity, 30-day mortality, hospital length of stay, and 30-day readmissions. Postoperative morbidity was defined as the occurrence of any of the following complications: unplanned reoperation, surgical site infection, wound disruption, pneumonia, venous thromboembolism, respiratory failure, renal failure, cardiac event, postoperative sepsis, urinary tract infection, stroke, bleeding requiring transfusion, and mortality. Venous thromboembolism was defined as any occurrence of deep vein thrombosis or pulmonary embolism in the 30 days after surgery. Bleeding requiring transfusion was defined as the need for at least one unit of packed or whole red blood cells between surgical start to 72 hours after surgery. Respiratory failure was defined as any unplanned intubation or if mechanical ventilation was needed for more than 48 hours after surgery. Renal failure was defined as a rise in serum creatinine of 2 mg/dL from preoperative levels or need for dialysis in the 30 days after surgery, in a patient that did not require dialysis preoperatively. Cardiac event was defined as acute myocardial infarction or cardiac arrest requiring cardiopulmonary resuscitation in the 30 days after surgery. Readmissions were considered 30 days from discharge and included readmissions to any hospital within that time period, not exclusively the hospital in which the index surgery was performed. All other postoperative complications were defined based on reporting in the patient's medical record, having occurred in the 30 days after surgery.

Statistical analysis

Analyses were performed using SPSS 22.0 software (SPSS, IBM, Armonk, NY). Pearson's chi-squared test was used to measure association between liver disease severity and all categorical variables. One-way analysis of variance was used in to measure association between liver disease severity and all continuous variables. The unadjusted and

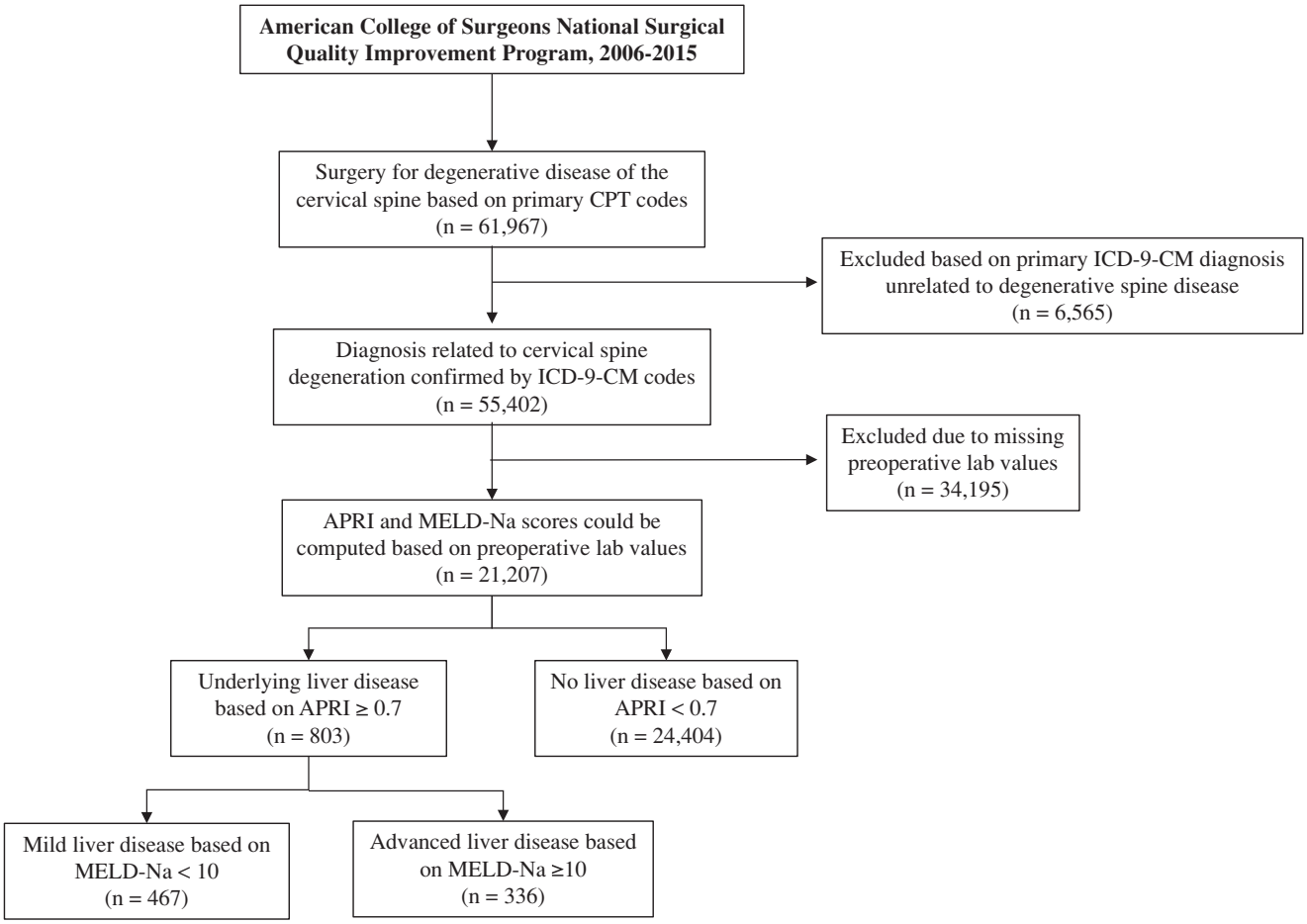

Fig. 1. Flowchart of inclusion criteria and study population.

adjusted odds ratio (OR) among risk factors and relevant outcomes were reported with 95% confidence intervals (CI). Multivariate logistic regression was used to assess the independent effect of liver disease on outcome, including all risk factors as covariates. Cases with missing data were excluded from the relevant analysis, and the fraction of all study cases with missing data is reported for all preoperative variables and outcome measures. p Value less than .05 was considered significant.

Results

Liver disease was assessed in 21,207 patients undergoing surgery for degenerative disease of the cervical spine (Fig. 1). Mild and advanced liver diseases were identified in 2.2% and 1.6% of patients, respectively. The preoperative and operative factors associated with liver disease are shown in Table 1. Liver disease was significantly associated with older patients, African-American race, lower BMI, smoking, diabetes, hypertension, chronic steroid use, disseminated cancer, preoperative sepsis, open or infected wound, pulmonary comorbidity, bleeding comorbidity, renal comorbidity, inpatient status, posterior surgical approach, and surgery involving a single spinal level. Liver disease showed no association with spinal fusion or instrumentation during surgery. Preoperative laboratory data for patients with liver disease are given in Table 2. Liver disease was associated with low serum sodium, serum albumin, hematocrit, and platelet count. Liver disease was also associated with elevated blood urea nitrogen (BUN), serum creatinine, bilirubin, AST, alkaline phosphatase, white blood cell count, PTT, and INR.

Univariate associations between liver disease and outcomes are given in Table 3. Liver disease showed univariate association with all complications measured except for stroke (OR=2.18, 95% CI=0.67−2.11, p=.17). Rates of 30-day mortality were 5.1%, 1.7%, and 0.6% in patients with advanced liver disease, mild liver disease, and no liver disease, respectively. Rates of 30-day morbidity were 31.5%, 11.8%, and 8.8% in these same patient groups. Rates of 30-day in readmissions were 10.7%, 4.6%, and 5.5% in these same patient groups. Average length of hospital stay was 10.0 days, 5.3 days, and 3.3 days in these same patient groups as well. Multivariate analysis of liver disease (mild or advanced) and outcome are shown in Table 4. Liver disease showed significant independent association with mortality (OR=2.00, 95% CI=1.12−3.55, p=.019), morbidity (OR=1.35, 95% CI=1.07−1.70, p=.012), and length of hospital stay longer than 7 days (OR=1.73, 95% CI=1.40−2.13, p< .001). This was three of the four primary outcome measures. Liver disease was also independently associated with perioperative respiratory failure (OR=1.80, 95% CI=1.21−2.68, p=.004), bleeding requiring transfusion (OR=1.43, 95% CI=1.01−2.02, p=.044), wound disruption (OR=2.82, 95% CI=1.04−7.66, p=.042), and unplanned reoperation (OR=1.49, 95% CI=1.05−2.11, p=.025).

In Table 5, the independent effect of liver disease on 30-day morbidity and mortality is compared with all other preoperative and operative factors. Seven of nineteen factors were independently linked to mortality: age, disseminated cancer, preoperative sepsis, pulmonary comorbidity, bleeding comorbidity, surgical approach, and liver disease. Among these factors, liver disease showed the fifth strongest independent association with mortality. Seventeen of nineteen operative and preoperative factors were independently associated with morbidity, and among these factors liver disease showed the thirteenth strongest independent association with morbidity.

Discussion

In this study, we measured the effect of underlying liver disease on perioperative outcomes in 21,207 patients undergoing surgery for degenerative disease of the cervical spine from the ACS-NSQIP database. To our knowledge, this is the first study that specifically examines liver disease in surgery for degeneration of the cervical spine. We found by bivariate and multivariate analyses that liver disease was a strong, independent predictor of increased mortality, morbidity, and length of hospital stay following surgery. We also found strong correlation between the severity of underlying liver disease and worse outcome. Rates of 30-day mortality were 5.1% and 1.7% and rates of 30-day morbidity were 31.5% and 11.8% in patients with advanced and mild liver diseases, respectively. This compares with 30-day mortality and morbidity rates of 0.6% and 8.8%, respectively, in patients with healthy livers. Mean length of hospital stay was 10.0 days, 5.3 days, and 3.3 days in patients with advanced, mild, and no liver diseases, respectively. Liver disease also showed independent association with the following postoperative complications: unplanned reoperation, respiratory failure, wound disruption, and bleeding requiring transfusion.

Though liver biopsy remains the gold standard for the diagnosis of liver fibrosis and cirrhosis, in recent years various noninvasive surrogate tests for the presence of liver disease have been developed. One of these is the aspartate APRI, which has been validated as a predictor of liver disease across a number of disease etiologies [23−26]. In a meta-analysis, APRI marked the presence of liver fibrosis with 77% sensitivity and 72% specificity [25]. The MELD-Na score is an extension of the traditional MELD score, which has been shown to outperform the MELD score in predicting outcomes following surgery in patients with liver disease [27−33]. Recently, a combined model utilizing both APRI and MELD-Na scores has been used to assess both the presence and severity of underlying liver disease in surgical patients based on preoperative laboratory values [13, 16]. These values, which include serum AST, sodium, creatinine, BUN, and bilirubin levels, are all readily available within in the NSQIP dataset, thus allowing for the

Table 2
Preoperative laboratory values in patients with liver disease

		Healthy liver	Mild disease	Advanced disease	Unknown liver function*	Total	p Value	Healthy liver %	Mild disease %	Advanced disease %	Unknown liver function %	Total %
Total	–	20,404	467	336	34,195	55,402		96.2	2.2	1.6	60.7	–
Sodium (meq/L)	Low (<135)	1,139	0	102	1,300	2,541	<.001	5.6	0.0	30.4	4.8	5.3
	Normal	1,9159	467	234	25,593	45,453		94.4	100.0	69.6	95.2	94.7
	Unknown†	106	0	0	7,302	7,408		0.5	0.0	0.0	21.4	13.4
BUN (mg/dL)	High (>20.0)	3,497	64	104	3,916	7,581	<.001	17.4	13.7	31.0	15.2	16.2
	Normal	1,6635	402	231	21,916	39,184		82.6	86.3	69.0	84.8	83.8
	Unknown	272	1	1	8,363	8,637		1.3	0.2	0.3	24.5	15.6
Creatinine (mg/dL)	High (>1.2)	1,768	13	99	2,051	3,931	<.001	8.7	2.8	29.5	7.7	8.2
	Normal	18,543	454	237	24,664	43,898		91.3	97.2	70.5	92.3	91.8
	Unknown	93	0	0	7,480	7,573		0.5	0.0	0.0	21.9	13.7
Albumin (g/dL)	Low (<3.5)	1,757	89	158	155	2,159	<.001	8.9	19.5	48.5	9.5	9.8
	Normal	17,940	368	168	1,472	19,948		91.1	80.5	51.5	90.5	90.2
	Unknown	707	10	10	32,568	33,295		3.5	2.1	3.0	95.2	60.1
Bilirubin (mg/dL)	High (>1.0)	1,077	51	110	73	1,311	<.001	5.4	10.9	32.7	11.0	6.2
	Normal	18,738	416	226	589	19,969		94.6	89.1	67.3	89.0	93.8
	Unknown	589	0	0	33,533	34,122		2.9	0.0	0.0	98.1	61.6
AST (U/L)	High (>40)	1,129	408	284	221	2,042	<.001	5.5	87.4	84.5	40.6	9.4
	Normal	19,275	59	52	324	19,710		94.5	12.6	15.5	59.4	90.6
	Unknown	0	0	0	33,650	33,650		0.0	0.0	0.0	98.4	60.7
Alkaline phosphatase (U/L)	High (>125)	1,024	57	100	54	1,235	<.001	5.2	12.3	30.3	7.9	5.8
	Normal	18,833	408	230	630	20,101		94.8	87.7	69.7	92.1	94.2
	Unknown	547	2	6	33,511	34,066		2.7	0.4	1.8	98.0	61.5
White blood cells (cell/μL)	High (>11,000)	1,931	24	52	2,227	4,234	<.001	9.5	5.2	15.5	7.7	8.4
	Low (<4,500)	1,137	64	57	1,548	2,806		5.6	13.8	17.0	5.3	5.6
	Normal	17,320	377	227	25,260	43,184		85.0	81.1	67.6	87.0	86.0
	Unknown	1,947	26	52	7,387	5,178		8.7	5.3	13.4	20.3	9.3
Hematocrit (%)	High (>45)	3,460	97	39	5,204	8,800	<.001	17.0	20.8	11.6	17.5	17.3
	Low (<38)	1,903	53	140	1,787	3,883		9.3	11.4	41.7	6.0	7.6
	Normal	1,5004	316	157	22,698	38175		73.7	67.8	46.7	76.5	75.1
	Unknown	3,497	98	39	9,710	4,544		14.7	17.4	10.4	24.6	8.2
PTT (seconds)	High (>35)	891	28	51	904	1874	<.001	6.3	6.8	18.4	5.3	5.8
	Normal	1,3324	382	226	16,243	30,175		93.7	93.2	81.6	94.7	94.2
	Unknown	6,189	57	59	17,048	23353		30.3	12.2	17.6	49.9	42.2
INR	High (>1.2)	355	3	85	314	757	< 0.001	2.3	0.6	25.3	1.6	2.1
	Normal	1,5309	464	251	18,992	35,016		97.7	99.4	74.7	98.4	97.9
	Unknown	4,740	0	0	14,889	19629		23.2	0.0	0.0	43.5	35.4
Platelets (1,000 cells/μL)	Low (<150)	837	171	191	1,320	2,519	<.001	4.1	36.6	56.8	4.6	5.0
	Normal	19,567	296	145	27,674	47,682		95.9	63.4	43.2	95.4	95.0
	Unknown	0	0	0	5,201	5,201		0.0	0.0	0.0	15.2	9.4

BUN = blood urea nitrogen; AST = aspartate transaminase; PTT = partial thromboplastin time; INR = international normalized ratio for prothrombin time.

* Patients with undetermined liver function were excluded from chi-squared statistical testing.

† Unknown percentages are expressed as a fraction of all cases (known and unknown). All other percentages are expressed as a fraction of all cases whose value is known.

Table 3
Thirty-day outcomes in patients with liver disease

		Healthy Liver	Mild disease	Advanced disease	Unknown liver function*	Total	p Value	Healthy liver %	Mild Disease %	Advanced disease %	Unknown liver function %	Total %
Mortality	Dead	121	8	17	104	250	<.001	0.6	1.7	5.1	0.3	0.5
	Alive	20,283	459	319	34,091	55,152		99.4	98.3	94.9	99.7	99.5
	Unknown†	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Morbidity	Complicated	1,792	55	106	2,071	4,024	<.001	8.8	11.8	31.5	6.1	7.3
	Uncomplicated	18,612	412	230	32,123	51,377		91.2	88.2	68.5	93.9	92.7
	Unknown	0	0	0	1	1		0.0	0.0	0.0	0.0	0.0
Hospital LOS (SD)	Number of days	3.3	5.3	10.0	2.4	2.8	<.001	6.5	9.8	13.2	6.5	6.6
	Unknown	16	1	4	20	41		0.1	0.2	1.2	0.1	0.1
Readmission	Readmitted	886	17	29	1,026	1,958	.001	5.5	4.6	10.7	3.8	4.5
	Not readmitted	15,367	350	241	25,808	41,766		94.5	95.4	89.3	96.2	95.5
	Unknown	4,151	100	66	7,361	11,678		20.3	21.4	19.6	21.5	21.1
Unplanned reoperation	Complicated	539	19	37	699	1,294	<.001	2.6	4.1	11.0	2.0	2.3
	Uncomplicated	19,865	448	299	33,495	54,107		97.4	95.9	89.0	98.0	97.7
	Unknown	0	0	0	1	1		0.0	0.0	0.0	0.0	0.0
Surgical site infection	Complicated	234	6	13	355	608	<.001	1.1	1.3	3.9	1.0	1.1
	Uncomplicated	20,170	461	323	33,840	54,794		98.9	98.7	96.1	99.0	98.9
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Pneumonia	Complicated	252	12	20	274	558	<.001	1.2	2.6	6.0	0.8	1.0
	Uncomplicated	20,152	455	316	33,921	54,844		98.8	97.4	94.0	99.2	99.0
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
PE-DVT	Complicated	183	6	8	178	375	.014	0.9	1.3	2.4	0.5	0.7
	Uncomplicated	20,221	461	328	34,017	55,027		99.1	98.7	97.6	99.5	99.3
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Respiratory failure	Complicated	313	20	36	301	670	<.001	1.5	4.3	10.7	0.9	1.2
	Uncomplicated	20,091	447	300	33,894	54,732		98.5	95.7	89.3	99.1	98.8
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Sepsis	Complicated	210	8	23	154	395	<.001	1.0	1.7	6.8	0.5	0.7
	Uncomplicated	20,194	459	313	34,041	55,007		99.0	98.3	93.2	99.5	99.3
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
UTI	Complicated	243	4	15	260	522	<.001	1.2	0.9	4.5	0.8	0.9
	Uncomplicated	20,161	463	321	33,935	54,880		98.8	99.1	95.5	99.2	99.1
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Stroke	Complicated	35	2	1	37	75	.38	0.2	0.4	0.3	0.1	0.1
	Uncomplicated	20,369	465	335	34,158	55,327		99.8	99.6	99.7	99.9	99.9
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Required transfusion	Complicated	525	18	46	504	1,093	<.001	2.6	3.9	13.7	1.5	2.0
	Uncomplicated	19,879	449	290	33,691	54,309		97.4	96.1	86.3	98.5	98.0
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Cardiac event	Complicated	107	1	12	114	234	<.001	0.5	0.2	3.6	0.3	0.4
	Uncomplicated	20,297	466	324	34,081	55,168		99.5	99.8	96.4	99.7	99.6
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0

Table 3 (*Continued*)

		Healthy Liver	Mild disease	Advanced disease	Unknown liver function*	Total	p Value	Healthy liver %	Mild Disease %	Advanced disease %	Unknown liver function %	Total %
Renal failure	Complicated	26	1	5	33	65	<.001	0.1	0.2	1.5	0.1	0.1
	Uncomplicated	20,378	466	331	34,162	55,337		99.9	99.8	98.5	99.9	99.9
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0
Wound disruption	Complicated	40	2	5	57	104	<.001	0.2	0.4	1.5	0.2	0.2
	Uncomplicated	2,0364	465	331	34,138	55,298		99.8	99.6	98.5	99.8	99.8
	Unknown	0	0	0	0	0		0.0	0.0	0.0	0.0	0.0

LOS = length of stay; SD = standard deviation; VTE = venous thromboembolism; UTI = urinary tract infection.

* Patients with undetermined liver function were excluded from chi-squared statistical testing.

† Unknown percentages are expressed as a fraction of all cases (known and unknown). All other percentages are expressed as a fraction of all cases whose value is known.

assessment of underlying liver function in our large study population.

Liver disease has previously been shown to correlate strongly with poor surgical outcomes across a wide spectrum of surgical procedures, including cardiac surgery [3–5], abdominal surgery [3–10], bariatric surgery [11], head and neck surgery [12,13], orthopedic surgery [14], and trauma [15]. Two prior studies could be identified measuring the effect of liver disease in spinal surgery. Bessey et al. studied 10,841 patients with cervical spine trauma from the Massachusetts Statewide Inpatient Sample and identified 117 patients with documented chronic liver disease [20]. These patients experienced significantly greater rates of mortality, morbidity, failure-to-rescue, and extended length of hospital stay, which generally agrees with the results of the present study. However, this study did not comment on the specific postoperative complications that may be driving poor outcome in cirrhotic patients. Bessey et al. also did not study the severity of liver disease within the cirrhotic population or the relationship between disease severity and outcome. Liao et al. presented 29 patients with confirmed liver cirrhosis from a single institution, and compared outcomes in these patients with a cohort of matched controls following instrumented lumbar surgery [19]. No mortalities were reported in the cirrhotic group, but these patients did experience a significantly increased rate of complications, including wound infection, respiratory failure, renal failure, and bleeding. Again, these results in a much smaller set of patients largely agree with the findings of the present study.

Chronic liver disease is a multisystem process, and its effect on surgical outcomes likely stems from a mix of factors, including coagulopathy, immunocompromise, impaired wound healing, respiratory dysfunction, renal dysfunction, encephalopathy, among others [16,17]. Coagulopathy may be one of the most important of these factors to the practicing surgeon. In our study, liver disease showed significant independent association with both postoperative bleeding and unplanned reoperation, and these complications in particular were major drivers of the increased morbidity seen in patients with liver disease. Prior work has shown that one of the major causes of unplanned reoperation within 30 days of spinal surgery is postoperative hematoma at the surgical site [34,35]. Thus, both of these important complications may stem from the coagulopathy of liver disease. Of note, the presence of any documented bleeding comorbidity, including a prolonged PTT in preoperative workup, was included as a covariate in our multivariate analysis. Thus, our results suggest that the coagulopathy of liver disease, insofar as it affects surgical outcomes, may not always be captured in routine coagulation studies. At the same time, this coagulopathy is shown to be an important driver of the increased perioperative morbidity seen in liver disease.

Table 4
Comparison of 30-day outcomes in patients with mild or advanced liver disease versus patients with healthy livers

	Unadjusted odds ratio (95% CI)	Bivariate p value	Adjusted ratio (95% CI)	Multivariable p value
Mortality	5.38 (3.48–8.33)	<.001	2.00 (1.12–3.55)	**.019**
Morbidity	2.61 (2.18–3.12)	<.001	1.35 (1.07–1.70)	**.012**
Hospital LOS 7+ days	3.45 (2.95–4.03)	<.001	1.73 (1.40–2.13)	**<.001**
Readmission	1.35 (0.99–1.84)	.055	0.83 (0.59–1.18)	.29
Unplanned reoperation	2.76 (2.08–3.67)	<.001	1.49 (1.05–2.11)	**.025**
Surgical site infection	2.09 (1.30–3.35)	.004	1.37 (0.78–2.41)	.27
Pneumonia	3.32 (2.28–4.83)	<.001	1.30 (0.79–2.13)	.30
VTE	1.96 (1.13–3.39)	.022	0.96 (0.48–1.92)	.91
Respiratory failure	4.81 (3.59–6.45)	<.001	1.80 (1.21–2.68)	**.004**
Sepsis	3.86 (2.63–5.67)	<.001	1.61 (.97–2.78)	.052
UTI	2.01 (1.25–3.23)	.008	1.32 (0.75–2.33)	.33
Stroke	2.18 (0.67–7.11)	.17	1.37 (0.35–5.35)	.65
Bleeding requiring transfusion	3.28 (2.50–4.29)	<.001	1.43 (1.01–2.02)	**.044**
Wound disruption	4.48 (2.00–10.02)	.002	2.82 (1.04–7.66)	**.042**
Cardiac event	3.12 (1.75–5.58)	.001	1.27 (0.60–2.71)	.53
Renal failure	5.90 (2.42–14.38)	.001	2.87 (0.84–9.78)	.091

CI, confidence interval; LOS, length of stay; SD, standard deviation; VTE, venous thromboembolism; UTI, urinary tract infection.
Statistically significant associations on multivariate analysis are shown in bold.

Respiratory failure was also an important complication noted to show significant independent association with liver disease in our study. Decompensated liver disease has previously been linked to acute respiratory failure, especially in the context of hepatopulmonary syndrome [36,37]. Hepatopulmonary syndrome is defined as hypoxemia in the setting of liver disease due to aberrant pulmonary vasoconstriction, and its prevalence in the cirrhotic population is estimated between 16% and 34% [38–41]. Last, liver disease also showed significant independent association with wound disruption in this study. Wound disruption typically results from superficial infection at the incision site, though impaired wound healing and impaired hemostasis may also play a role and liver disease may predispose patients to all three of these contributing factors [17,18].

Overall, our study shows that patients with underlying liver disease represent a high-risk population following surgery for degenerative conditions of the cervical spine. While it may not be surprising to many spinal surgeons that a medical comorbidity like liver disease negatively impacts outcomes, to our knowledge this study is the first to empirically confirm and quantify this effect within this patient population. This data may be of value to surgeons in patient counseling, informed decision-making, and the management of postoperative expectations among this patient population. These results also suggest that careful preoperative screening of underlying liver function by laboratory testing may prove valuable in many cases. Indeed, liver disease is an often asymptomatic and thus underdiagnosed condition. Preoperative screening with coagulation studies, complete blood count, and comprehensive metabolic panel ought to be considered in every patient. Furthermore, our results show clearly that the severity of underlying disease, assessed by laboratory testing, is closely associated with risk. These study results also lend support for certain preoperative interventions with the aim of mitigating risk in cirrhotic patients. Coagulopathy was shown to be a significant driver of poor outcome, and optimization of prothrombin time with intravenous vitamin K or cryoprecipitate may be indicated in certain cases. Nutritional support, correction of any other metabolic abnormalities, and aggressive management of ascites may also be recommended preoperatively. In general, given their risk profile as identified in this study, consultation with a gastroenterologist to aid in both risk assessment and medical optimization should be considered for patients with known or suspected liver disease prior to cervical spine surgery.

There are a few important limitations of this study that must be considered. First, our assessment of liver disease relied upon preoperative laboratory testing that was not completed for many patients in the NSQIP in the dataset. Full assessment could not be performed in 61.7% of patients meeting all other inclusion criteria. This discrepancy represents a potential source of selection bias, as patients with medical comorbidities or other preoperative risk factors may be more likely to have laboratory testing performed. Indeed, we noted that patients with undetermined liver function due to missing data had lower rates of morbidity and mortality and shorter mean length of hospital stay compared to the patients without liver disease that were included in the study. These findings suggest that we may overestimate the prevalence of liver disease in the study population and underestimate the surgical risk associated with liver disease by using a control population that is less healthy than true baseline. Another limitation of this study to consider is that the presence of liver disease was based on a surrogate marker, APRI, and not on definitive diagnostic testing. Lastly, the NSQIP dataset is meant to survey outcomes across a wide spectrum of surgical disciplines and lacks certain preoperative and postoperative

Table 5
Comparison of liver disease versus other risk factors in the effect on 30-day morbidity and mortality

	Mortality				Morbidity			
	Unadjusted odds ratio (95% CI)	Bivariate p values	Adjusted odds ratio (95% CI)	Multivariate p values	Unadjusted odds ratio (95% CI)	Bivariate p values	Adjusted odds ratio (95% CI)	Multivariate p values
Age Over 65	7.02 (5.35–9.23)	<.001	4.67 (2.94–7.47)	**<.001**	2.83 (2.65–3.02)	<.001	1.74 (1.53–1.98)	**<.001**
Gender (Male)	2.08 (1.59–2.73)	<.001	1.37 (0.91–2.08)	.13	1.25 (1.17–1.34)	<.001	1.21 (1.08–1.37)	**.002**
Race (non-white)	1.72 (1.25–2.37)	.001	1.27 (0.79–2.04)	.33	1.57 (1.44–1.71)	<.001	1.46 (1.27–1.68)	**<.001**
Obesity	0.74 (0.57–0.96)	.022	1.36 (0.90–2.05)	.15	0.88 (0.83–0.95)	<.001	0.95 (0.84–1.07)	.40
Smoking	0.68 (0.50–0.92)	.013	0.75 (0.44–1.29)	.30	0.89 (0.82–0.95)	.001	1.03 (0.90–1.18)	.67
Diabetes	1.87 (1.41–2.49)	<.001	1.09 (0.70–1.71)	.71	1.78 (1.65–1.92)	<.001	1.20 (1.04–1.38)	**.014**
Hypertension	2.78 (2.12–3.65)	<.001	1.24 (0.78–1.98)	.36	1.88 (1.76–2.01)	<.001	1.15 (1.01–1.31)	**.037**
Chronic steroid use	2.30 (1.47–3.65)	<.001	0.77 (0.39–1.53)	.45	2.20 (1.94–2.51)	<.001	1.40 (1.13–1.75)	**.003**
Preoperative sepsis	22.65 (16.32–31.45)	<.001	5.86 (3.45–9.95)	**<.001**	11.71 (9.94–13.78)	<.001	6.03 (4.61–7.89)	**<.001**
Disseminated cancer	32.49 (22.68–46.53)	<.001	11.77 (6.89–20.09)	**<.001**	9.74 (7.86–12.07)	<.001	3.32 (2.41–4.56)	**<.001**
Open of infected wound	17.05 (1..29–25.73)	<.001	2.08 (0.98–4.42)	.057	7.28 (5.94–8.92)	<.001	2.84 (2.07–3.90)	**<.001**
Pulmonary comorbidity	4.53 (3.45–5.94)	<.001	2.05 (1.31–3.21)	**.002**	2.40 (2.19–2.61)	<.001	1.75 (1.49–2.05)	**<.001**
Bleeding comorbidity	5.40 (4.09–7.13)	<.001	2.09 (1.35–3.24)	**.001**	2.73 (2.49–3.00)	<.001	1.61 (1.37–1.88)	**<.001**
Renal comorbidity	14.00 (8.32–23.57)	<.001	2.48 (0.94–6.54)	.067	7.82 (6.11–9.92)	<.001	2.61 (1.75–3.89)	**<.001**
Patient care setting (inpatient)	14.64 (5.45–39.32)	<.001	3.84 (0.93–15.87)	.063	5.16 (4.45–5.98)	<.001	3.37 (2.54–4.46)	**<.001**
Surgical approach (posterior)	2.77 (2.16–3.55)	<.001	1.80 (1.12–2.88)	**.015**	3.16 (2.96–3.37)	<.001	2.03 (1.76–2.34)	**<.001**
Fusion or instrumentation	0.83 (0.62–1.11)	.200	0.97 (0.60–1.59)	.92	0.92 (0.85–0.99)	.033	1.26 (1.08–1.47)	**.004**
Extent of surgery (single spinal level)	0.79 (0.68–1.03)	.09	0.83 (0.52–1.31)	.41	0.45 (0.42–0.48)	<.001	0.64 (0.56–0.73)	**<.001**
Liver disease	5.39 (3.48–8.33)	<.001	2.00 (1.12–3.55)	**.019**	2.61 (2.18–3.12)	<.001	1.35 (1.07–1.70)	**.012**

CI, confidence interval.
Statistically significant associations on multivariate analysis are shown in bold.

metrics of particular relevance to spinal surgery. These might include presenting symptoms and levels of preoperative neurologic impairment, as well as outcome metrics such as cerebrospinal fluid leak, postoperative hematoma, or nerve damage, though some of these may be captured indirectly as causes for unplanned reoperation. Nonetheless, this lack of clinical granularity somewhat limits the robustness of this study's findings.

Conclusion

This study is the first to quantify the impact of underlying liver disease on outcomes following surgery on the degenerative cervical spine, and one of only a few studies to address liver disease in the context of spinal surgery. We show in a multi-institutional cohort of 21,207 patients that the severity of underlying liver disease is strongly and independently associated increased morbidity, mortality and length of hospital stay. These results may prove of value to surgeons in preoperative counseling and decision-making for patients with liver disease, and in postoperative monitoring and management of these patients. At a minimum, these data illustrate the importance of identifying underlying liver disease in this surgical population.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.spinee.2018.07.010.

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