ARTICLE IN PRESS

Injury, Int. J. Care Injured xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Injury

Journal homepage: www.elsevier.com/locate/injury

Hepatic dysfunction: A common occurrence in severely injured patients

, MBBCh (Wits)A. Saloojee, FCS(SA)[d], , MBChBD.L. Skinner, FCS(SA)[a,*],
, MBChB (Pret)E. Loots, FCS (SA)[b],
T.C. Hardcastle, MB,ChB(Stell); M.Med(Chir)(Stell); PhD, FCS(SA), Trauma Surgery(HPCSA), Honorary Clinical Fellow & Head[c],
D.J.J. Muckart, FRCS MMSc Crit Care (SA), Associate Professor[d]

[a] Department of Anaesthetics and Critical Care, Perioperative Research Group, University of KwaZulu-Natal, South Africa
[b] Department of Surgery, Inkosi Albert Luthuli Central Hospital and University of KwaZulu-Natal, South Africa
[c] University of KwaZulu-Natal Trauma Surgery Training Unit, Deputy Director: IALCH Trauma Service and Trauma ICU, KwaZulu-Natal Department of Health, South Africa
[d] Department of Surgery, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa

ARTICLE INFO

Keywords:
Trauma critical care
Hepatic dysfunction

ABSTRACT

Background: Hepatic dysfunction (HD) is a common finding in critically ill patients. The underlying pathophysiological process is one of either cholestasis or hypoxic liver injury (HLI). Using serum bilirubin, our study aimed to determine the incidence of HD in a critically ill trauma population, identify risk factors and analyse the impact on outcomes.

Methods: A retrospective observational study was performed on all patients admitted to the Level 1 Trauma Unit ICU at Inkosi Albert Luthuli Central Hospital in Durban, South Africa (IALCH) from 01/01/2012 until 31/12/2012. HD was defined as a total bilirubin greater than 34.2 μmol/l (2 mg/dL). Additional demographic, physiological, biochemical, and pharmaceutical risk factors for hepatic dysfunction were identified and recorded.

Results: Two hundred and twenty five patients were included in the study of whom 48 (21.3%) developed HD. An increased duration of ventilation (median 15 days [inter-quartile range 6–19] vs 6 days [IQR 3–11] $p < 0.001$), prolonged length of stay (median 19 days [IQR 8.5–31] vs 7 days [IQR 3–13] $p < 0.001$), and higher mortality rate (31.3% vs. 14.7% $p = 0.01$) were all significantly associated with HD. Shock on admission was twice as common in patients developing HD ($p < 0.001$). The only drugs associated with HD were piperacillin-tazobactam ($p < 0.001$) and enalapril ($p = 0.04$). On multivariable analysis however, HD was not associated with mortality.

Conclusion: HD was common in our study population, and was associated with other organ dysfunction, increased mortality and length of stay.

Introduction

Hepatic dysfunction in critical illness is due most frequently to either cholestasis or ischaemic hepatitis [1]. In addition, critically ill patients are exposed to a number of drugs which may contribute to hepatic dysfunction, namely antibiotics, benzodiazepines and analgesics. Contrary to initial reports suggesting that hepatic dysfunction is a late feature in critical illness, recent literature suggests that liver cell necrosis and cholestasis occur early and are risk factors for complications and increased mortality [1–3].

In contrast to the extensive literature on respiratory and renal dysfunction [4,5] there is a paucity of information on acute hepatic dysfunction associated with critical illness in trauma patients [2]. Although a number of objective scoring systems exist for liver disease such as the Child-Pugh and Model for End-Stage Liver Disease (MELD) in chronic hepatic disease [6] and the Kings College criteria for acute liver failure [7], no absolute definition of hepatic dysfunction in critically ill patients has been proposed. Serum bilirubin is the most commonly used indicator of liver dysfunction in general organ dysfunction scoring systems [8].

* Corresponding author.
E-mail address: drdavidskinner@gmail.com (D.L. Skinner).

http://dx.doi.org/10.1016/j.injury.2016.08.017
0020-1383/

Our study aimed to investigate the incidence of hepatic dysfunction, as defined by an increased serum bilirubin, amongst a cohort of critically ill trauma patients. Potential hepatic insults such as severity of injury, shock, sepsis, liver trauma, and drug administration were investigated as risk factors for the development of hepatic dysfunction. Outcomes evaluated were duration of ventilation, length of stay, and ICU mortality.

Patients, methodology & definitions

A retrospective observational study was performed on patients admitted to the Level 1 Trauma Intensive Care Unit (TICU) at Inkosi Albert Luthuli Central Hospital (IALCH) during the 12 month period January to December 2012. Patients who died within 12 h of admission were excluded from the study. The TICU is a ten bedded closed unit situated in KwaZulu-Natal, South Africa, serving a population base of approximately 10 million people. The TICU admits patients as a transfer from other hospitals lacking ICU facilities or directly from the scene of trauma via a resuscitation area in the hospital that is capable of performing emergency surgery.

All data were obtained from electronic patient chart records on the Medicom/Soarian® and Innovian® systems used at IALCH. Ethics approval (reference BE207/09) for retrospective database review was obtained prior to the commencement of the study.

Hepatic dysfunction (HD) was defined as a total serum bilirubin level >34.2 μmol/l (2 mg/dL) [9–11]. Hypoxic liver injury (HLI) was defined when a patient presented with acute circulatory or respiratory failure with subsequent increase in serum alanine aminotransferase (ALT) levels to 20 x upper limit of reference range (700 IU) [9].

Data extracted included:

- Pulse, blood pressure, temperature, arterial blood gas, full blood count, electrolytes on admission
- Admission, peak and discharge bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP).
- Sepsis, severe sepsis and septic shock as defined by the SIRS criteria [10]
- Shock requiring inotropic support on admission to the TICU
- Packed red blood cell (PRBC) and freeze dried plasma (FDP) transfusion
- Parenteral nutrition administration

The use of potential hepatotoxic drugs included;

- Antibiotics (amoxicillin-clavulanic acid, piperacillin-tazobactam and erythromycin),
- Sedatives and hypnotics (benzodiazepines and haloperidol),
- Cardiac rate controlling agents (atenolol and amiodarone),
- ACE inhibitors (enalapril)
- Analgesics (non-steroidal anti-inflammatory agents and intravenous paracetamol).

Liver trauma was graded according to the American Association for the Surgery of Trauma (AAST) liver injury scoring system and the Injury Severity Score (ISS) calculated [11]. Acute kidney injury (AKI) was diagnosed via serum creatinine measurement according to the Kidney Disease Improving Global Outcomes (KDIGO) system [12].

Outcome data extracted were duration of ventilation, length of ICU stay, and mortality.

Statistical analysis

Continuous data were reported by either the mean and standard deviation or by median and inter-quartile range. Range is reported for all ages. The $\chi 2$ test with continuity correction was used for categorical data, and Student's *t*-test and Mann-Whitney *U* test for continuous data where appropriate.

We conducted multivariable logistic regression to identity independent predictors for mortality. To avoid model overfitting, one factor was used for every 10 events. In the mortality prediction model we evaluated the following risk factors: ISS (categorised as <30 for the reference value, 30–45 and >45), HD, AKI, shock on presentation requiring inotropic support, septic shock in the ICU and the need for ventilation.

All *p*-values are reported to two decimal places and statistical significance was defined as a two-sided p-value ≤ 0.05. All data analyses were performed using SPSS 23.0 for Windows (SPSS, Chicago, IL).

Results

A total of 225 patients were included in the study (Table 1). The majority (76.9%) were severely injured young males (mean age 28.4yrs) with a median ISS of 25 (interquartile range [IQR] 16–34). 181 patients (80.4%) were referred from another hospital. The commonest mechanism of injury (80.0%) was blunt trauma. HD

Table 1
Demographics of all patients admitted to TICU January 2012 – December 2012.

Admission data	Total Population (n = 225)	Hepatic Dysfunction (n = 48)	No Hepatic Dysfunction (n = 177)	P Value
Age (mean, SD)	28.4 (14.7)	29.6 (11.8)	28.13 (15.0)	0.54
Male gender (n, %)	173 (76.9)	40 (83.3)	133 (75.1)	0.32
ISS (median, IQR)	25 (16–34)	25 (16–34)	25 (16–34)	0.54
Blunt trauma (n, %)	180 (80.0)	38 (79.2)	142 (80.2)	1.00
Penetrating trauma (n, %)	45 (20.0)	10 (20.8)	35 (19.8)	1.00
Liver trauma (n, %)	31 (13.8)	10 (20.8)	21 (11.9)	0.17
Temperature (mean, SD)	36.8(0.9)	36.9 (1.0)	36.8 (0.8)	0.41
SBP (mean, SD)	128.7 (26.5)	132.6 (24.9)	127.7 (27.0)	0.37
MAP (mean, SD)	88.5 (18.5)	89.1 (16.8)	88.3 (19.0)	0.92
Pulse (bpm) (mean, SD)	109.1 (23.1)	112.2 (24.0)	108.2 (23.9)	0.19
Shock requiring inotropes (n, %)	91 (40.4)	32 (66.7)	59 (33.3)	<0.001*
Mortality (n, %)	41 (18.2)	15 (31.3)	26 (14.7)	0.02*
Length of stay – days (median, IQR)	8 (4–17)	19 (8.3–31)	7 (3–13)	<0.001*
Length of ventilation – days (median, IQR)	7 (4–14)	15 (6–19)	6 (3–11)	<0.001*

* $p \leq 0.05$ SBP = Systolic Blood Pressure (mmHg) MAP = Mean Arterial Pressure (mmHg).

Table 2
Serum biomarkers of all patients admitted to the TICU from January 2012 to December 2012.

	Total Population (n = 225)	Hepatic Dysfunction (n = 48)	No Hepatic Dysfunction (n = 177)	p value
Admission Hb (mean, SD)	10.0 (2.2)	9.6 (2.1)	10.1 (2.3)	0.16
Admission serum creatinine (median, IQR)	76 (55–107)	109 (82–178.5)	68 (53–88)	<0.001*
Admission pH (mean, SD)	7.37 (0.10)	7.35 (0.10)	7.37 (0.09)	0.05*
Admission base excess (mean, SD)	−2.2 (5.9)	−3.8 (6.2)	−1.8 (5.7)	0.03*
Admission serum lactate (median, IQR)	1.4 (1.0–2.5)	2.1 (1.1–3.3)	1.2 (0.9–2.1)	<0.01*
Admission bilirubin (median, IQR)	9 (6–13)	12 (7–17)	9 (6–11)	<0.01*
Highest bilirubin (median, IQR)	18 (10–31)	60 (46–86)	14 (9–22)	<0.001*
Discharge bilirubin (median, IQR)	8 (6–16)	17 (9–38)	8 (5–14)	<0.001*
Admission AST (median, IQR)	97 (55–255)	176.5 (67–352)	89 (51–225)	0.01*
Highest AST (median, IQR)	177 (89–403)	245 (160–662)	161 (84–365)	<0.01*
Discharge AST (median, IQR)	61 (37–107)	60 (28–110.5)	62 (39–107)	0.62
Admission ALT (median, IQR)	49 (28–116)	93 (39–163)	48 (26–97)	0.01*
Highest ALT (median, IQR)	112 (54–224)	155.5 (85–317)	103 (49–216)	0.01*
Discharge ALT (median, IQR)	56 (31–107)	55.5 (22–103)	57 (33–111)	0.66
Admission ALP (median, IQR)	63 (47–90)	61 (43–83)	65 (48–94)	0.38
Highest ALP (median, IQR)	152 (90–243)	238 (135–340)	135 (82–213)	<0.001*
Discharge ALP (median, IQR)	119 (77–193)	147 (96–254)	113 (82–213)	0.01*
Admission GGT (median, IQR)	23 (14–41)	36 (18–78)	20 (13–36)	<0.001*
Highest GGT (median, IQR)	106 (36–283)	250 (81–494)	71 (31–225)	<0.001*
Discharge GGT (median, IQR)	66 (31–180)	121 (54–239)	61 (27–148)	<0.01*

* p = ≤0.05. Hb = haemoglobin (g/dL). ALT = alanine aminotransferase (IU/L). AST = aspartate aminotransferase (IU/L). ALP = alkaline phosphatase (IU/L). GGT = gamma-glutamyl transferase (IU/L).

was identified in 48 (21.3%) patients. Baseline serum values on admission are shown in Table 2.

Forty-three (19.1%) patients suffered sepsis and 31 (13.7%) were diagnosed with septic shock. Eighteen patients with septic shock were also diagnosed with HD ($p < 0.001$). Thirty-one (13.8%) of the patient cohort sustained liver trauma, with a median AIS of 2 (IQR 1–3). This was not associated with HD ($p = 0.11$)

Fifteen (6.7%) patients had a history of hypoxia or hypotension combined with an elevated ALT of >700IU compatible with a diagnosis of hypoxic induced liver injury (HLI). Of these, 8 were diagnosed with HD. There was no statistical difference in the mortality between patients admitted with HLI and those without ($p = 0.40$).

The use of PRBC and FDP were both significantly associated with HD with PRBC (41 (85.4%) vs. 98 (55.4%) $p < 0.001$) and FDP use 18 (37.5%) vs 28 (15.8%) $p = 0.001$) respectively.

A greater proportion of patients given parenteral nutrition developed HD (4 (2.3%) vs. 10 (20.8%) $p < 0.001$). The mean length of administration of PN was 17.1 days. Three patients developed acute acalculous cholecystitis all of whom had HD.

The HD group had a significantly higher creatinine on admission to the ICU (median 109 (IQR 82-178.5) vs 68 (53–88) μmol/l $p < 0.001$). Fifty-seven (25.3%) patients were diagnosed with AKI, 27 (56.3%) in the HD group and 30 (16.9%) in the non-HD group ($p < 0.001$).

Three patients with HD (6.3%) had no other organ failures, whilst 21 patients with HD (43.8%) had multiple organ failures (AKI, shock requiring inotropes and the need for ventilation). 20 patients with no HD (11.2%) had the same level of multiple organ dysfunction (of AKI, shock and need for ventilation), which was significant ($p < 0.001$).

Admission, peak, and discharge liver function tests are shown in Table 2 and day of mean peak values in Fig. 1.

On analysis of the potential hepatotoxins to which the patients may have been exposed (Table 3), piperacillin-tazobactam and enalapril were associated with HD ($p < 0.001$ and $p = 0.04$ respectively). Despite a large proportion of the total population being exposed to paracetamol, a known hepatotoxin, there was no significant association with HD ($p = 0.12$).

For the mortality logistic regression calculation, ISS, HD, inotropic support on admission, need for ventilation and septic shock were entered. Of these, the ISS group, AKI and the need for inotropic support on admission remained significant for risk of death (Table 4). Only 12 patients (5.3%) were diagnosed with an ISS > 45. HD was associated with a significantly prolonged need for ventilation, length of ICU stay, and death (Table 1).

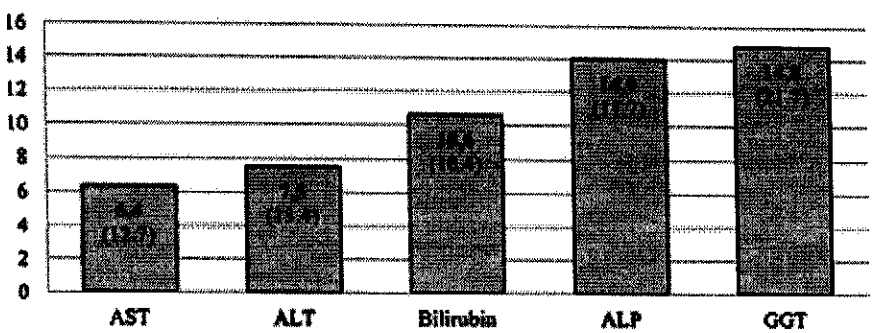

Fig. 1. Day of peak value of liver biomarkers measured (mean, SD) ALT = alanine aminotransferase. AST = aspartate aminotransferase. ALP = alkaline phosphatase. GGT = gamma-glutamyl transferase.

Table 3
Hepatotoxin exposure in all patients admitted to the TICU from January 2012 to December 2012.

	Total Population (n = 225)	Hepatic Dysfunction (n = 48)	No Hepatic Dysfunction (n = 177)	P Value
Amoxicillin-clavulanic acid (n, %)	75 (33.3)	17 (35.4)	58 (32.8)	0.86
Piperacillin-tazobactam (n, %)	62 (27.6)	27 (56.3)	35 (19.8)	<0.001*
Midazolam (n, %)	171 (76.0)	42 (87.5)	129 (72.9)	0.06
Haloperidol (n, %)	61 (27.1)	16 (33.3)	45 (25.4)	0.36
Atenolol (n, %)	10 (4.4)	5 (10.4)	5 (2.8)	0.06
Paracetamol (n, %)	190 (84.4)	44 (91.7)	146 (82.5)	0.18
Enalapril (n, %)	33 (14.7)	12 (25.0)	21 (11.9)	0.04*
NSAID[a] (n, %)	14 (6.2)	2 (4.2)	12 (6.8)	0.74

* $p \leq 0.05$.
[a] NSAID = Non-steroidal anti-inflammatory drug.

Table 4
Logistic regression for death in all patients admitted to the TICU January to December 2012.

	OR	95% Confidence Interval		P Value
		Lower	Upper	
ISS (<30) Reference				
ISS 30–45	5.28	1.25	22.39	0.03*
ISS > 45	2.09	0.47	9.25	0.02
Need for inotropic support on admission	6.80	2.53	18.25	0.33
AKI	4.94	2.07	11.83	<0.001
a. Variable(s) entered on step 1: ISS, Hepatic Dysfunction, Septic shock, Inotropes on admission, AKI, Ventilation.				<0.001

* $p \leq 0.05$ (test of equality of all 3 ISS categories) .ISS = Injury Severity Score. AKI = Acute Kidney Injury.

Discussion

The impact of HD in critically ill trauma patients has not been studied extensively. Two major mechanisms have been proposed for hepatic dysfunction in critical illness, namely hypoxic liver injury (HLI) also known as shock liver or ischaemic hepatitis, and cholestasis [1,13,14].The latter is reportedly the commonest cause of HD in intensive care units [1]. Critically injured patients are especially at risk for both hypoxic and cholestatic jaundice due to the possibility of direct liver trauma, hypovolaemic shock from blood loss and the subsequent development of sepsis in the ICU. Furthermore, patients in ICU are exposed to potentially hepatotoxic drugs during their stay.

The incidence of HD in our study was 21.3% which is markedly higher than previous reports documenting an incidence of less than 10% amongst trauma patients [2]. This may be due to selection bias whereby patients who require admission to an ICU are severely injured with multiple system trauma and may be more prone to organ dysfunction, with other authors included all patients with trauma. Regardless of the discrepancy in incidence, hepatic dysfunction from whatever cause has a strong association with mortality.

Although HLI was not found to be a significant factor with regard to outcome, the association of HD with the need for inotropic support on admission, a more pronounced base deficit, significantly elevated serum lactate levels, blood and plasma transfusion, and an early rise in liver enzymes suggests that hypoperfusion is the principle mechanism of early HD in the critically injured. This is also reflects the finding that HD was experienced more commonly with other organ failures (such as AKI, cardiovascular or respiratory failure) and rarely as a single organ dysfunction.

Inadequate liver perfusion via the portal venous system results in a compensatory rise in hepatic artery blood flow which may maintain oxygenation at a mean arterial pressure as low as 50 mmHg. Once blood loss exceeds 30% of circulating volume this compensatory mechanism fails, leading to hypoxic hepatitis [15]. Brief periods of a shock state produce a reduction in hepatic ATP formation which, although reversible, is associated with pericentral hepatocyte apoptosis and reversible hepatic dysfunction [16]. Prolonged hypotension results in profound loss of ATP production and liver necrosis. The association with mortality will depend on the magnitude of hepatic injury. That AKI was significantly more common in those with HD suggests that hypoxia plays a major role, with renal ischaemia being one of the principle causes of AKI in trauma patients.

The pattern of peak hyperbilirubinaemia that we observed in our patient population was similar to that observed by other authors with a peak bilirubin reached at a mean of day 10.6 [1,17]. This is initially preceded by a rise in the transaminases, followed by a subsequent rise in the ductal enzymes. This pattern may suggest a sequential type of HD that occurs in critically ill trauma patients, with an initial hepatocellular injury from hypoperfusion, leaving the liver vulnerable to develop cholestasis secondary to other hepatic insults, such as sepsis, PN or drugs. In the light of this pattern, care should be taken in the prescription of any drugs which are metabolised via the hepatic system if an initial transaminaemia with a concurrent hyperbilirubinaemia are observed in a critically ill trauma patient.

Liver trauma was not found to be associated with HD. This may be due to the fact that direct liver injury normally results in release of transaminases, rather than a rise in bilirubin, or that the liver trauma was not severe enough to cause dysfunction. The median AIS score of 2 for liver injury suggests that this may be the case.

Of the possible drug therapies which potentially contribute to HD, piperacillin-tazobactam and enalapril were found to be significantly associated. Based on microbiological surveillance data in the TICU, piperacillin-tazobactam is the empiric antimicrobial of choice for nosocomial sepsis. The association with HD

may be as a result of nosocomial sepsis, which is a well-documented cause of hyperbilirubinaemia, rather than a direct drug effect from the antibiotic.

Enalapril is a known hepatotoxin postulated to act by idiopathic hypersensitivity and modulation of eicosanoid metabolism by inhibition of kininase II with subsequent increased hepatic bradykinin activity [18]. Hypertension is commonly associated with AKI and our policy is to use an ACE inhibitor as the first oral anti-hypertensive agent for the management of hypertension secondary to AKI. As more patients with HD presented with or developed AKI, a number of these patients would have developed hypertension as a result of AKI. Therefore, the association between enalapril and HD may not be causal, but rather an association with AKI, which is a risk factor both for HD and mortality.

Midazolam, a commonly used benzodiazepine in critical care which undergoes hepatic metabolism, tended towards significance as a potential hepatotoxin in our study. Care should be taken with patients at risk for HD with the use of any drug which undergoes hepatic metabolism. Paracetamol is a known hepatotoxin and was used in 84% of the study population. Despite this, no significant association could be found with its use and the development of HD.

The greater use of blood products and plasma in the group of patients diagnosed with HD is unsurprising. The most common cause of hypovolaemia in trauma is secondary to acute blood loss, with the mainstay of therapy being transfusion of blood components. Large volume blood transfusion is also associated with the development of jaundice, with haemolysis of red blood cells contributing to the hyperbilirubinaemia.

Parenteral nutrition (PN) was administered to very few patients in the cohort. As PN is associated with cholestasis, it is unsurprising that this was significant for HD. Care should always be taken to monitor liver function tests in patients are receiving parenteral nutrition, especially in critical illness.

HD was statistically significant with regards to duration of ventilation, length of stay and higher mortality on univariate analyses. However, on multivariable logistic regression analysis for risk of mortality, the significance of HD fell away. The only factors that remained were the presence of AKI, need for inotropic support on admission and an ISS <45. The dual blood supply of the liver and hepatic artery buffering for low flow states in the portal circulation will preserve hepatic function whereas the single vascular supply to an organ such as the kidney which has a high metabolic demand and is profoundly vulnerable to ischaemia results in AKI.

Limitations

This is a single centre study in a select group of severely injured critically ill patients, which may show a selection bias towards the more injured patient. As a result, one would expect a greater degree of organ dysfunction in these patients. The baseline chronic diseases (such as hypertension, diabetes mellitus, chronic liver disease or alcohol abuse) of the patients was unknown. The average age of the patients was quite young, so the incidence of these diseases would be likely be less than in an older population group and less likely to affect our findings.

We used a total serum bilirubin levels greater than 34.2 μmol/l (2 mg/dL) to determine the presence of HD. As other authors had chosen the same levels of cut-off for the hyperbilirubinaemia, we found it pragmatic to use the same cut-off.

HLI also lacks consensus definition. We used a definition of a 20 fold increase in transaminases in combination with circulatory or respiratory failure as has been suggested by a number of authors. This was a practical definition as the upper limit of serum transaminases can vary according to the laboratory reference, and excludes the transient mild transaminaemia that can occur from muscle tissue damage from trauma [9].

Serum albumin was not used as a variable in the evaluation of HD as it is a negative phase reactant in critical illness and sepsis and can be artificially elevated with human albumin transfusion. International normalised ratio (INR) is commonly used in the assessment of acute liver failure, but this was also omitted from data extracted as it is affected by the coagulation disturbances that occur in trauma (from blood loss, an acute coagulopathy of trauma or the use of haemostatic products).

Blood glucose, another indicator of acute liver dysfunction, was not amongst the data extracted as all patients were subjected to moderate glycaemic control achieved with intravenous rapid acting insulin or glucose, as required.

The exact timing of the administration of the potential hepatotoxins that the patients were exposed to, in relation to the development of HD, was not captured. This is a significant limitation and does not allow us to comment on the direct association between the hepatotoxins identified in our study and HD. Alternate reasons for the association have been suggested in our discussion.

Conclusion

HD is common amongst critically ill trauma patients. Our study shows that HD leads to increased mortality, increased risk of other organ dysfunction, increased length of ventilation and prolonged length of hospital stay. We were unable to demonstrate significance of HD on multivariable analysis for risk of death. The pattern of liver enzyme derangement we observed suggests two forms of injury to the liver that occur, the initial insult being due to HLI, which may then render the liver vulnerable to further injury from second hits such as drugs, PN, and sepsis. As there is no definitive therapy for HD, careful assessment of critically ill trauma patients should be performed when initiating therapy that may be potentially harmful to the liver.

Conflict of interest statement

All authors declare that there is no conflict of interest noted for the submitted paper.

References

[1] Horvatits T, Trauner M, Fuhrmann V. Hypoxic liver injury and cholestasis in critically ill patients. Curr Opin Crit Care 2013;19(2):128–32.
[2] Harbrecht BG, Zenati MS, Doyle HR, McMichael J, Townsend RN, Clancy KD, et al. Hepatic dysfunction increases length of stay and risk of death after injury. J Trauma 2002;53(September (3)):517–23.
[3] Harbrecht BG, Doyle HR, Clancy KD, Townsend RN, Billiar TR, Peitzman AB. The impact of liver dysfunction on outcome in patients with multiple injuries. Am Surg 2001 Feb;67(2):122–6.
[4] McIntyre RC, Pulido EJ, Bensard DD. Thirty years of clinical trials in acute respiratory distress syndrome. Crit Care Med 2000;28(9):3314–31.
[5] Ostermann M, Chang R, T.R.I.P.U. Group. Correlation between the AKI classification and outcome. Crit Care 2008;12(6):R144.
[6] Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007;45(3):797–805.
[7] Williams R, Schalm S, O'Grady J. Acute liver failure: redefining the syndromes. Lancet 1993;342(8866):273–5.
[8] Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286(October (14)):1754–8.
[9] Henrion J, Schapira M, Luwaert R. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore) 2003;82(6):392–406.
[10] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Springer-Verlag 2003;530–8.
[11] Baker SP, O'Neill B, Haddon Jr W. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14(3):187–96.
[12] Kellum JA, Lameire N, for the KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17(1):204.

[13] Brienza N, Dalfino L, Cinnella G, Diele C, Bruno F, Fiore T. Jaundice in critical illness: promoting factors of a concealed reality. Intensive Care Med 2006 Feb;32(2):267–74.
[14] Fuhrmann V, Kneidinger N, Herkner H, Heinz G, Nikfardjam M, Bojic A, et al. Hypoxic hepatitis: underlying conditions and risk factors for mortality in critically ill patients. Intensive Care Med 2009 Aug;35(8):1397–405.
[15] Soultati AA, Dourakis SP. Liver dysfunction in the intensive care unit. Ann Gastroenterol 2007;18(1):34–45.
[16] Paxian M, Bauer I, Rensing H, Jaeschke H, Mautes AEM, Kolb SA, et al. Recovery of hepatocellular ATP and pericentral apoptosis after hemorrhage and resuscitation. FASEB J. Fed. Am. Soc. Exp. Biol. 2003;17(June (9)):993–1002.
[17] Sarfeh IJ, Balint JA. The clinical significance of hyperbilirubinemia following trauma. J Trauma 1978;18(1):58–62.
[18] Hagley M, Hulisz D, Burns C. Hepatotoxicity associated with angiotensin-converting enzyme inhibitors. Ann Pharmacother 1993;27(2):228–31.