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Association of Liver Function Serum Markers and Unfavorable Outcomes in Traumatic Liver Injury Patients

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ABSTRACT

OBJECTIVE To evaluate serum markers in liver function tests (LFT) at various intervals after traumatic liver injury to identify serum markers associated with unfavorable outcomes.

METHODS A retrospective cohort analysis was conducted of trauma center patients older than 18 years with traumatic liver injury. Liver function test (LFT) results of patients with favorable and unfavorable outcomes were compared at different post-injury time points. Statistical significance was established as *p*-value less than 0.05.

RESULTS Of the 206 patients with severe liver injuries in the unfavorable outcome group, 119 (57.8%) needed intervention. Aspartate aminotransferase (AST) and alanine transaminase (ALT) were seen to increase in correlation with injury severity at initial admission. On days 1-5 and 6-10 after admission, the unfavorable outcome group had a slower decline in AST. In the unfavorable group, total bilirubin (TB) and direct bilirubin (DB) levels rose significantly 5 days after the injury and were higher than normal with a higher odds ratio (OR) of unfavorable outcome 11-15 days after injury in multivariable analysis [OR (95% confidence intervals): 2.7 (1.02-7.37) and 6.9 (1.08-44.14), respectively].

CONCLUSIONS Liver function tests can help identify individuals at risk for traumatic liver injury complications. Elevated levels of TB and DB are statistically significantly associated with adverse outcomes, particularly after day 5 following the injury. Early repeating LFT in first five days after injury may be less beneficial in determining patient risk. Blood test results may be affected by the amount of fluid resuscitation, particularly on the first day of admission in cases of high-grade injuries.

KEYWORDS aspartate aminotransferase, liver injury, liver function test, unfavorable outcome, alanine transaminase, bilirubin

INTRODUCTION

The liver is frequently affected by abdominal trauma. Surgical therapy is dependent on the patient's hemodynamics (1). In cases receiving non-operative treatment, patients must be hospitalized for one to two weeks and are often discharged within two weeks (2,3). In some cases, non-operative treatment may be unsuccessful and the patient may then need intervention such as interventional radiology or

surgery (4,5). Complications after non-operative management can include bile leakage, bile collection or biloma, re-bleeding, infected hematoma, or intra-abdominal abscess, with mortality being the worst result (6,7). Negative medical outcomes have a significant impact on patients and can prolong their hospital stay. Patients' symptoms, laboratory test results, and radiologic findings should be taken into account in the clinical assessment of these cases. The liver function serum markers are the most frequently requested laboratory test. Based on previous studies, individuals with severe liver injury have higher alanine transaminase (ALT) and aspartate aminotransferase (AST) levels. Higher levels of liver enzyme correlate with higher severity of damage (8-11). Recommendations for follow-up liver function serum marker testing have not yet been established (6). The purpose of this study was to observe the changes in serum markers in liver function tests after traumatic injury to determine the most accurate serum marker associated with unfavorable outcomes which could potentially assist in the prognosis and follow-up of these patients.

METHODS

Population

We conducted a retrospective observational analysis using hospital and trauma center database information. Our hospital is a level 1 trauma center for tertiary referrals located in the northern region of Thailand. From March 2006 to June 2015, we identified patients included in the hospital trauma registry database using the category S36 of The International Statistical Classification of Diseases and Related Health, 10th Revision (ICD10). The inclusion criteria were individuals over the age of 18 who had thoracoabdominal or abdominal trauma with liver injury and who had had a liver function test (LFT) performed after the injury. Exclusion criteria included individuals with known abnormal LFT or absence of LFT data, cases where the degree of injury could not be determined, and patients who were lost to follow-up.

Ethics

This study was approved by Ethical Review Committee of the Faculty of Medicine, Chiang Mai University. The approval registration identification number is SUR-2558-03527

Definition, data collection, and statistical analysis

This study defined unfavorable outcomes as patients who died, required surgery or other interventions, were in the hospital for more than two weeks, or experienced post-treatment problems such as bile collection or biloma, re-bleeding, pseudoaneurysm, intra-abdominal abscess, and surgical site infection.

Patients' age, gender, mechanism of injury, shock grade, injury severity score (ISS), treatment, intensive care unit and hospital length of stay, outcome, and complications were documented. The results of liver function tests (LFT) conducted at various times (including admission, during the first five days after injury, the sixth to tenth day after injury, and the eleventh to fifteenth day after injury) were analyzed. The relevant liver function blood indicators were aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TB), and direct bilirubin (DB).

STATA version 14 software was used for the analysis. The continuous variables for two predictors were examined using the t-test or the Rank-sum test, and the multiple predictors were analyzed using either the ANOVA or the Kruskal-Wallis test. Findings were made based on the distribution of the data. For categorical data, the chi-square test was used. Results of the multivariable analysis include the adjusted odds ratio together with the 95% confidence interval (95% CI) of the outcomes. Statistical significance was set at p-values lower than 0.05.

RESULTS

Demographics and outcomes

A total of 433 patients were included in the database for the 110 months period of the study. Of that total, 227 patients were excluded (Figure 1). Data for the remaining of 206 patients with liver injury was analyzed of whom 87 were treated non-operatively without any complications, while 119 (57.2%) had an unfavorable outcome. Of the unfavorable results, 15 patients died, 83 survived but needed intervention, 4 patients

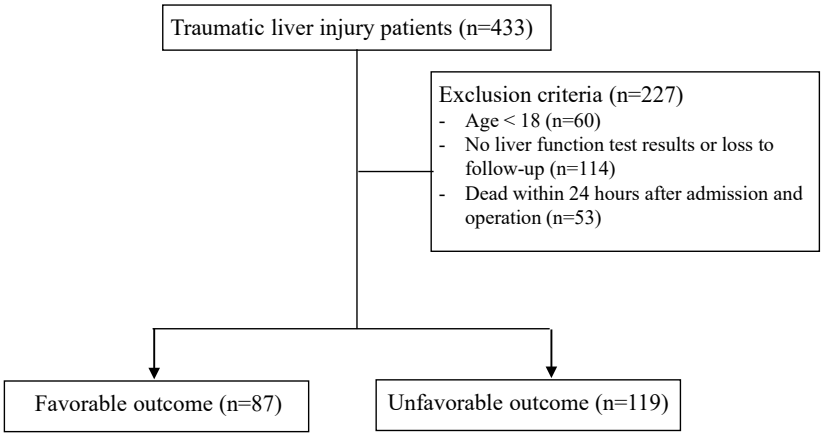

Figure 1. Study flow

survived with complications but without intervention, and 17 patients had a prolonged hospital stay of more than 2 weeks (Table 1). Both the favorable and unfavorable outcome groups were comparable for age, gender, severity of liver injury, degree of shock, injury severity score (ISS), and related solid organ injury. The only statistical significant difference was the kind of injury, with more patients in the unfavorable group sustaining penetrating injuries (Table 2). The liver injury related complications in the unfavorable outcomes group included biloma, bile collection or bile leakage (11/119, 9.2%), pseudoaneurysm of the hepatic artery and its branches (7/119, 5.9%), and infected hematoma (5/119, 4.2%).

Table 1. Unfavorable outcomes

Unfavorable events	Number (%) (n = 119)
Dead	15 (12.6)
Survived with complications and needed interventions	83 (69.7)
Survived with complications but no needed interventions	4 (3.4)
Hospital stay longer than 2 weeks	17 (14.3)

Table 2. Patient characteristics

Characteristic	Favorable Outcome (n = 87)	Unfavorable Outcome (n = 119)	*p*-value
Median age (IQR)	30 (22-40.5)	30 (22-41)	0.963
Male - n, (%)	70 (79.55)	102 (85.71)	0.242
Mechanism of injury - n (%)			0.015
Blunt	82 (93.18)	97 (81.51)	
Penetrating	6 (6.82)	22 (18.49)	
Grading of liver injury - n (%)			0.226
Grade I	10 (11.36)	13 (10.92)	
Grade II	27 (30.68)	23 (19.33)	
Grade III	23 (26.14)	27 (22.69)	
Grade IV	18 (20.45)	37 (31.09)	
Grade V	10 (11.36)	17 (14.29)	
Grade VI	0 (0.00)	2 (1.68)	
Shock at emergency department - n (%)			0.132
Class 1	42 (47.73)	39 (32.77)	
Class 2	25 (28.41)	37 (31.09)	
Class 3	17 (19.32)	33 (27.73)	
Class 4	4 (4.55)	10 (8.40)	
Injury severity score ISS (IQR)	24 (17-33)	24 (16-33)	0.667
Associated solid organ injury - n (%)	28 (31.82)	31 (26.05)	0.363

Association of liver function markers and outcomes

At the time of hospital admission, the AST and ALT levels in patients with liver damage were considerably higher than normal and were correlated with injury severity (p = 0.003 for AST and p = 0.001 for ALT) (Table 3). Even though the median levels of AST and ALT were lower in patients with grade VI injuries, the majority of those patients had an emergency operation. ALP, TB, and DB levels at the time of arrival in both groups were all within the normal range and did not show any signs of elevation in conjunction with the severity of the injury (p = 0.282 for ALP, p = 0.261 for TB, and p = 0.458 for DB). All grade VI injuries were fatal the day after an emergency operation despite rigorous resuscitation. The blood tests have been inaccurately low and diluted.

Comparison of each serum marker at various periods during hospitalization found that the serum AST levels were highest upon arrival then gradually decreased over time [median (IQR) 124.5 (73-410) at day 1-5, 41.5 (30-62) at day 6-10, and 35 (27-47), respectively]. AST levels in the unfavorable group were statistically higher than in the favorable group. AST levels in both groups decreased with time, but did so at a slower rate in the unfavorable group [median (IQR) 235 (99-735), p = 0.028 at day 1-5 and 59.5 (42 - 90.5), p = 0.008 at day 6-10]. In addition, levels remained above normal in the unfavorable group, but were tendency significantly higher only between days 11-15 [51 (32-68), p = 0.083]. (Table 4). Although serum ALT changed in the same direction as serum AST over time, there was no statistically significant difference in ALT between the favorable and unfavorable groups [191 (116-384) vs. 215 (98-432), p = 0.755 on days 1-5; 157.5 (75-340) vs. 250 (92-563), p = 0.088 on days 6-10; and 60 (33-85) vs. 53 (33-100), p = 0.909 at day 11-15. Although the median value of serum ALP increased with time, there was no significant difference between the groups (Table 4).

The admission values of markers for both TB and DB were normal with no statistically significant difference between the groups. The median value of both markers was elevated between days 1 and 5 and between days 6 and 10, while it declined between days 11-15. Statistically significant differences between the groups were only observed on days 6-10 (p = 0.033) and days 11-15 (p = 0.009) for TB, and on days 1-5 (p = 0.030), days 6-10 (p = 0.005), and days 11-15 (p = 0.012) for DB (Table 4 and Figure 2).

In order to investigate the association between liver function markers and the occurrence of an unfavorable outcome after liver injury, we performed multivariable analysis utilizing shock grade, ISS, mechanism of injury, and individual admission markers. Only TB and DB demonstrated a statistically significant association with an unfavorable outcome on days 6-10 and 11-15. There were no statistically significant differences in any of the liver function markers over the first five days (Figure 2).

Table 3. Liver function serum markers at admission and grading of liver injury

Serum marker	Grade I (n=23)	Grade II (n=30)	Grade III (n=50)	Grade IV (n=55)	Grade V (n=27)	Grade VI (n=2)	p-value
Aspartate aminotransferase Units/L (IQR)	183 (63-693)	261 (151-548)	319.5 (181-516)	517 (264-749)	526 (353-968)	189 (162-216)	0.003
Alanine transaminase Units/L (IQR)	77 (40-244)	157.5 (94-370)	183.5 (116-336)	304 (179-540)	344 (148-565)	145 (66-224)	0.001
Alkaline phosphatase Units/L (IQR)	62.5 (52-84)	59 (44-76)	61.5 (50-75)	61 (50-77)	58 (40-96)	29.5 (24-35)	0.282
Total bilirubin mg/dL (IQR)	0.54 (0.42-0.87)	0.60 (0.39-0.81)	0.56 (0.38-0.76)	0.70 (0.41-0.95)	0.69 (0.43-1.37)	0.50 (0.42-0.58)	0.261
Direct bilirubin mg/dL (IQR)	0.13 (0.10-0.25)	0.18 (0.11-0.22)	0.16 (0.12-0.24)	0.18 (0.12-0.29)	0.25 (0.11-0.33)	0.14 (0.05-0.22)	0.458

Table 4. Liver function serum markers at different periods after liver injury

Serum marker	N	Favorable Outcome	Unfavorable Outcome	*p*-value
Aspartate aminotransferase (units/L)				
Admission	206	388 (225-629)	364 (157-726)	0.440
Day 1 - 5	129	124.5 (73-410)	235 (99-735)	0.028
Day 6 - 10	100	41.5 (30-62)	59.5 (42-90.5)	0.008
Day 11- 15	64	35 (27-47)	51 (32-68)	0.083
Alanine transaminase (units/L)				
Admission	206	191 (116-384)	215 (98-432)	0.755
Day 1 - 5	129	157.5 (75-340)	250 (92-563)	0.088
Day 6 - 10	100	73.5 (49-113)	109 (59-157.5)	0.052
Day 11 - 15	64	60 (33-85)	53 (33-100)	0.909
Alkaline phosphatase (units/L)				
Admission	206	57 (48-77)	62 (44-77)	0.962
Day 1 - 5	129	59 (43-87)	63 (49-87)	0.608
Day 6 - 10	100	91.5(73-148)	111 (80.5-165)	0.139
Day 11 - 15	64	156 (102-247)	184 (122-247)	0.638
Total bilirubin (mg/dL)				
Admission	206	0.61 (0.42-0.81)	0.64 (0.39-0.96)	0.533
Day 1-5	129	1.22 (0.86-1.52)	1.28 (0.91-2.29)	0.312
Day 6-10	100	1.22 (0.79-1.83)	1.74 (0.90-4.77)	0.033
Day 11-15	64	0.79 (0.61-1.16)	1.35 (0.8-3.08)	0.009
Direct bilirubin (mg/dL)				
Admission	206	0.16 (0.1-0.24)	0.19 (0.12-0.27)	0.165
Day 1-5	129	0.32 (0.24-0.5)	0.47 (0.29-0.92)	0.030
Day 6-10	100	0.4 (0.24-0.61)	0.91 (0.32-2.96)	0.005
Day 11-15	64	0.34 (0.22-0.5)	0.56 (0.33-1.65)	0.012

DISCUSSION

In cases of abdominal trauma, the liver is the most often injured organ (12). The frequency of liver injuries varies by nation and historical period. According to the findings of Chien et al. from their population-based research in Taiwan, the incidence rate was 13.9 per 100,000 people, with both incidence and mortality rates increasing with age (13). Between 1975 and 1999 in a trauma center in the United States, the number of cases involving liver injuries caused by penetrating mechanisms remained constant over time, whereas the number of cases involving injuries caused by blunt mechanisms increased over the same period (14). The choice between operative management and non-operative management (NOM) was dependent on the patient's hemodynamic and overall health status. The World Society of Emergency Surgery (WSES) defines adult hemodynamic instability as an admission systolic blood pressure less than 90 mmHg with clinical evidence of hemorrhagic shock, alteration of consciousness and/or shortness of breath, or blood pressure greater than 90 mmHg but requiring bolus fluid or transfusion and/or vasoactive agents and/or base excess greater than -5 mmol/L or blood transfusion greater than 4 units within 8 hours of admission to hospital (12). NOM is the therapy of choice for all patients who are hemodynamically stable and have no other internal organ injuries requiring surgery (12).

During hospital admission, LFT is one of the most frequently conducted investigations. Bilirubin, ALT, AST, and APT are biochemical markers of liver injury (15). Albumin, bilirubin, and prothrombin time are hepatocellular function indicators (16). These are used in conjunction with clinical symptoms and radiologic results. However, there is no uniform recommended practice regarding the appropriate time(s) for repeating a laboratory test after an injury. A prospective observational study of 122 patients with blunt abdominal injury revealed that 97% of the patients had substantial elevations of ALT that were associated with hepatic injury. Additionally, 16% of the patients had elevated ALT levels without ultrasonographic

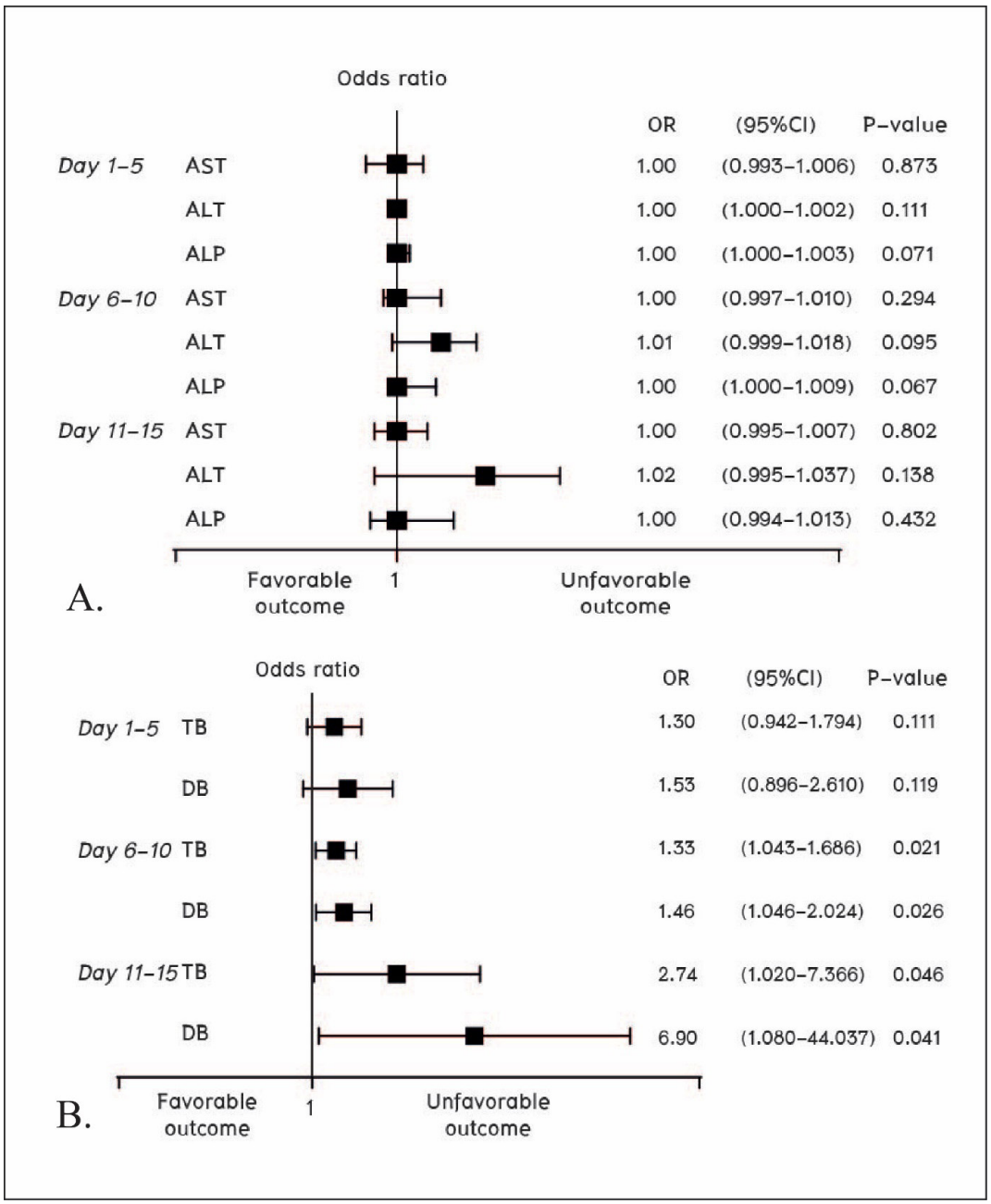

Figure 2. Multivariable analysis of liver enzyme at different periods [A] AST (aspartate aminotransferase), ALT (alanine transaminase), and ALP (alanine transaminase), [B] TB (total bilirubin), DB (direct bilirubin)

evidence . The authors suggested that elevated blood ALT was a sensitive diagnostic measure for blunt liver injury and was associated with the degree of the injury (8). According to the findings of research conducted in Singapore, an increase in ALT and AST levels of more than 2 times of normal level is a reliable indicator of hepatic injury [OR (95% CI): 8.44 (1.64-43.47)]. In our study, both AST and ALT were elevated upon admission and the level of AST and ALT correlated with the grading of damage except in grade VI injuries where both AST and ALT were artificially low. This might be a result of the dilution effect as grade VI patients commonly arrived with a more severe degree of shock and required a greater amount of fluid resuscitation. Comparing AST and ALT levels at different time points following an injury in the favorable and unfavorable groups, we found that the AST level upon admission was essentially same in both groups. However, at 1-5 and 6-10 days following injury, despite the impact of ALT having less influence on the difference between the groups than AST, both variables in the unfavorable group decreased at a slower rate than those in the favorable group. Considering the

shorter half-life in circulation of AST of about 17 hours versus about 47 hours for ALT (16), we can assume that the unfavorable group's livers continued to be injured even after the initial trauma, resulting in the continuing release of additional AST and ALT into the blood. ALP, on the other hand, did not vary between groups. Thus, based on our data, ALP may not be a suitable predictor for identifying potential negative outcomes. These results are consistent with previous research conducted in Singapore (10). These results might be explained by the prolonged half-life of AST and ALT of about one week in blood. These factors explain why ALP levels often increase late in cases of bile duct obstruction then decline slowly after resolution (16). AST and ALT elevation in different types of accidents, particularly acute muscle injuries without liver injury, could return a false positive high of AST and ALT, in which cases interpretation should proceed cautiously.

At the time of admission, the TB and DB levels in both groups were normal, but began to rise between days 6-10, particularly in the unfavorable group. Patients with unfavorable characteristics, e.g., high levels of TB and DB, were more likely to have biliary problems. In a recent study, the elevation of total bilirubin following blunt abdominal trauma was reported to be an independent risk factor for biliary injury (17). However, the number of patients in our study who had biliary problems was insufficient (9.2%) to evaluate this. To discover the precise level of aberrant TB or DB that might aid in predicting individuals at risk for biliary complications, subgroup analysis in the biliary complication group with more patients would be valuable. In a multivariable analysis with adjustment for the severity of shock, the injury severity score (ISS), the mechanism of injury, and the individual admission blood marker, TB and DB were the only statistically significant independent predictor variables of unfavorable outcomes for both days 6-10 and 11-15. Other serum markers (AST, ALT, and ALP) demonstrated almost no difference between the two patient groups at any of the time periods on multivariable regression analysis in our study (Figure 2). In situations where availability of resources is limited, we propose performing at least TB and DB during the second week after the injury. However, we were unable to establish the relative predictive power of these two markers during the first 5 days after injury.

A strength of this study was that no prior research has compared the levels of serum indicators at different times across patient groups with favorable and unfavorable outcomes. This study's findings might be put into practice, particularly in situations where resources are limited. This research also has limitations, first, because of its retrospective design and the lack of a defined protocol at our hospital for liver function follow-up testing following liver injury. The liver function tests were performed at various periods, and several patients lacked repeated LFTs. Thus, the sets of data collected for analysis on days 6-10 and 11-15 were less robust than those collected upon admission. In practice, if a patient's physical examination is normal, a repeat blood test is not often prescribed. A future prospective study may provide more accurate findings if this schedule for the LFT procedure is followed. Second, this study did not investigate differences in outcome between immediate and delayed surgery in liver injury patients. Therefore, the study was unable to determine the influence of surgery type or duration of surgery on outcomes.

CONCLUSIONS

The liver function test might be useful as a guide to identifying individuals who are susceptible to developing complications because of severe liver injury. A high level of AST and ALT in the first five days after trauma is associated with a more severe liver injury and adverse outcomes. Elevated levels of TB and DB are statistically significantly associated with unfavorable results, particularly from days 6-15 following injury, although repeated LFT during the first 5 days after injury does not assist in identifying patients likely to have unfavorable outcomes. In addition, a normal or mildly abnormal liver function test conducted a few days after admission cannot rule out the possibility that the patient is complication-free. However, blood test results may be influenced by the amount of fluid resuscitation, particularly on the first day of admission for severe injuries.

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CONFLICTS OF INTEREST

The authors of this study have no conflicts of interest.

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