Digestive and Liver Disease 52 (2020) 889–894

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Secondary hepatic dysfunction in pediatric intensive care unit: Risk factors and outcome

Engy A. Mogahed*, Haytham Ghita, Mona S. El-Raziky, Seham A. El-Sherbini, Doaa Meshref, Hanaa El-Karaksy

Department of Pediatrics, Kasr Alainy Medical School, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 8 December 2019
Accepted 30 April 2020
Available online 8 June 2020

Keywords:
Children
Critically ill patients
Length of stay
Mortality

ABSTRACT

Background: Hepatic dysfunction has a significant role in intensive care unit patients' morbidity and mortality.
Aim: To study the frequency, risk factors and outcome of secondary hepatic dysfunction in children admitted to the pediatric intensive care unit.
Methods: Secondary hepatic dysfunction was defined as the development of abnormal liver functions in a patient without a previous liver disease during intensive care unit stay. The following data were collected: age, gender, indication of admission, type of organ dysfunction, presence of sepsis, shock, need for inotropic support or mechanical ventilation, administered medications and mortality scores. Liver function tests were done on admission and at 7-day intervals.
Results: One hundred and fifty-one patients were included. Forty-three (28.5%) acquired secondary hepatic dysfunction. Several risk factors were significantly associated with secondary hepatic dysfunction: sepsis ($p<0.001$), cardiovascular events ($p<0.001$), hypoxia ($p<0.001$), number of administered antibiotics ($P=0.001$), use of inotropes ($p<0.001$) and mechanical ventilation ($p=0.001$). Secondary hepatic dysfunction was significantly associated with mortality and prolonged length of stay ($P=<0.001$).
Conclusion: Secondary hepatic dysfunction is a common finding in the pediatric intensive care unit. Sepsis, cardiovascular events and hypoxia, are the main risk factors for secondary hepatic dysfunction. Mortality and prolonged length of stay are strongly related to secondary hepatic dysfunction.

1. Introduction

Liver is the orchestrator of metabolic arrangements in critically ill patients. It promotes production and clearance of inflammatory mediators, scavenging of bacteria and bacterial endotoxin and synthesis of acute phase proteins [1]. Therefore, hepatic dysfunction has a significant role in intensive care unit (ICU) patients' morbidity and mortality. Hepatic dysfunction emerges in ICU patients without a previous liver disease as a cause or a complication of their critical illness and ICU admission [2]. Different grades of hepatic dysfunction can affect up to 50% of all ICU patients [3].

Hyperbilirubinemia, an increase in serum transaminases, alkaline phosphatase (AP) and γ glutamyl-transferase (GGT) and a decrease in serum albumin and coagulation factors levels are the main laboratory parameters on which the diagnosis of hepatic dysfunction is based [3]. Although these parameters lack sensitivity and specificity, they usually reflect hepatocellular or biliary injury and so they are widely used to detect liver dysfunction [4].

Various risk factors are involved in secondary hepatic dysfunction including shock, sepsis, heart failure, trauma, surgery, and drugs [5]. Drug-induced liver injury (DILI) has a broad spectrum of manifestations ranging from asymptomatic liver test derangement to acute liver failure [6]. It is one of the leading causes of acute liver failure in the United States [7]. The risk of hepatotoxicity in critically ill patients is increased because of the frequent number of pharmacologic agents used with significant potential interactions. In addition, drug pharmacokinetics is altered, and there is coexistence with other causes of liver injury, such as impaired hepatic perfusion, sepsis, and parenteral nutrition [8].

In most cases hepatic dysfunction in critically ill patients starts without any noticeable changes in the patient's clinical profile. Therefore, clinical suspicion of liver affection depends mainly on abnormal biochemical tests [5]. In adult studies, hepatic dysfunction represents a specific and independent risk factor for poor prognosis in critically ill patients [9]. To our knowledge, no similar data are available in children.

* Corresponding author at: 2B Sama City, Katamya, Cairo 11439, Egypt.
E-mail address: engy.mogahed@kasralainy.edu.eg (E.A. Mogahed).

https://doi.org/10.1016/j.dld.2020.04.035
1590-8658/

The main objective of our work was to study the frequency of secondary hepatic dysfunction among critically ill children in pediatric ICU (PICU), and to identify potential risk factors for hepatic dysfunction and outcome of these patients.

2. Materials and methods

This prospective study was carried out in a 10-bed PICU at Cairo University Specialized Children's Hospital after the study protocol was approved by the institutional review board. All patients admitted to PICU within a period of 9 months from 1st of April to 31st of December 2015 were included. Patients were enrolled after an informed consent was obtained from their parents/guardians. Patients were excluded if they had length of stay (LOS) in the PICU $\leq$ 24 h.

Secondary hepatic dysfunction indicates the development of any sort of hepatic dysfunction in a patient without a previous liver disease during PICU stay either as a complication of the primary illness or as a complication of the PICU interventions.

In our study, hepatic dysfunction was defined as any abnormality in liver function tests (LFTs). Excluded from this definition was the isolated abnormality of aspartate aminotransferase (AST), AP, international normalized ratio (INR) or albumin. This is because abnormalities in any of these tests, with otherwise normal other LFTs, could be caused by other conditions not related to the liver. AST could be elevated in hemolysis [10] and convulsions [11], AP in bone disease [12], INR in disseminated intravascular coagulopathy [13] and albumin decreases in malnutrition [14] and as a negative acute phase reactant in inflammation [15].

Data were collected throughout the patients' stay in PICU and patients were followed until they were discharged from or died in the PICU. For each patient the following data were recorded: demographic data, indication of admission to PICU, anthropometric measurements, vital signs, clinical physical signs, need for mechanical ventilation, inotropes, parenteral nutrition and their durations, medications used and their durations, need for blood product transfusions and number of transfusions given.

Laboratory investigations done at first day of admission and at 7-days interval included:

- LFTs: total and direct serum bilirubin, alanine aminotransferase (ALT), AST, AP, GGT, serum albumin, prothrombin time (PT) and INR. Normal values for age, with their upper limits of normal (ULN) were adopted from Lo, 2016 [16]
- Other labs: blood urea nitrogen, serum creatinine, calcium, potassium, complete blood count (CBC), random blood glucose, blood gases (PaO_2, $PaCO_2$) and PaO_2/FiO_2 ratio was calculated.

Criteria of organ dysfunction and sepsis with its stages either systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis or septic shock, were identified according to Goldstein et al. (2005) classification [17].

Pattern of hepatic dysfunction was determined in all patients either hepatocellular (elevated transaminases) or cholestatic (elevated total and direct serum bilirubin).

Mortality scores were calculated in the 1st 24 h of admission and at 7 days intervals. In this study we used PRISM III (Pediatric Risk of Mortality) score and PELOD (Pediatric Logistic Organ Dysfunction) scores. They are widely used in clinical practice and more importantly, they include more than one variable to asses hepatic dysfunction; (bilirubin, PT) and (AST, PT) respectively. PRISM III was calculated in the 1st 24 h of admission, while PELOD was calculated on admission and every 7 days.

Potential risk factors for secondary hepatic dysfunction were analyzed and they included the following parameters: hypoxia (defined as $PaO_2/FiO_2 < 300$), cardiovascular events (heart failure, shock or cardiac arrest), grade of sepsis, surgery, mechanical ventilation, blood product transfusion, parenteral nutrition, inotropic support and medications used with duration of each.

Two main outcomes were assessed, mortality and LOS in PICU. LOS was divided into: long LOS > 7 days and short LOS $\leq$ 7 days.

2.1. Statistical analysis

Data were statistically analyzed using SPSS version 22. Data were described in terms of mean $\pm$ standard deviation (SD), median (interquartile range; IQR), or frequencies and percentages when appropriate. To compare between patients with and without hepatic dysfunction Student *t*-test was used for normally distributed data and Mann Whitney *U* test for non-normal data. For comparing categorical data, Chi-square (χ^2) test or Fisher's Exact test was used. Relative risk (RR) and its 95% confidence interval (CI) were calculated for all qualitative comparisons including the risk factors for secondary hepatic dysfunction and risk factors for mortality. A multivariate logistic regression analysis was performed to evaluate the independent effect of risk factors on secondary hepatic dysfunction. *P* values less than 0.05 were considered statistically significant.

3. Results

One hundred and fifty-one patients were included in this study; eighty-seven (57.6%) were males. Their median age (IQR) was 18 [7]$^{-40}$ months, ranging between 1 month and 16 years. The majority (42%) were infants (below one year of age).

Respiratory problems constituted the most common indication of admission being present in fifty-seven patients (37.8%) followed by cardiovascular problems in 31 patients (20.5%), neurological dysfunction in 31 patients (20.5%), post-operative admission in 22 patients (14.6%) and primary liver disease in 10 patients (6.6%).

3.1. Frequency of hepatic dysfunction

After excluding 23 patients who had solitary abnormality of AST, AP, albumin or INR with otherwise normal LFTs, 53 patients (35.1%) of our study group were considered to have hepatic dysfunction (10 patients with primary hepatic dysfunction whether acute or chronic and 43 patients with secondary hepatic dysfunction) (Fig. 1). Secondary hepatic dysfunction constituted 28.5% of total number of PICU admissions. Hepatocellular dysfunction i.e. elevated transaminases was the most commonly encountered form of hepatic dysfunction (90%).

3.2. Analysis of risk factors

In order to assess the potential risk factors for development of secondary hepatic dysfunction, patients were classified into 2 groups, a group with secondary hepatic dysfunction (43 patients), and a group with no hepatic dysfunction (98 patients). Both groups were matched regarding age and gender.

Forty-nine patients had sepsis (34.8%), according to Goldstein et al. (2005) definitions [17], including the sepsis continuum (sepsis, severe sepsis, and septic shock). Out of them, 27 patients (55%) developed secondary hepatic dysfunction. The prevalence of sepsis among patients increased with increased LOS, reaching 100% among patients who stayed in PICU for more than 30 days. Sepsis was significantly associated with secondary hepatic dysfunction (Table 1).

Forty-eight patients (34%) experienced a sort of severe cardiovascular compromise in the form of shock, heart failure or survived a cardiac arrest; thirty of them (62.5%) had secondary

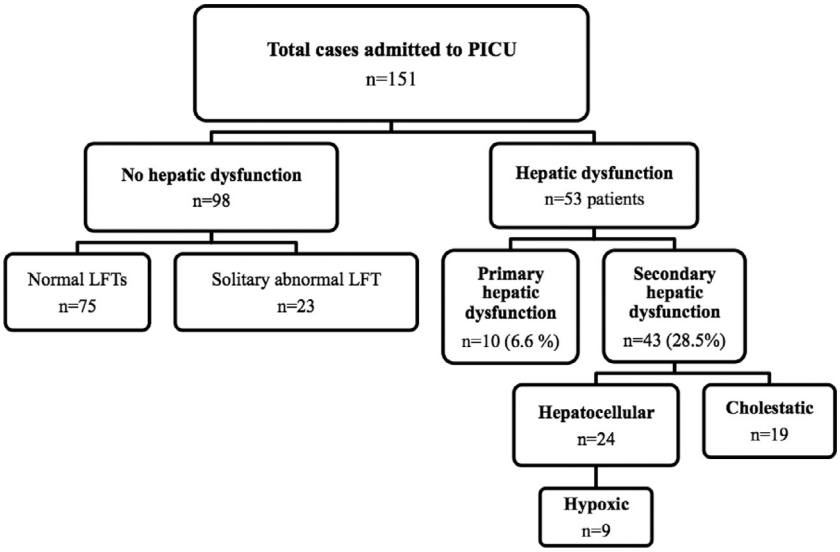

Fig. 1. Classification of pediatric intensive care unit patients according to liver function tests results
LFTs: liver function tests; PICU: pediatric intensive care unit.

Table 1
Risk factors for secondary hepatic dysfunction in critically ill children.

Risk factor	Secondary hepatic dysfunction ($n=43$)	No hepatic dysfunction ($n=98$)	Odds ratio	95% Confidence interval	*P* value
Sepsis ($n=49$)	27 (62.8%)	22 (22.4%)	5.83	2.674–12.71	< 0.001
Cardiovascular events ($n=48$)	30 (69.8%)	18 (18.4%)	10.256	4.48–23.47	< 0.001
- Heart failure ($n=11$)	8 (25.6%)	3 (3.1%)	7.238	1.82–28.84	0.002
- Shock ($n=38$)	23 (53.5%)	15 (15.3%)	6.363	2.82–14.35	< 0.001
- Cardiac arrest ($n=8$)	7 (16.3%)	1 (1.02%)	18.861	2.24–158.7	< 0.001
Total Inotropes ($n=59$)	33 (76.7%)	26 (26.5%)	9.138	3.95–21.12	< 0.001
- Dopamine ($n=20$)	13 (30.2%)	7 (7.1%)	5.633	2.06–15.43	< 0.001
- Dobutamine ($n=49$)	27 (62.8%)	22 (22.4%)	5.829	2.67–12.71	< 0.001
- Adrenaline ($n=33$)	25 (58.1%)	8 (8.2%)	15.625	6.08–40.14	< 0.001
- Noradrenaline ($n=11$)	10 (23.6%)	1 (1.02%)	29.394	3.62–238.43	0.002
Hypoxia ($n=70$)	31 (72.1%)	39 (39.8%)	3.9	1.79–8.52	< 0.001
Mechanical ventilation	28 (65.1%)	33 (33.7%)	3.68	1.73–7.82	0.001
Blood product transfusion ($n=66$)	35 (81.4%)	31 (31.6%)	9.455	3.93–22.76	<0.001
- Blood ($n=49$)	30 (69.8%)	19 (19.4%)	5.951	2.57–13.77	<0.001
- Plasma ($n=38$)	21 (48.8%)	17 (17.3%)	4.548	2.01–10.07	<0.001
- Platelets ($n=5$)	4 (9.3%)	1 (1.02%)	9.949	1.08–91.84	0.043
- Albumin ($n=29$)	14 (32.6%)	15 (15.3%)	1.864	1.14–3.04	0.013
Surgery ($n=35$)	8 (18.6%)	27 (27.6%)	0.601	0.25–1.46	0.258
Abdominal surgery ($n=29$)	9 (20.9%)	20 (20.4%)	1.032	0.43–2.5	0.944
Antimicrobials ($n=141$)	35 (81.4%)	57 (58.2%)	3.147	1.32–7.48	0.009
-Aminoglycosides ($n=92$)	21 (48.8%)	24 (24.5%)	2.943	1.38–6.26	0.005
- Carbapenems ($n=45$)	12 (27.9%)	9 (9.2%)	3.828	1.47–9.96	0.006
- Quinolones ($n=21$)	28 (65.1%)	38 (38.8%)	2.947	1.39–6.22	0.004
- Vancomycin ($n=66$)	21 (48.8%)	19 (19.4)	3.968	1.82–8.66	<0.001
- Antifungals ($n=40$)					
Other medications	26 (60.5%)	32 (32.7%)	3.154	1.50–6.63	0.002
- Anticonvulsants ($n=58$)	21 (48.8%)	23 (32.5%)	3.112	1.46–6.65	0.003
- Sedatives ($n=44$)					
Total parenteral nutrition ($n=22$)	9 (20.9%)	13 (13.3%)	1.730	0.68-4.423	0.251

hepatic dysfunction, which was significantly associated with all forms of cardiovascular events (Table 1).

Inotropic support was needed in 59 patients (41.8%), of whom 33 patients (55.9%) significantly had secondary hepatic dysfunction (Table 1). Similarly, the mean duration of inotropic support in general was significantly higher in patients with secondary hepatic dysfunction (7.1 days compared to 3.2 days in patients without hepatic dysfunction; $P=0.002$). Meanwhile, the mean duration of use of each inotrope (dopamine, adrenaline and noradrenaline) showed no significant difference between patients with and without hepatic dysfunction, except for dobutamine, whose mean duration (6.74 days) was significantly higher in the secondary hepatic dysfunction group ($P=0.004$).

Seventy patients suffered hypoxia (49.7%), of whom 31 patients (44%) had secondary hepatic dysfunction. Patients with hypoxia were at significantly higher risk of hepatic dysfunction (Table 1).

Nine patients developed hypoxic liver injury (HLI). Although 8 of them (88.9%) suffered moderate to severe hypoxia, yet the degree of hypoxia did not show a statistically significant effect on the development of HLI ($P=0.105$).

Sixty-one patients required mechanical ventilation with a median duration of 4 days (IQR 2–8). Hepatic dysfunction significantly occurred in 28 mechanically ventilated patients ($P=0.001$) (Table 1). The mean duration of mechanical ventilation in patients with hepatic dysfunction was significantly higher than patients without hepatic dysfunction (mean difference: 4.7; 95% CI: 1.8–7.5; $P=0.002$).

Sixty-six cases received blood product transfusion including blood, plasma, platelets or albumin; 35 of them (53%) had hepatic dysfunction. Transfusion of blood products in general was significantly associated with hepatic dysfunction ($P< 0.001$) as well as each type of blood products separately (Table 1). However, the mean number of transfusions of each of the blood products was not statistically associated with the occurrence of hepatic dysfunction ($P=0.163$, $P=0.195$, $P=0.495$, $P=797$ for blood, plasma, platelets and albumin respectively).

Surgery, including abdominal surgeries, was not significantly associated with hepatic dysfunction ($P=0.258$ and 0.944 respectively) (Table 1).

All patients admitted to the PICU received antibiotics. The median number of antibiotics given to each patient was 4 antibiotics (ranging from 1 to 15). The antibiotic group mostly used was penicillins followed by aminoglycosides and vancomycin. The mean number of antibiotics used in patients with hepatic dysfunction was 5 compared to 3 antibiotics in patients without hepatic dysfunction (mean difference: 1.85; 95% CI: 0.8–2.8; $P=0.001$). Comparison between the frequency of different antibiotic groups in patients with and without hepatic dysfunction revealed that hepatic dysfunction was significantly more prevalent in patients who received aminoglycosides, carbapenems, quinolones and vancomycin (Table 1). Other medications as antifungals, anticonvulsants and sedatives were also used more frequently in patients with hepatic dysfunction (Table 1). On the other hand, the rate of using penicillins, cephalosporins, antivirals, acetaminophen, steroids, proton pump inhibitors and parenteral nutrition did not show any statistically significant difference between patients with and without hepatic dysfunction. Comparing the duration of medications rather than their frequency showed that the mean durations of administration of penicillins, aminoglycosides, carbapenems, vancomycin and antifungals were significantly higher in patients with hepatic dysfunction.

Twenty-two patients received TPN. There was no statistically significant difference in the prevalence of development of secondary hepatic dysfunction regarding TPN administration (Table 1).

Logistic regression analysis revealed that hypoxia and the use of inotropes are independent risk factors for the development of secondary hepatic dysfunction ($P=0.02$ and 0.008 respectively).

3.3. Assessment of patients' outcome

To assess the effect of hepatic dysfunction on patient outcome, we targeted 2 main parameters: mortality rate and LOS in the PICU. The median (IQR) LOS was 6 [3-9] days, ranging between 2–50 days. LOS was divided into short ($\leq$7 days) and long (>7 days). Fifty-two patients (34.4%) had long LOS. Secondary hepatic dysfunction was associated with a significant increase in the LOS in the PICU (Table 2). When we divided our cases according to the pattern of hepatic dysfunction, we found that hepatocellular and cholestatic patterns had comparable results regarding LOS ($P=0.120$).

Mortality scores (PRISM and PELOD) on admission as well as PELOD at day 7 and 21 of admission were significantly associated with mortality ($P< 0.001$). Patients with secondary hepatic dysfunction had significantly higher both mortality scores on admission as well as PELOD at day 7, compared to patients without hepatic dysfunction ($P<0.001$) (Table 2).

The overall mortality rate in the study group was 25.2%. Secondary hepatic dysfunction per se was a significant risk factor of mortality, where mortality rate in patients with secondary hepatic dysfunction was 53.5% compared to 8.2% in patients without hepatic dysfunction (Table 2). Patients with cholestatic pattern of hepatic dysfunction had significantly higher mortality rate than hepatocellular pattern ($P=0.022$; Relative risk: 4.7).

In the current study, even mild abnormalities of LFTs were considered as secondary hepatic dysfunction. For better data analysis, patients with secondary hepatic dysfunction were divided into two groups according to ALT: ALT <2xULN and ALT $\geq$2xULN for age; and according to bilirubin; bilirubin $\leq$2 mg/dl and bilirubin >2 mg/dl. ALT >2xULN and bilirubin >2 mg/dl were not associated with higher mortality.

4. Discussion

Patients with a primary liver disease may need intensive care due to acute liver failure or acute de-compensation of chronic liver disease [18]. On the other hand, there are those critically ill patients who are not known to have a liver disease and yet they develop abnormal LFTs during their critical illness. Those patients with secondary hepatic dysfunction are usually overlooked and underestimated [19]. ICU patients could have more life-threatening conditions, especially those including the respiratory and cardiovascular systems, which withdraw the physicians' attention from the "apparently less important" hepatic dysfunction. For this reason several studies have emerged that focus on the significance of hepatic dysfunction in the ICU morbidity and mortality. These studies were mostly in adult patients. One of the strength points of our study is that to our knowledge no similar studies were done in PICU. The last study addressing this problem in the pediatric population was in 1992 by Jacquemin et al. [20]. who studied HLI in patients with circulatory shock. In the current study we focused on the frequency, risk factors and outcomes of secondary hepatic dysfunction in critically ill children.

Secondary hepatic dysfunction constituted 28.5% of the study group. The incidence of hepatic dysfunction among critically ill adult patients varied in different studies. Kramer et al. in 2007 [9] reported an 11% incidence of early hepatic dysfunction within 48 h of ICU admission. Another study by Thomson et al. (2009) [21] reported that 61% of patients admitted to ICU had abnormal LFTs (ALT, GGT, AP and bilirubin) after excluding patients with primary liver disease. Recently in 2017, Saloojee et al. [22]. reported a 21.3% incidence among critically ill trauma patients.

It is worth noting that elevated ALT levels in the absence of other evidence of liver disease should lead to consideration of muscle injury, which is confirmed by elevated creatine kinase and lactate dehydrogenase levels [11].

In the current study, the prevalence of sepsis among patients increased with longer PICU stay, reaching 100% among patients who stayed in PICU for more than 30 days. This was mostly attributable to PICU acquired infections secondary to increased exposure to several interventions and multiple skin pricks for sampling during their long LOS making them more susceptible to sepsis. In a study by Porto et al. (2012) [23] the presence of an invasive device and longer time of hospitalization in PICU were major risk factors for the acquisition of nosocomial infection in PICU patients.

In our study, the incidence of secondary hepatic dysfunction in patients with sepsis was 55%. Sepsis was significantly associated with hepatic dysfunction where patients with sepsis were found to be 5.8 more times susceptible to have hepatic dysfunction

Table 2
Outcome of critically ill children with secondary hepatic dysfunction.

Outcome	Secondary hepatic dysfunction ($n=43$)		No hepatic dysfunction ($n=98$)		Relative risk Or Mean/Median difference*	95% Confidence interval	*P* value
Length of stay - Long (>7 days) ($n=50$) - Short (≤ 7 days) ($n=91$)	26 (60.5%) 17 (39.5%)		24 (24.5%) 74 (75.5%)		4.716	2.19–10.14	< 0.001
Mortality - Died ($n=31$) - Discharged ($n=110$)	23 (53.5%) 20 (46.5%)		8 (8.2%) 90 (91.8%)		12.937	5.06–33.10	<0.001
Mortality scores	N	Mean/median	N	Mean/median			
- PRISM III ($n=141$)	43	8.58	98	3.36	−5.22	−3.2 to −7.2	<0.001
- PELOD 1 ($n=141$)	43	13.47	98	4.69	−8.77	−11.7 to −5.8	<0.001
- PELOD 7 ($n=53$)	27	12	26	1.73	−10.27	−15.5 to −5	<0.001
- PELOD 14 ($n=18$)	11	1	7	2	1	−9 to 9	0.963
- PELOD 21 ($n=12$)	8	0.5	4	0.5	0	-	0.724

* Relative risk was used for length of stay and mortality, while mean/median difference was used for mortality scores (Mean was used for large samples> 30, while median was used for small samples ≤ 30)PRISM: pediatric risk of mortality; PELODL pediatric logistic organ dysfunction.

than patients without sepsis. Liver dysfunction that comes after sepsis is an independent risk factor for multiple organ dysfunction and sepsis-induced mortality. Liver acts as a double-edged sword in sepsis, the liver-mediated immune response is responsible for clearing bacteria and toxins but also causes inflammation, immunosuppression, and organ damage. Attenuating liver injury and restoring liver function lowers morbidity and mortality rates in patients with sepsis [24].

Regarding patients who experienced cardiovascular events, 62.5% of them had secondary hepatic dysfunction. Hepatic dysfunction was significantly associated with all forms of cardiovascular events including heart failure, shock and cardiac arrest. In these situations, the liver is affected due to decreased blood flow to the liver leading to diminished oxygen delivery, especially in the presence of sepsis that increases oxygen demand and impairs its extraction by the hepatocytes [25]. Similarly, the liver is affected in cases of hypoxia. In our study, 44% patients with hypoxia had secondary hepatic dysfunction.

Inotropes were administered to 42% of the patients, of whom 56% had secondary hepatic dysfunction. The use of inotropes was significantly associated with secondary hepatic dysfunction ($P=0.002$). The principal response of the hepatic vascular bed to vasopressors is vasoconstriction. Noradrenaline and adrenaline divert blood flow away from the mesenteric circulation and decrease microcirculatory blood flow in the gastrointestinal tract despite increased perfusion pressure and increased systemic blood flow [26]. Furthermore, experimental data suggest that catecholamines may deteriorate hepatocellular function by induction of an inflammatory response syndrome [27].

All patients admitted to our PICU received antibiotics. The median number of antibiotics given to each patient was 4 antibiotics (ranging from 1 to 15). The most frequently administered antibiotic groups were penicillins (mainly ampicillin/sulbactam), aminoglycosides (mainly amikacin) and vancomycin. In a study by Abbas et al. in 2016 [28], the median number of antibiotic use per patient in PICU was 3, with range of 1–7. Most commonly used antibiotics in their study were cefazolin, meropenem, vancomycin and ceftriaxone. In another study by Pandiamunian et al. (2017) [29], penicillins and cephalosporins were the most frequently used antimicrobials in PICU.

Comparison between patients with and without hepatic dysfunction showed that hepatic dysfunction was significantly more prevalent in patients who received aminoglycosides, carbapenems, quinolones, vancomycin and antifungals. On the other hand, the rate of using penicillin and cephalosporins were comparable in patients with and without hepatic dysfunction. This association does not imply causality i.e. carbapenems did not necessarily cause hepatic dysfunction. Penicillins are usually the 1st line empirical antibiotics in our PICU, so they were used in most patients, with or without hepatic dysfunction. While other antibiotics as carbapenems, quinolones and vancomycin are usually used later during the ICU stay, in patients who are not doing well on the previous antibiotics or in cases with severe sepsis. This is the type of patient who would probably have hepatic dysfunction as well and might have a longer PICU stay. Causality assessment in case of DILI is challenging. Generally, DILI is a diagnosis of exclusion that relies on multiple elements in the medical history, presentation, laboratory results, and subsequent course [30].

The occurrence of DILI is associated with genetic vulnerability, and multiple studies have focused on the exploration of single nucleotide polymorphisms (SNP) within transporter genes [31]. The pharmacology of drugs subject to inherited variability in metabolism is very complex and only partially understood. The genetic predisposition towards certain drug–drug interactions must be increasingly taken into account. It is anticipated that studies will propel the routine use of many more genetic tests in the future and ultimately lead to genetically guided decisions about drug therapies in patients at risk to develop DILI [32]. In the immediate future, genetics will allow further stratification of liver diseases and contribute to personalized medicine. Challenges exist with regard to clinical implementation of rapidly developing technologies and interpretation of the wealth of accumulating genetic data [33].

In the current study, cholestatic pattern of hepatic dysfunction was significantly associated with mortality than the hepatocellular one. In a study by Kramer et al. (2007) [9], hyperbilirubinemia was found to complicate 11% of ICU admissions and was a risk factor of poor prognosis. Another study by Jenniskens et al. (2016) [34] suggested that the increase in bilirubin in response to acute sepsis/critical illnesses might not necessarily point to cholestasis as a pathophysiological entity. Instead, it may be the result of an adaptively altered bile acid production and transport back towards the systemic circulation. How these changes could be beneficial for survival should be further investigated.

Most studies about hepatic dysfunction in critical adult patients defined hepatic dysfunction as serum bilirubin level above 2 mg/dl or ALT above 2 folds the ULN. In the present study, on comparing the mortality rates between patients with mild elevations in ALT/bilirubin and patients with the previously mentioned levels there was no statistically significant impact on mortality. This implies that even mild elevations in LFTs should be considered as hepatic dysfunction and should be taken seriously and considered as a predictor of poor prognosis.

In conclusion, secondary hepatic dysfunction is a common finding in PICU with a frequency of 28.5%. Sepsis, cardiovascular events, hypoxia, mechanical ventilation, number of administered antibiotics and the use of inotropes were significantly associated with the occurrence of secondary hepatic dysfunction. Hypoxia and inotropes are independent factors for secondary hepatic dysfunction. Secondary hepatic dysfunction is significantly associated with PICU mortality and prolonged LOS. Cholestatic pattern of liver dysfunction has higher risk for mortality than hepatocellular pattern.

Conflict of interest

None declared.

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