The effect of cirrhosis on trauma outcomes: A systematic review and meta-analysis

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BACKGROUND: The negative effect of cirrhosis on mortality following traumatic injury has been quantified in multiple observational studies. However, to our knowledge, the information contained in these studies has never been synthesized. The aims of this study were: (1) to determine the magnitude of the effect of liver cirrhosis on mortality, morbidity, and hospital course among trauma patients and (2) to analyze sources of study heterogeneity that may lead to differing estimates in the observed mortality rate among patients with cirrhosis.

METHODS: A systematic search of EMBASE and PubMed was conducted. Data were extracted from eligible studies and analyzed using a random-effects model to compare trauma outcomes in cirrhotic and noncirrhotic patients (PROSPERO Registration CRD42018088464). Mortality was the primary outcome. Secondary outcomes included complication rate, length of hospital stay, length of intensive care unit stay, and mechanical ventilation days.

RESULTS: Title and abstract review of 15,958 articles led to the identification of 31 relevant articles. Ultimately, 18 observational studies were included in this meta-analysis. The pooled effect sizes for mortality (odds ratio [OR], 4.52; 95% confidence interval [CI], 3.13–6.54) and complication rate (OR, 1.92; 95% CI, 1.30–2.85) were higher in the cirrhotic group than the noncirrhotic group. Trauma patients with cirrhosis also incurred longer hospital stays (mean difference, 3.81 days; 95% CI, 1.22–6.41) and longer ICU stays (mean difference, 2.40 days; 95% CI, 0.65–4.15). There was no difference in days spent on mechanical ventilation.

CONCLUSION: Preexisting liver cirrhosis is associated with increased mortality rate, complication rate, and length of hospitalization among trauma patients, even after adjusting for confounding factors and potential sources of between-study heterogeneity. Trauma patients with cirrhosis would benefit from heightened surveillance and injury prevention interventions. (*J Trauma Acute Care Surg.* 2020;88: 536–545. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic review and meta-analysis, level III.

KEY WORDS: Trauma; cirrhosis; mortality; complications; meta-analysis.

Unintentional injury, suicide, and homicide are among the five leading causes of death in people ages 10 years to 44 years, and unintentional injury is the third leading cause of death in the United States for all ages.[1] Additionally, studies have demonstrated that comorbid conditions, most notably liver cirrhosis, are independently associated with increased mortality in trauma patients.[2–5]

Cirrhosis affects over 633,000 adults in the United States (about 0.27% of the adult population) and, combined with chronic liver disease, is the twelfth leading cause of death in the United States.[6,7] The association between cirrhosis and increased mortality is magnified in patients undergoing surgery, whether elective or emergent.[8–10] Several studies, most of which are included in this meta-analysis, have documented the deleterious effects of cirrhosis in patients suffering traumatic injury.

The increased mortality observed in cirrhotic trauma patients can be partly explained by the pathologic changes attributed to cirrhosis. Cirrhosis is considered an immunosuppressed state[11] that increases susceptibility to infection in acute stress states, such as traumatic injury. Additionally, liver dysfunction caused by chronic liver disease leads to decreased production of clotting factors,[12] which contributes to the risk of bleeding following trauma.

Based on these risk factors, we expect our meta-analysis to demonstrate a positive association between cirrhosis and increased mortality in trauma patients. The aim of this systematic review and meta-analysis is to generate a pooled estimate of the effect size of cirrhosis on mortality in trauma patients and analyze sources of between-study heterogeneity that may have led to different estimates in mortality rate. Additionally, this investigation aims to analyze other outcomes in trauma patients with cirrhosis, such as length of hospital stay (HLOS), length of stay in the intensive care unit (ILOS), and mechanical ventilator days (MVD), which tend to be associated with higher morbidity and increased hospital costs.

METHODS

The protocol for this study was prospectively registered on PROSPERO under registration number CRD42018088464. This project was conducted and reported according to the Preferred Reporting Items for Systematic Reviews guidelines.[13]

Search Strategy

Articles were identified using the EMBASE and PubMed databases (from inception through June, 2018) and by manually searching the bibliographies of relevant articles. The search terms *("liver cirrhosis"/exp OR cirrhosis:ti,ab) AND (trauma:ti,ab OR traumatic:ti,ab OR "injury"/exp)* were used in the EMBASE database while the search terms *("liver cirrhosis"[MeSH Terms] OR cirrhosis[tiab]) AND (trauma[tiab] OR traumatic[tiab] OR injury[tiab] OR injuries[tiab] OR "Wounds and Injuries"[Mesh])* were used in PubMed. This initial search was not limited by language. Results from EMBASE and PubMed were exported to the reference management software EndNote X7.8 (Thomson Reuters, New York, NY).

Selection Process and Data Extraction

After removal of duplicate articles using the EndNote deduplication feature, the "Author" and "Journal" fields were hidden to avoid bias during study selection. Two investigators independently screened the titles and abstracts of all original articles and selected studies for full-text review based on specific inclusion criteria. Studies where inclusion criteria could not be determined solely by title and abstract screening were also selected for full-text review. Any discrepancy between reviewers was discussed and resolved.

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All of the studies included in this meta-analysis met the following criteria: (1) population: patients with burns, blunt or penetrating trauma, single or multiple injuries; (2) exposure: documented diagnosis of liver cirrhosis; (3) outcomes: mortality rate as primary outcome was required while the secondary outcomes of complication rate (reported as OR with 95% confidence interval [CI]), HLOS, ILOS, and MVD (reported as nonstandardized mean differences [MDs] with 95% CI) were optional; and (4) study design: prospective or retrospective cohort studies, or case-control studies.

Poster presentations, reviews, case reports, and other descriptive studies without comparative data were excluded. When multiple studies had overlapping patient populations, only the study with the longest period of observation and largest study population was included. Data were independently extracted by two investigators and compared for accuracy. Data extracted from the eligible articles included name of first author, publication year, study design, location, data source, study population size, inclusion and exclusion criteria, variables adjusted, measured outcomes, effect estimates, and CIs.

Quality Assessment

The Newcastle-Ottawa Scale,[14] a risk of bias assessment tool for observational studies, was adapted to assign a quality score to each study based on participant selection, comparability of the groups, ascertainment of exposure, outcome assessment, and sample size (Supplemental Digital Content 1, Table 2, http://links.lww.com/TA/B460).

Statistical Analysis

Statistical analysis was conducted using STATA/IC version 15.1 (StataCorp, College Station, TX). The random-effects model was used to generate a pooled estimate for each outcome of interest. The pooled effect size for mortality and complication rate was reported as an OR with 95% CI. The pooled effect sizes for HLOS, ILOS, and MVD were reported as MDs with 95% CI. Subgroup and sensitivity analyses were conducted to examine sources of between-study heterogeneity. Subgroup analysis explored the relationship between cirrhosis and mortality by injury type and variables adjusted. Statistical heterogeneity was

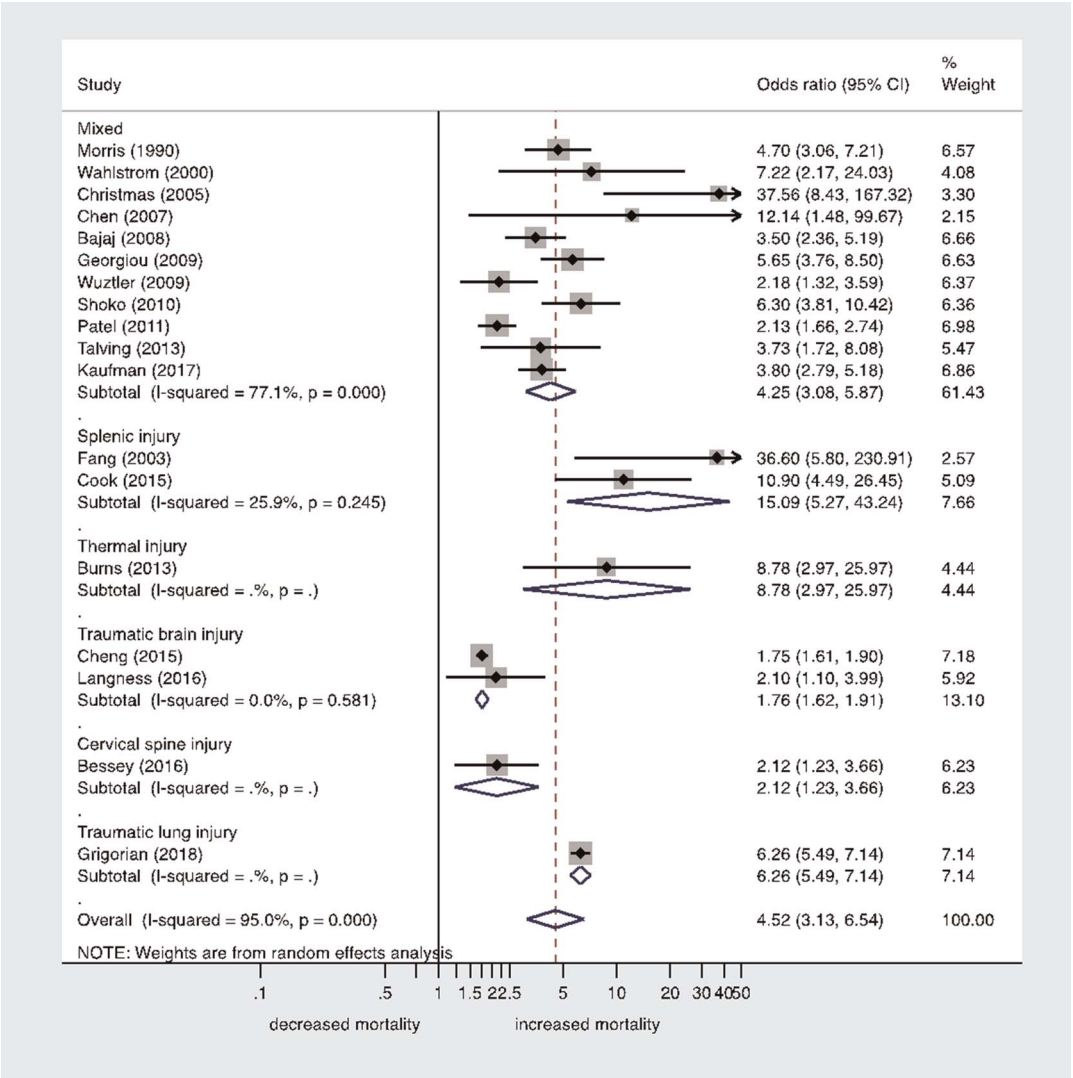

Figure 1. Flow diagram of study selection process.

TABLE 1. Characteristics of Studies Included in the Meta-Analysis

Study, Year (Reference)	Design	Country	Data Source —Trauma Level	No. CP/Total (% CP)	Ascertainment of Exposure	Inclusion (I) and Exclusion (E) Criteria	Matched (M) or Statistically Adjusted (A) Variables	Outcomes
Morris et al., 1990[3]	CC	United States	Acute care hospitals in California (1983) – unspecified trauma level	52/12,943 (0.4)	Chronic liver disease and cirrhosis (ICD-9 571)	I: Age ≥ 15, all trauma E: late effects, foreign bodies, and complications	A: Age, comorbid conditions, ISS	In-hospital mortality
Wahlstrom et al., 2000[24]	RC	United States	Hennepin County Medical Center (1997–1997) – level I	17/90 (19)	Biopsy-proven cirrhosis	I: Trauma patients requiring laparotomy and biopsy-proven cirrhosis	M: Age, sex, ISS, AIS	In-hospital mortality
Fang et al., 2003[35]	RC	Taiwan	Chang Gung Memorial Hospital (1997–2001) – unspecified trauma level	11/74 (14.9)	Clinical, pathologic, or radiographic evidence of cirrhosis	I: BSI	Failed to mention	In-hospital mortality, complications, HLOS, ILOS
Christmas et al., 2005[25]	RC	United States	Unspecified source population (1993–2003) – unspecified trauma level	61/217 (28)	Documented cirrhosis (previously documented biopsy or biopsy at time of operation)	I: All trauma	M: Age, sex, ISS, GCS	In-hospital mortality, HLOS, ILOS
Chen et al., 2007[26]	RC	China	College of Medicine, Zhejiang University (2000–2005) – unspecified trauma level	64/150 (43)	Documented cirrhosis (confirmed by past medical history, clinical examination, operation findings, biopsy, and/or imaging)	I: All trauma	M: Age, sex, AIS	In-hospital mortality, HLOS, ILOS
Bajaj et al., 2008[27]	RC	United States	Nationwide Inpatient Sample (2004) – unspecified trauma level	1,565/263,809 (0.6)	Cirrhosis (ICD-9 571.2, 571.5, 571.6), portal hypertension (572.3), spontaneous bacterial peritonitis (567.23), hepatic encephalopathy (572.2), variceal bleeding (456.0, 456.2), and ascites (789.5)	I: Diagnosis of MVC	A: Age, sex, race, ISS, insurance, hospital size, and location	In-hospital mortality, HLOS
Georgiou et al., 2009[28]	RC	United States	LAC + USC Medical Center (1997–2006) – level I	468/36,038 (1.3)	Documented cirrhosis (ICD-9 codes 571, 571.2, 571.5)	I: All trauma	A: Age, sex, ISS, head, chest, and extremity AIS, mechanism of injury (blunt vs. penetrating), laparotomy	In-hospital mortality, complications, HLOS, ILOS
Wutzler et al., 2009[2]	RC	Germany	Trauma Registry of the German Society for Trauma Surgery (2002–2007) – levels I, II, and III	162/5,163 (3.1)	Documented hepatitis/ cirrhosis	I: Multiple trauma, ISS ≥ 16 (or suspicion of severe head injury)	A: Pre-existing medical conditions, RISC score	In-hospital mortality
Shoko et al., 2010[4]	RC	Japan	Japan Trauma Data Bank (2004–2007) – some level I	9,272/11,590 (80)	Documented cirrhosis (ICD-10)	I: All trauma, age ≥16	A: Comorbidities, ISS	In-hospital mortality
Patel et al., 2011[5]	RC	United States	National Trauma Data Bank (2002–2006) – Levels I and II	898/2,592 (35)	Documented cirrhosis (chart abstraction by trauma registrar)	I: All trauma	M: Age, sex, injury type (blunt, penetrating, burn), each of the top 3 regional AIS values, ISS	In-hospital mortality, complications, HLOS, ILOS, MVD

TABLE 1. *(Continued)*

Study, Year (Reference)	Design	Country	Data Source —Trauma Level	No. CP/Total (% CP)	Ascertainment of Exposure	Inclusion (I) and Exclusion (E) Criteria	Matched (M) or Statistically Adjusted (A) Variables	Outcomes
Burns et al., 2013[29]	RC	United States	US Army Institute of Surgical Research Burn Center (2003–2010) – unspecified trauma level	24/808 (3)	Documented cirrhosis (hospital electronic medical records and/or autopsy reports)	I: Thermally injured E: Battlefield, mechanical, chemical or electrical injuries	A: Age, total body surface area burned, full thickness burn size, inhalation injury	In-hospital mortality
Talving et al., 2013[23]	PC	United States	LAC + USC Medical Center (2008–2011) – level I	92/276 (33)	Documented cirrhosis (based on medical history, radiologic findings, laboratory profiles, and intraoperative findings)	I: All trauma	M: Age, sex, mechanism of injury, AIS for each body region, ISS, GCS, hypotension, surgical interventions at admission	In-hospital mortality, complications, HLOS, ILOS, MVD
Cheng et al., 2015[30]	RC	Taiwan	National Health Insurance Research Database in Taiwan (1997–2007) – unspecified trauma level	2,432/7,296 (33)	Documented alcoholic cirrhosis and cirrhosis without mention of alcohol (ICD-9 codes 571.2, and 571.5)	I: Undergoing brain surgery for TBI	A: Age, sex, MVD, ILOS, comorbidities, liver-related diseases	1-year mortality, HLOS, ILOS, MVD
Cook et al., 2015[32]	RC	United States	Pacific Northwest Trauma Research Consortium (1993–2003) – level I	67/306 (22)	Documented cirrhosis (clinical chart review)	I: Age ≥ 18, splenic injury	A: Age, ISS, splenic injury grade	In-hospital mortality
Bessey et al., 2016[31]	RC	United States	Massachusetts Statewide Inpatient Dataset (2003–2010) – unspecified trauma level	117/10,841 (1)	Chronic liver disease, chronic hepatitis, cirrhosis, or hepatic encephalopathy (ICD-9 codes 571.2–571.6, 572.2–572.8)	I: Cervical spine fracture or dislocation	A: Age, sex, race, insurance status, comorbidities, surgical intervention	In-hospital mortality, complications, HLOS
Langness et al., 2016[19]	RC	United States	University of California San Diego Trauma Center (2000–2013) – level I	65/260 (25)	Documented cirrhosis or end-stage liver disease on trauma registry	I: Isolated TBI, ISS ≤ 1 for all other body regions	M: Age, sex, injury mechanism, head AIS, ISS	In-hospital mortality, complications, HLOS, ILOS, MVD
Kaufman et al., 2017[33]	RC	United States	Levels I and II Pennsylvania trauma centers (2011–2014)	—/95,806 (–)	Documented cirrhosis on trauma registry	I: Age ≥ 18 E: Isolated hip fractures and injuries from drowning, poisoning, asphyxiation, or in-hospital injury; burn as primary injury	A: Age, sex, mechanism of injury, ISS, GCS, and SBP on admission, comorbidities	In-hospital mortality, infectious and noninfectious complications in the cirrhotic group
Grigorian et al., 2018[34]	RC	United States	National Trauma Data Bank (2007–2015) – unspecified trauma level	1,971/576,912 (0.34)	Documented cirrhosis ICD-9 codes 456–456.2, 571.2, 571.5	I: Traumatic lung injury	A: Age, sex, mechanism of injury, ISS, hypotension on admission, pre-existing COPD, development of ARDS, AKI, CVA, MI, pneumonia	In-hospital mortality, HLOS, ILOS

AIS, Abbreviated Injury Scale; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CC, case control; CP, cirrhotic patients; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; GCS, Glasgow coma scale; ISS, injury severity score; MI, myocardial infarction; MVC, motor vehicle crash; MVD, mechanical ventilator days; PC, prospective cohort; RC, retrospective cohort; RISC, revised injury severity classification; SBP, systolic blood pressure; TBI, traumatic brain injury.

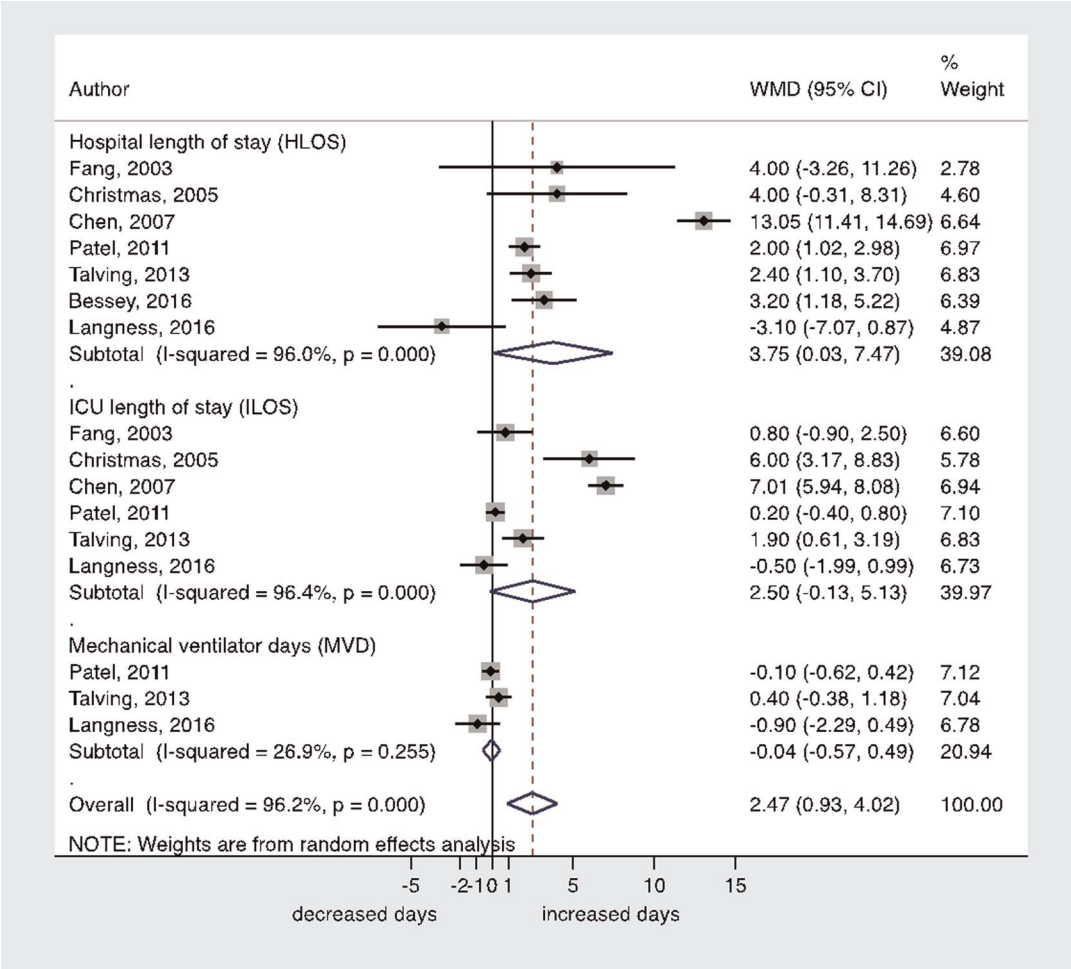

Figure 2. Forest plot comparing odds of mortality among cirrhotic vs. noncirrhotic trauma patients by injury type.

quantitatively determined using the I^2 score. Pooled analysis of a subset of studies was conducted to explore the relationship between mortality and the severity of liver cirrhosis as indicated by Child-Turcotte-Pugh (CTP) classification, with classes A, B, and C representing mild, moderate, and severe liver disease respectively. Subgroup analysis by MELD score was not possible as the studies that examined the relationship between mortality and MELD score[15–20] did not report MELD scores in a consistent manner, some reported mean score, others change in score, and others broke down scores into categories. A funnel plot and both Egger's[21] and Begg's[22] tests were used to assess publication bias.

RESULTS

Our search strategy identified 15,958 original articles, which underwent title and abstract screening (Fig. 1). Full-text analysis of potentially relevant articles led to the exclusion of 16 studies (Supplemental Digital Content 2, Table 1, http://links.lww.com/TA/B461). Eighteen studies were ultimately included

TABLE 2. Mortality as a Function of CTP Classification Among Cirrhotic Trauma Patients *n/total* (%)

Study, Year (Reference)	Class A	Class B	Class C	Statistically Significant Association
Wahlstrom et al., 2000[24]	4/7 (57.14)	3/8 (37.5)	1/2 (50)	No
Dangleben et al., 2006[36]	1/20 (0.05)	1/16 (6.25)	9/14 (64.3)	Yes
Chen et al., 2007[26]	5/44 (11.36)	2/15 (13.33)	1/5 (20)	No
Seamon et al., 2010[15]	0/6 (0)	7/30 (23.3)	9/13 (69.2)	Yes
Corneille et al., 2011[20]	3/40 (7.5)	7/71 (9.86)	4/12 (33.3)	No
Talving et al., 2013[23]	4/50 (8)	10/31 (32.3)	5/11 (45.5)	Yes
Total	17/167 (10.18)	30/171 (17.54)	29/57 (50.88)	Yes

*χ^2 analysis was used to compare mortality of class A versus B, $p = 0.050$; A versus C, $p < 0.001$; and B versus C, $p < 0.001$.

TABLE 3. Mortality Among Cirrhotic Versus Noncirrhotic Trauma Patients by Variables Adjusted

Variables (n)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)
Age (16)	4.16 (2.84–6.10)	12.04 (2.28–63.51)
Sex (13)	3.89 (2.48–6.09)	6.06 (3.44–10.66)
Injury severity (14)	4.50 (3.30–6.13)	3.85 (1.71–8.63)
Comorbidities (8)	3.45 (2.03–5.88)	6.26 (3.57–10.98)

n, number of studies that adjusted for that particular variable.

in our meta-analysis: one case-control study,[3] one prospective cohort study,[23] and 16 retrospective studies.[2,4,5,19,24–35] All articles were in the English language, and the majority were conducted in the United States (Table 1). All but two of the studies were of fair or good quality (Supplemental Digital Content 3, Table 3, http://links.lww.com/TA/B462). The quality of the two studies was considered poor because the case and control selection process was not described.[25,33]

Mortality

One study reported 1-year mortality while the rest reported in-hospital mortality (Table 1). The pooled analysis for the selected studies generated an odds ratio (OR) estimate (OR, 4.52; 95% CI, 3.13–6.54; $p < 0.001$) that represents a statistically significant increase in mortality among trauma patients with cirrhosis compared with trauma patients without cirrhosis (Fig. 2). The resultant I^2 of 95% is consistent with significant between-study heterogeneity. Excluding the only case-control study[3] did not significantly change the OR estimate (OR, 4.53; 95% CI, 3.08–6.65; $p < 0.001$), but excluding the two studies that were determined to have poor quality[25,33] led to a small decrease in the OR estimate (OR, 4.26; 95% CI, 2.87–6.32; $p < 0.001$) as did excluding studies that were not conducted in the United States (OR, 4.44; 95% CI, 3.21–6.15; $p < 0.001$).

Mortality by Injury Type

The OR for mortality comparing cirrhotic and noncirrhotic trauma patients differed dramatically by injury type (Fig. 2). The combined OR for mortality was greater for cirrhotic patients than for noncirrhotic patients in all studies, regardless of injury type. The two studies that analyzed mortality among patients with splenic injury generated a pooled OR (15.09) that was more than three times higher than the pooled OR generated by studies that had sample populations with mixed traumatic injuries (4.25).

Mortality as a Function of Child-Turcotte-Pugh Classification

Three[15,20,36] studies that were excluded from the main meta-analysis due to lack of a noncirrhotic comparison group were combined with three of the included studies[23,24,26] to generate pooled estimates of mortality by CTP classification (Table 2). One other study that analyzed mortality by CTP class was not included in the pooled analysis as the number of patients in each CTP category was not clearly indicated.[25] Independently, three studies had demonstrated a statistically significant association between more severe cirrhosis and increased mortality, while the other three did not find an association. Combining these studies resulted in a statistically significant increase in mortality, from 10.2% in CTP class A to 17.5% in class B and 50.9% in class C.

Mortality by Variables Adjusted

Studies that adjusted for age, sex, and comorbid conditions generated a lower mortality pooled estimate, while studies that adjusted for injury severity yielded a higher pooled estimate than studies that did not adjust for these variables (Table 3).

Complications

Six studies[5,19,23,28,31,35] reported an overall complication rate (Supplemental Digital Content 4, Figure 1, http://links.lww.com/TA/B463). Trauma patients with cirrhosis had a higher rate of complications than trauma patients with no cirrhosis (OR, 1.92; 95% CI, 1.30–2.85; $p = 0.001$; $I^2 = 74.9\%$). Among studies that reported specific complications, acute respiratory distress syndrome,[28] coagulopathy,[28] sepsis,[23,28] and urinary tract infection[5] were significantly more common in the cirrhotic group. One study[23] found that renal failure was also more common among cirrhotic trauma patients while two studies[5,28] did not find a statistically significant association between cirrhosis and worsening renal function following traumatic injury.

Hospital Course

The pooled MD in HLOS was 3.81 days greater for cirrhotic patients than for noncirrhotic patients (Supplemental Digital Content 5, Figure 2, http://links.lww.com/TA/B464). Cirrhotic patients also appeared to have a longer ILOS (MD 2.40 days; 95% CI 0.65–4.15; $p < 0.007$; $I^2 = 95.7\%$) (Supplemental Digital Content 6, Figure 3, http://links.lww.com/TA/B465). The MD for the number of days spent on mechanical ventilation was not statistically significant (Supplemental Digital Content 7, Figure 4, http://links.lww.com/TA/B466).

Publication Bias

The funnel plot showed asymmetry, with small studies showing larger effect sizes (Fig. 3). However, Egger's test ($p = 0.065$) and Begg's test ($p = 0.426$) were inconsistent with publication bias.

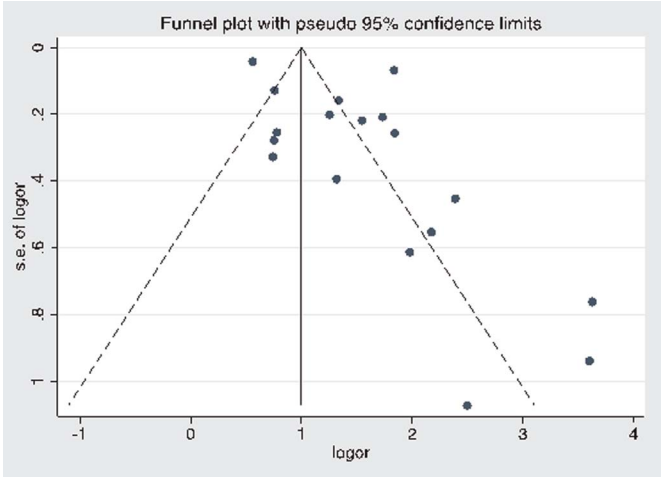

Figure 3. Asymmetric funnel plot showing small study effects, in which smaller studies at the bottom of the graph show larger mortality estimates.

DISCUSSION

To our knowledge, this is the first meta-analysis to examine the relationship between cirrhosis and in-hospital mortality among trauma patients. Although observational studies consistently report a positive association between cirrhosis and increased mortality after traumatic injury, the effect size of this association varies widely. Our analysis yielded a pooled mortality OR that was 4.52 times higher in cirrhotic patients with traumatic injuries compared with their noncirrhotic counterparts. Additionally, our results showed that cirrhotic trauma patients have more complications and incur longer hospital and ICU stays compared with noncirrhotic patients.

While three studies did not detect a significant difference in mortality as a function of CTP classification, the pooled estimate demonstrated that mortality was higher in patients with more severe cirrhosis. The inability of some individual studies to detect an association could be due to small sample size and limited statistical power. Additionally, the CTP classification system is limited by the difficulty of accurately assessing the severity of ascites and encephalopathy. Interobserver variability in the way these two subjective parameters are scored could lead to exposure misclassification. A method based solely on objective laboratory data, the MELD score, has been proposed to predict short- and intermediate-term mortality more accurately among cirrhotic patients in general and among cirrhotic patients awaiting liver transplantation in particular.[37,38] However, a study comparing chronic liver disease scoring systems found that CTP was a better predictor of hepatic complications and survival in hospitalized trauma patients than MELD.[15] More studies comparing these two scoring systems are needed.

Not surprisingly, cirrhotic patients with splenic injury had a much higher mortality risk than cirrhotic patients in the general injured population. However, only two studies contributed to the pooled effect size for mortality among cirrhotic patients with splenic injury and additional studies in this patient population are needed to generate a more precise estimate. The high mortality rate in cirrhotic patients with splenic injury appears to be associated with failure of nonoperative management (NOM), which is a widely used and effective treatment modality in hemodynamically stable patients. In Fang et al.,[35] both cirrhotic and noncirrhotic patients with blunt splenic injury (BSI) were managed following the same standard protocol, where hemodynamic instability despite adequate resuscitation or hollow organ injury warranted laparotomy. Despite having lower injury severity scores and lower splenic injury severity grade, cirrhotic patients with BSI who initially underwent NOM had increased blood transfusion requirements, prompting surgical intervention, and a higher mortality rate than noncirrhotic patients with BSI. Among cirrhotic patients with BSI, those who died had worse coagulation parameters as evidenced by prolonged prothrombin time compared with patients who survived.[35] The higher than expected mortality rate and failure of NOM among cirrhotic patients with splenic injury warrants close monitoring, including a low threshold for admission to the ICU, and consideration of operative management despite stable hemodynamic status. Since transfusion requirements of more than 1 unit of blood and splenic injury grade III and higher have been identified as independent risk factors for failure of NOM, the presence of these characteristics should prompt an increased level of vigilance.[39]

In addition to heightened surveillance in the setting of BSI, patients with cirrhosis would also benefit from injury prevention interventions. Community-based interventions to increase helmet use among cyclists and seatbelt use among drivers have the potential to reduce morbidity and mortality among cirrhotic patients with traffic-related injuries. Because patients with cirrhosis are also at increased risk of falls and are more likely to sustain severe injuries compared with noncirrhotic patients,[40] measures to prevent falls should be encouraged by physicians.

The pooled estimate for mortality across studies that did not adjust for comorbid conditions was significantly higher than that reported by studies that adjusted for comorbidities. This suggests that adjusting for other possible confounders, such as age and injury severity, is not sufficient to eliminate the independent effect of comorbidity on mortality following traumatic injury among cirrhotic patients. It also suggests that in addition to cirrhosis, there are other comorbid conditions leading to worse trauma outcomes in this population. Medical conditions that have been identified as independent risk factors for increased mortality among trauma patients include coagulation disorders,[2–5] end-stage renal disease,[2] chronic obstructive pulmonary disease (COPD),[3,4] heart disease,[2,3] cancer,[2,4] hematologic disorders,[4] diabetes mellitus,[3] peripheral arterial occlusive disease,[2] and obesity.[41] Future research in this patient population should focus on investigating the independent impact of these more prevalent chronic conditions on mortality and complication rate.

Several mechanisms contribute to the higher mortality and complications in cirrhotic patients following traumatic injury. In addition to the well-documented risk of clotting and bleeding events due to impaired production of vitamin K-dependent factors[12] and increased susceptibility to infection,[11] chronic liver disease is also associated with osteoporosis.[42] There is evidence that cirrhotic patients have higher risks of orthopedic fractures compared with noncirrhotic patients.[43] Additional research is needed to determine whether decreased bone density makes cirrhotic patients more susceptible to bone fractures following even minor traumatic injury.

Strengths and Limitations

We conducted a very rigorous review of the literature, identifying studies that cover a wide range of traumatic injuries. Our study was strengthened by an in-depth analysis of possible sources of between-study heterogeneity and analysis of clinical outcomes other than mortality. There was consistency across the different outcomes examined, as cirrhotic trauma patients not only had an increased mortality rate but also a higher complication rate and a longer hospital stay and ICU stay compared with their noncirrhotic counterparts.

This analysis has some limitations. Patients with early cirrhosis may have been misclassified as noncirrhotic. Studies have shown that the diagnosis of cirrhosis via visualization of a diffusely nodular and firm surface of the liver is more accurate than a diagnosis made via histologic examination[44,45]; therefore, there is a higher probability of misclassified cases when biopsy is used for diagnosis compared with macroscopic examination. For studies using IDC codes to ascertain exposure, failure of

clinical personnel to correctly code a clinical diagnosis of cirrhosis may lead to exclusion of cases, causing cirrhotic patients to be misclassified as noncirrhotic. This misclassification of cases would bias measures of association toward the null, leading to an underestimate of the true mortality OR. Another limitation is that cirrhosis is not truly binary in clinical practice—it is more ordinal, with more advanced cirrhosis (by CTP or MELD score) usually portending worse disease and higher likelihood of death and complications. Since most administrative and trauma registry data rely on ICD codes, this nuance is lost. Additionally, due to the retrospective nature of most of the included studies, data required to calculate CTP or MELD score were often missing.

Confounding also affects the validity of the included studies. While most studies made an effort to control for potential confounders (age, sex, injury severity, and comorbid conditions) through matching or statistical analysis, these variables were not uniformly addressed. Importantly, while three studies provided information on the etiology of cirrhosis (viral vs. alcoholic and alcoholic vs. nonalcoholic), confounding by these variables was not assessed.[26,27,32] Patients with alcoholic liver cirrhosis may be at higher risk of traumatic injury due to alcohol intoxication.

Among studies that analyzed the effect of cirrhosis on ICU length of stay, only one specified the type of ICU patients were admitted to.[23] Since the management of traumatic injury may vary by ICU type, the relationship between cirrhosis and trauma outcomes is likely to be modified or confounded by this variable. Unfortunately, due to the limited data provided, it was not possible to conduct a subgroup analysis to further characterize this relationship.

Publication bias could be a threat to the validity of this meta-analysis. The presence of publication bias means that studies with negative results large enough to counteract the large positive effect sizes of the studies included in this meta-analysis have not been published, or if they have, we missed them due to limitations in our search. While the funnel plot asymmetry can indicate publication bias, two widely used methods for assessing publication bias, Egger's test and Begg's test, yielded a p value greater than 0.05, inconsistent with publication bias. Funnel plot asymmetry can also be due to chance or, as in this case, it can be attributed to true heterogeneity.[46]

CONCLUSION

Cirrhosis is associated with increased mortality among trauma patients, and this association varies according to age, injury type, injury severity, and constellation of coexisting medical conditions. While the effect of cirrhosis on several in-hospital outcomes has been widely studied, studies analyzing the long-term effects of cirrhosis on mortality, quality of life, and functional status after traumatic injury are lacking. From a public health perspective, interventions aimed at reducing traumatic injury in the general population, and more specifically in patients with chronic liver disease, are greatly needed. Even if cirrhotic patients constitute a small subset of the trauma population, their high burden of complications and mortality warrants rapid diagnosis and treatment of injuries. Irrespective of injury type and injury severity, these patients may benefit from preemptive admission to the ICU, where they can be closely monitored. The results from this meta-analysis underscore the need for optimizing the medical and surgical management of trauma patients with cirrhosis.

AUTHORSHIP

E.S. participated in the study concept and design. E.S. and P.L. participated in the acquisition and analysis of data. E.S. and C.J. participated in interpretation of data. E.S. participated in the drafting of the article. C.J., S.L., A.N., P.L. participated in the critical revision of the article. A.N. participated in the administrative support. All authors reviewed and approved the final article.

DISCLOSURE

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