Incidence, predictors and outcome of sepsis-associated liver injury in children: a prospective observational study

Kanwar Saini1 · Rishi Bolia1 · Nowneet Kumar Bhat1

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Abstract
Sepsis-associated liver injury (SALI) occurs as a result of the systemic and microcirculatory changes that happen because of sepsis. Its prognostic significance in the paediatric population is unclear. We enrolled all children < 19 years, admitted between July, 2020 and July, 2021 to the paediatric unit (ward or intensive care unit) with a diagnosis of sepsis for this study. Clinical and biochemical parameters of children with sepsis who developed SALI were compared with those without SALI to determine the risk factors of SALI and its impact on in-hospital mortality. A total of 127 children, median age 72 (1–204) months, 74 males were included. SALI developed in 45 (31.3%) at a median 1 (1–13) days after the diagnosis of sepsis. The SALI pattern was cholestatic in 18 (40%), hepatocellular in 17 (37.7%) and hypoxic hepatitis in 10 (22.3%). Paediatric sequential organ failure assessment (pSOFA) was an independent predictor of SALI — OR 1.17 (95% CI 1.067–1.302), \( p = 0.001 \). A pSOFA score of > 9.5 predicted the development of SALI with 66.7% sensitivity and 77.1% specificity. SALI was an independent predictor of mortality in children with sepsis — OR 1.9 (95% CI 1.3–3.4), \( p = 0.01 \).

Conclusions: SALI develops in 45 (31.3%) with sepsis. A higher pSOFA score is associated with SALI. Children who develop SALI have a ~twofold higher risk of mortality than those without SALI.

What is Known:
• During the process of sepsis, the liver plays a role by scavenging bacteria and producing inflammatory mediators. However, at times the liver itself becomes a target of the dysregulated inflammatory response. This is known as sepsis-associated liver injury (SALI).
• The incidence of sepsis-associated liver injury and its prognostic significance in children is not known.

What is New:
• SALI develops in one-third children with sepsis and is associated with a higher pSOFA score.
• Children who develop SALI have a higher risk of mortality.

Keywords Sepsis · Transaminases · Cholestasis · Hepatitis · Prognosis

Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| ALT          | Alanine aminotransferase |
| AST          | Aspartate aminotransferase |
| GGT          | \( \gamma \)-Glutamyl transpeptidase |
| LFT          | Liver function test |
| HH           | Hypoxic hepatitis |
| pSOFA        | Paediatric sequential organ failure assessment |
| SALI         | Sepsis-associated liver injury |
| ULN          | Upper limit of normal |

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Rishi Bolia
rishibolia@yahoo.co.in

Kanwar Saini
ka345355@gmail.com

Nowneet Kumar Bhat
drnmdbhat@gmail.com

1 Division of Pediatric Gastroenterology, Department of Pediatrics, All India Institute of Medical Sciences, Virbhadra Road, Rishikesh, India

Introduction
Sepsis frequently leads to multiple organ failure and death. During the process of sepsis, the liver plays a role by scavenging bacteria and producing inflammatory mediators. However, at times the liver itself becomes a potential
target of the dysregulated inflammatory response. This is known as sepsis-associated liver injury (SALI) and occurs as a result of the systemic and microcirculatory changes that occur because of sepsis [1]. The incidence of SALI in children is unclear because of the lack of a homogenous definition. SALI has been found to be a predictor of poor prognosis in the adult population [2]. However, its role in the prognosis in the paediatric population is still unclear.

The aim of our study was to evaluate the incidence, predictors and prognostic significance of sepsis-associated liver injury in children.

Methods

We carried out a prospective observational cohort study in a tertiary referral hospital over a period of 12 months (1 July 2020 to 30 June 2021). All the patients aged 1 month to <19 years who were admitted to the paediatric unit (ward and intensive-care unit) and diagnosed with sepsis were assessed for enrolment. Written informed consent was obtained prior to enrolment.

Demographic variables (age, sex, co-morbid condition), clinical parameters (including need for fluid boluses, vasopressors during the hospital stay), paediatric sequential organ failure assessment (pSOFA) score, laboratory parameters (complete blood count, reticulocyte count, total bilirubin, direct bilirubin; alanine aminotransferase (ALT); aspartate aminotransferase (AST); γ-glutamyl transpeptidase (GGT), urea, creatinine, lactate), infectious indexes (site of infection, c-reactive protein, procalcitonin, cultures), mode of nutrition (enteral, parenteral), and drugs received were recorded.

Liver function tests (LFTs) were monitored serially during the hospital stay (minimum three times per week). In children who developed SALI, the day of onset (from day of admission) was recorded. If a patient had multiple admissions, only the first admission was included.

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The following definitions were used -

Sepsis Patients with sepsis were defined as those with confirmed or suspected infection who had an acute rise in the pSOFA score of 2 points or more from up to 48 h before the infection to 24 h after the infection and who received antimicrobial therapy [3].

Sepsis-associated liver injury (SALI) In a patient diagnosed to have sepsis, SALI was defined by the following conditions: [1] total bilirubin ≥ 4.0 mg/dL, or [2] ALT > 2 folds upper limit of normal (ULN) level for age. (females — 0–< 1 year — 33 U/L, 1–<13 years — 25 U/L, 13–<19 years — 22 U/L, males — 0–< 1 year — 33 U/L, 1–<13 years — 25 U/L, 13–<19 years — 24 U/L) [4] in the absence of another cause of hepatobiliary disease (viral hepatitis, drug-induced liver injury, immune-mediated injury, metabolic disease, biliary disease etc.) [5].

All the children with suspected SALI underwent a detailed history and physical examination including past/family history of liver disease, any physical findings suggestive of an underlying liver disease. If any previous laboratory/radiology reports (from previous illnesses) were available, they were reviewed.

In children in whom the history and examination were unremarkable, the following evaluation was performed (in all):

- Viral markers (Hepatitis A, B, C, E, CMV, Sars-COV2), creatinine phosphokinase (CPK), thyroid profile, celiac serology, fasting blood sugar and lipid profile
- Ultrasound + doppler — to rule out any biliary, infiltrative (including fatty liver), vascular or structural cause
- Evaluation for drug-induced liver injury using Roussel Uclaf Causality Assessment Method (RUCAM) [6]

All the children were evaluated by a paediatric gastroenterologist, and if required further testing including autoimmune liver markers, cerum ceruloplasmin etc. were performed on a case by case basis.

All the patients with a pre-existing or primary liver disease or an alternative cause for derangement of liver functions were excluded from the study.

SALI was classified into three categories: “cholestatic”, “hepatocellular” and “hypoxic hepatitis” [7].

1. “Hypoxic hepatitis” (HH) was defined as a liver function test with both AST and ALT over 200 IU/L after an episode of hypotension or shock.
2. Liver injury was designated “cholestatic” when there was an increase in GGT above upper limit of normal (ULN), and the R ratio i.e. (ALT/ULN):(GGT/ULN) was 2 or lower
3. The rest were designated to have “hepatocellular” injury.

Clinical and biochemical parameters of children with sepsis who developed SALI were compared with those without SALI to determine the risk factors of SALI and its impact on in-hospital mortality.

The study was approved by the ethics committee of the institute.

Statistical analysis

Data was analysed using SPSS (v.22.0) (SPSS Inc., Chicago, IL). Continuous variables were summarized as means ± standard derivations (SD) for normally distributed
data and as median (interquartile range) for data that did not have a normal distribution. Student’s t-test, Mann–Whitney U test and Kruskal–Wallis test were used to compare the means/medians of continuous variables. Chi-square test was used to compare categorical data. Predictors with significant values of \( p < 0.05 \) in a univariate analysis were entered into a multivariate analysis, enabling determination of independent predictors. In order to estimate the accuracy of a significant risk factor as predictor of SALI, a receiver operating characteristic (ROC) curve was generated. A value of \( p < 0.05 \) was considered statistically significant.

**Results**

A total of 379 children were admitted to the paediatric unit during the study period of which 188 were diagnosed to have sepsis. Out of these, 61 were excluded (suspected or confirmed pre-existing or primary liver disease (including liver tumour, metabolic liver disease) — 29, drug-induced liver injury — 9, congenital heart disease/congestive heart failure — 7, fatty liver disease — 4, rhabdomyolysis — 3, SARS-CoV2 disease — 7, celiac disease — 1, hypothyroidism — 1) and finally a total of 127 children, median age 72 (1–204) months, 74 males were included in the final analysis. Eighteen (14.1%) patients had underlying co-morbidities.

The most common site of infection was the respiratory tract 40 (31.4%) followed by urinary tract infection 26 (20%), central nervous system 15 (12%), abdomen (gastrointestinal tract, peritoneum) — 14 (11%), osteoarticular — 12 (9.4%) cardiovascular (infective endocarditis, pericarditis) — 11 (8.6%), skin and soft tissue — 10 (7.8%). One child had infection at > 1 site.

SALI developed in 45 (31.3%) at a median 1 (1–13) days after the diagnosis of sepsis.

**Age and SALI**

Most of the patients who had SALI were infants (13/45, 29%). Thereafter the age-wise distribution of SALI was relatively uniform across the ages 2 to 17 years (Fig. 1).

**Risk factors for SALI**

Children who developed SALI had a significantly higher pSOFA score [11 (IQR 7) vs. 6 (IQR 7), \( p < 0.001 \)] and lactate levels [1.85 (IQR 2) vs. 1.2 (IQR 2), \( p = 0.005 \) at admission as compared to those who did not develop SALI (Table 1). We found that pSOFA score was an independent predictor of SALI with OR 1.17 (95% CI 1.067–1.302), \( p = 0.001 \). Lactate levels were not [OR 1.014 (95% CI 0.824–1.250), \( p = 0.82 \)] independently associated with SALI.

On ROC analysis, pSOFA score had a AUROC of 0.7. A pSOFA score of > 9.5 predicted the development of SALI with 66.7% sensitivity, 77.1% specificity (Fig. 2).

**Pattern of SALI**

The SALI pattern was cholestatic in 18 (40%), hepatocellular in 17 (37.7%) and hypoxic hepatitis in 10 (22.3%). There was no statistically significant difference in the baseline parameters between individuals with the three different patterns of liver injury (Table 2).

Amongst children with HH, SALI was always diagnosed on the same day as the diagnosis of sepsis. The median age distribution of children with Sepsis - associated Liver Injury

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**Fig. 1** Age distribution of children with sepsis-associated liver injury

![Age distribution of children with sepsis-associated liver injury](image-url)
liver function parameters observed at the time of diagnosis of SALI were as follows: total bilirubin — 0.4 (0.1–3.1) mg/dL, direct bilirubin — 0.18 (0.09–0.74) mg/dL, ALT — 1265 (202–1906) U/L, AST — 383 (342–2779) U/L, albumin — 3.5 (2.9–4.9) mg/dL, globulin — 2 (1.4–2.4) mg/dL, GGT — 33.5 (11.9–234) mg/dL and INR — 1.1 (0.9–1.9).

Cholestasis developed a median 5 (1–13) days after the diagnosis of sepsis. We observed that it was the most common pattern of injury observed amongst infants seen in 7/13. The median LFTs were as follows: total bilirubin — 1.6 (0.26–12.4) mg/dL, direct bilirubin — 1.05(0.8–7.17) mg/ dL, ALT — 55 (6–338) U/L, AST — 84 (17–411) U/L, albumin — 3.5 (2.9–4.9) mg/dL, globulin — 2 (1.4–2.4) mg/dL, GGT — 33.5 (11.9–234) mg/dL and INR — 1.1 (0.9–1.9).

The trends of the average total bilirubin and ALT levels of the three different injury patterns have been depicted in Fig. 3.

### SALI and outcomes

Children with SALI had a higher need for invasive/non-invasive ventilation [36/45 vs. 45/82, \( p = 0.005 \)] than those without SALI. They also had a significantly higher mortality [31 (69%) vs. 22 (27%), \( p = 0.0001 \)].

SALI was found to be an independent predictor of mortality in children with sepsis — OR 1.9 (95% CI 1.3–3.4), \( p = 0.01 \) (Supplementary Table 1).

There was no significant difference in the length of hospital stay of the survivors in those with and without SALI — 22 (IQR 20) vs. 13 (IQR 13), \( p = 0.07 \).
No difference in mortality was observed according to the SALI pattern — [HH — 8/10 vs. cholestatic — 9/18, hepatocellular — 14/17, \( p = 0.08 \)].

There was no difference in the duration of the hospital stay of the survivors either [HH — 23 (19–27) vs. cholestatic — 20(5–33) vs. hepatocellular — 34(9–42), \( p = 0.43 \)].

Table 2

|                  | Hypoxic hepatitis (\( n = 10 \)) | Hepatocellular injury (\( n = 17 \)) | Cholestasis (\( n = 18 \)) | \( p \) value |
|------------------|-----------------------------------|--------------------------------------|-----------------------------|--------------|
| Age (months)     | 30 (180)                          | 84 (159)                             | 72 (144)                    | 0.07         |
| Gender (males)   | 5                                 | 8                                    | 13                          | 0.64         |
| Haemoglobin (g/dL) | 11.8 (4)                          | 11.4 (1.8)                           | 9.7 (4.2)                   | 0.08         |
| Total leucocyte count | 12,890 (8271)                  | 12,190 (9566)                        | 8525 (9197)                 | 0.77         |
| Platelets (per \( \text{mm}^3 \)) | 3.08 (3.8)                      | 2.03 (4.3)                           | 2.3 (2.5)                   | 0.77         |
| Urea (mg/dL)     | 78 (104.6)                        | 35 (97.3)                            | 26.8 (32.7)                 | 0.43         |
| Creatinine (mg/dL) | 0.9 (3.1)                         | 0.7 (2.1)                            | 0.5 (0.7)                   | 0.80         |
| Procalcitonin (ng/mL) | 5.9 (62)                         | 5 (64)                               | 12 (72)                     | 0.72         |
| C-reactive protein (mg/dL) | 13.4 (113)                     | 24 (186)                             | 53 (120)                    | 0.31         |
| Lactate (mg/dL)  | 2.65 (4)                          | 2 (2)                                | 1.7 (3)                     | 0.41         |
| Need for inotropes (during hospital stay) | 9                                | 12                                   | 9                           | 0.06         |
| pSOFA            | 11.5 (5)                          | 11 (7)                               | 7 (13)                      | 0.49         |

Data represented as median (IQR)
Fig. 3  Trend of a mean total bilirubin (mg/dL) and b alanine transaminase (U/L) levels in children with sepsis-associated liver injury
SALI–LFT follow-up

Amongst the survivors, in 7/14 children, the LFT normalized by the time of hospital discharge. It resolved in 7 (2–13) days after the initial derangement was detected. Amongst the remaining children (*n* = 7), 5 had an improving LFT trend at discharge, while 2 children with cholestatic jaundice continued to have a persistent derangement of LFTs.

Amongst the patients with SALI who died (*n* = 31), follow-up LFT (after the diagnosis of SALI) was available in 24. Seven children died before another LFT could be done.

Amongst children in whom a follow-up LFT was available, the ALT trend was as follows: improving — 9, worsening or similar — 15. For bilirubin values, it was found to be improving in 4 and worsening or similar in 20.

Discussion

Sepsis-associated liver injury has not been substantially recognized and its clinical implications in children are unclear. There is no consensus on the definition of SALI. While some authors have only considered biochemical alterations i.e. elevated serum activity of transaminases, others have also included clinical parameters such as hepatic encephalopathy, and ascites in the definition. Since there is no homogenous definition, there is a high variation in calculated incidence and ascites in the definition. Since there is no homogenous definition, there is a high variation in calculated incidence reported in literature ranging from 1 to 47% [2].

We found that SALI occurs in 31.3% of children with sepsis. Previously published studies using the same diagnostic criteria that we have used have reported an incidence ranging from 9.1 to 9.7% [8, 9]. This was likely an under-representation as these were retrospective audits, and it is conceivable that SALI was missed in a large proportion of patients because routine monitoring of LFTs was not performed. In one of these studies (Dou et al.), only the liver function parameters within the first 24 h of admission were recorded, and all the children who subsequently developed SALI were likely missed [8].

We are a tertiary referral centre, and the sickest children from our state and adjoining regions are referred to our hospital. The high degree of organ failure observed in our patients is testament to this fact. It is likely that it led to a higher prevalence of SALI.

Another possible explanation is that we used the sepsis-3 definition to define sepsis as compared to others who have used the International Paediatric Sepsis Consensus Conference (IPSSC) definition. The sepsis-3 criteria is more restrictive, and in a comparative study less than half of the children identified by IPSSC definitions fulfilled the sepsis-3 definitions [10]. So, it is plausible that our cohort included sicker children with more severe sepsis leading to SALI more often.

The pathophysiology of SALI is complex and still not well understood. The mechanism of SALI includes hypoxic liver damage due to shock and resuscitation and hepatocyte damage caused by the release of cytokines and reactive oxygen products released by Kupffer cells activated by lipopolysaccharide (LPS) from bacteria [11, 12]. There is recent data too that suggest that upregulation of guanylate-binding protein 5 (GBP-5), a component of innate immunity, promotes the progression of LPS-induced SALI [13]. Redistribution of intrahepatic blood flow together with a complex interplay between sinusoidal endothelial cells, macrophages and passing leucocytes lead to decreased perfusion and blood flow velocity in liver sinusoids leading to tissue hypoxia. The endotoxin also causes a dysfunction of bile acid transporters leading to cholestasis [14, 15]. Side effects of the therapy for sepsis may also contribute to liver dysfunction. Thus, liver injury in sepsis can be induced by a variety of mechanisms [16].

Most of the patients who had SALI were infants. A possible reason for the higher occurrence in infancy is the relative immaturity of the liver in early infancy as it undergoes changes in its functional capacity. Kobashi et al. who had recruited patients aged 1–101 years of age had found a bimodal distribution of SALI with infants and the age–group of 65–90 years being the most affected [7].

Our study shows that liver dysfunction is an early event in sepsis with most children developing SALI on the same day on which sepsis is diagnosed. This is similar to the study by Kobashi et al. in which majority (~85%) of the patients developed SALI either on the day or within a week of admission [7]. It was observed that the children with cholestatic dysfunction had a more insidious course with onset at a median 5 days (up to 2 weeks) after the diagnosis of sepsis. Similar observations have been made by other researchers as well [17].

Overall, the cholestatic pattern was the most common form of SALI. We could not identify any laboratory-related risk-factors for a particular pattern of SALI in our cohort. Though children with hypoxic hepatitis had a higher urea and lactate and children with cholestasis had a lower haemoglobin, none of these parameters attained statistical significance possibly as the numbers were relatively small. The higher in-hospital mortality in the SALI group suggests that SALI is associated with a poor prognosis of sepsis, which is consistent with the previous study by Dou et al. [8]. We find that children with SALI have a ~2 times higher risk of mortality as compared to other organ failures. The liver plays a central role in maintaining homeostasis, regulating the inflammatory cascade and clearing bacteria, and it is likely that liver dysfunction in SALI triggers excessive/dysregulated inflammation leading to multi-organ damage and a poor outcome [18]. We did not find any difference in our primary outcomes (hospital stay duration and in-hospital...
mortality) between children with different patterns of liver injury suggesting that children with SALI have an overall poor prognosis irrespective of the type or mechanism of hepatic dysfunction.

We have found that the occurrence of SALI is directly proportional to the severity of the sepsis with a higher pSOFA score predicting its occurrence. Though there is no specific therapy currently available for SALI, early resuscitation should be done to avoid further hypoperfusion of the liver, hepatotoxic drugs should be avoided and enteral feeding rather than parenteral nutrition should be preferred in these patients to prevent further liver injury. There is a need to develop and validate markers of early identification of SALI and specific liver-directed therapies. Lactate is a non-specific marker. Specific biomarkers like serum bilirubin, vitronectin and apolipoprotein A–V have been evaluated as predictors of SALI and look promising [19, 20]. La Mura et al. found that prophylactic simvastatin prevented endotoxemia-induced liver injury, reduced liver inflammation and prevented microvascular dysfunction in rodents [21]. Ursodeoxycholic acid and n-acetylcysteine are examples of other drugs that have been trialled in this sub-group of patients [17]. More data are needed before any recommendations regarding the use of these biomarkers and therapies can be made.

A strength of our study is the use of updated definitions to define sepsis and SALI. We used the pSOFA score (sepsis-3 criteria) to define sepsis which is a validated tool in children [3]. A possible limitation is that we may have inadvertently included a few patients who did not have “true” SALI. The diagnosis of SALI can be challenging with several confounding factors which can bring about alterations in liver functions. We evaluated all children for alternate causes of liver dysfunction and excluded those in whom the derangement in liver functions could be attributed to some other source. Another limitation is that our follow-up is limited to the duration of the hospital stay, and it is not possible to draw inferences regarding the effect of SALI on long-term mortality. Studies in adults have shown that SALI may have an adverse bearing on long-term (~1 year) outcomes also [22, 23].

To conclude, SALI develops in 45 (31.3%) with sepsis. Higher pSOFA are associated with SALI. Children who develop SALI have a higher risk of mortality. A multi-centre study should be carried out to confirm these findings in a larger cohort.

Supplementary information  The online version contains supplementary material available at https://doi.org/10.1007/s00431-022-04374-2.

Authors' contributions  K: acquisition of data and primary drafting of manuscript, RB: critical appraisal and final draft of manuscript, NKB: critical appraisal of manuscript and final draft of manuscript.

Data availability  Yes, with corresponding author.

Code availability  Not applicable.

Declarations

Ethics approval  All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Committee of AIIMS, Rishikesh, India.

Consent to participate  Informed, written consent was obtained from the parents of all individual participants included in the study.

Consent for publication  Obtained.

Competing interests  The authors declare no competing interests.

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