Liver injury and jaundice associated with sepsis

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Overview over the talk

- Jaundice and liver injury among patients with sepsis
- Pathophysiology of cholestasis in sepsis
- Hypoxic hepatitis induced by sepsis
- Sepsis induced cholestasis
- Identification of distinguishing features of drug-induced liver injury and liver injury associated with sepsis

Jaundice and cholestatic illness in sepsis: Sepsis induced liver dysfunction

- Hyperbilirubinemia, defined as >33 micromol/L (>2 mg/dL) has been reported in 10-38% in previous studies in these patients

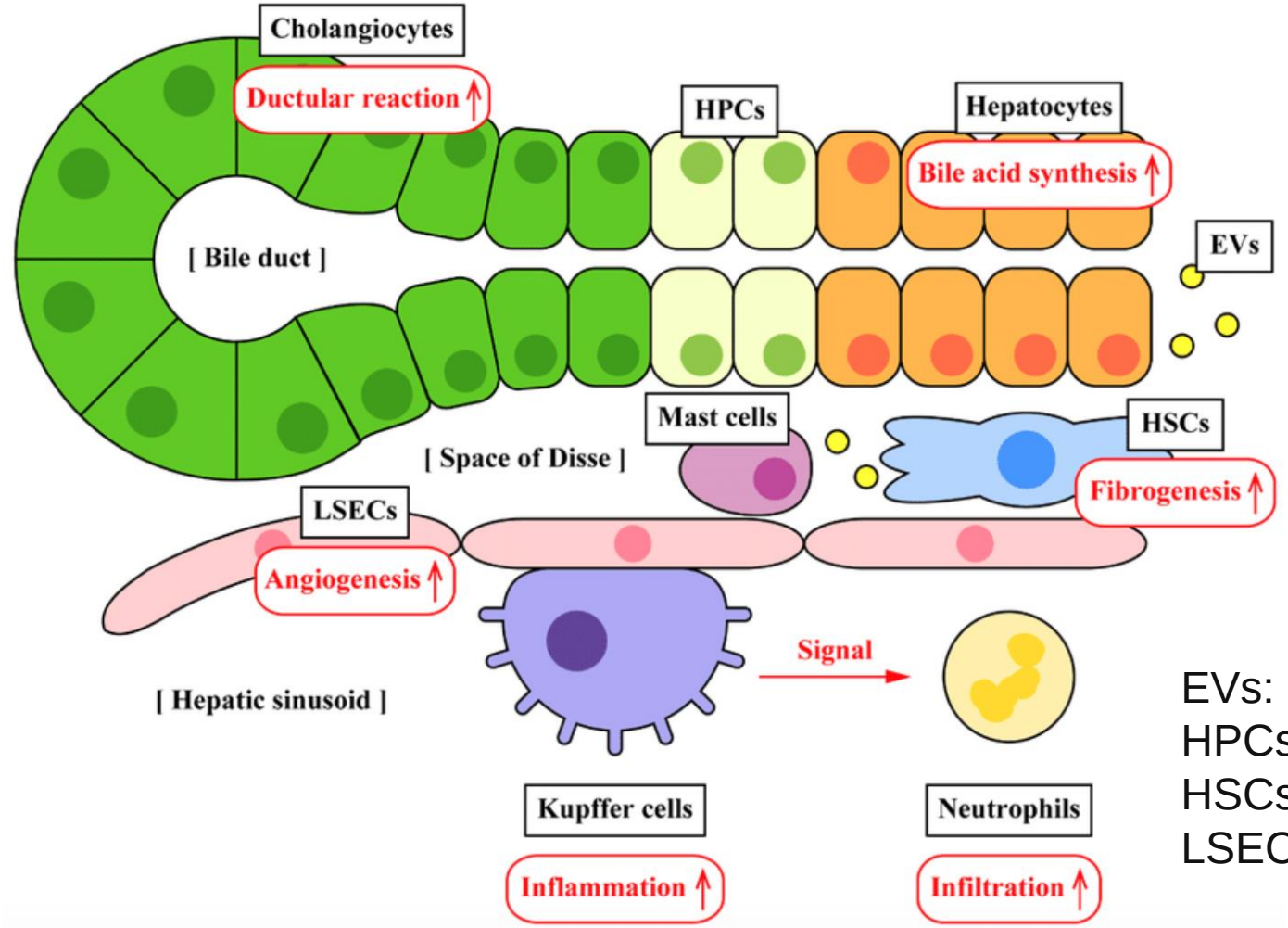
- The most common cause of hyperbilirubinemia in critically ill patients is hepatic dysfunction related to the underlying critical illness

Liver injury in the ICU (intensive care unit)

- Up to 20% of patients develop cholestasis during the ICU stay

- However cholestatic alterations are more frequently found in septic shock (33%), than in cardiogen shock (21%) or following surgery (5%)

The location of liver cells and their orchestration in liver diseases



EVs: Extracellular vesicles;
HPCs: Hepatic progenitor cells;
HSCs: Hepatic stellate cells;
LSECs: Liver sinusoidal endothelial cells.

Sepsis induced liver dysfunction

- In the course of sepsis/septic shock, the metabolism of the hepatocytes is modified towards the inflammatory response

- The main cytokine of the liver infl. response is Il-6: responsible for syntesizing acute phase proteins: CRP, alpha-antitrypsin,fibrinogen, haptoglobin

- Secretion of Il-6 is induced by endotoxins

Two main clinical phenotypes:
(1)Hypoxic hepatitis,& (2) sepsis-induced cholestasis

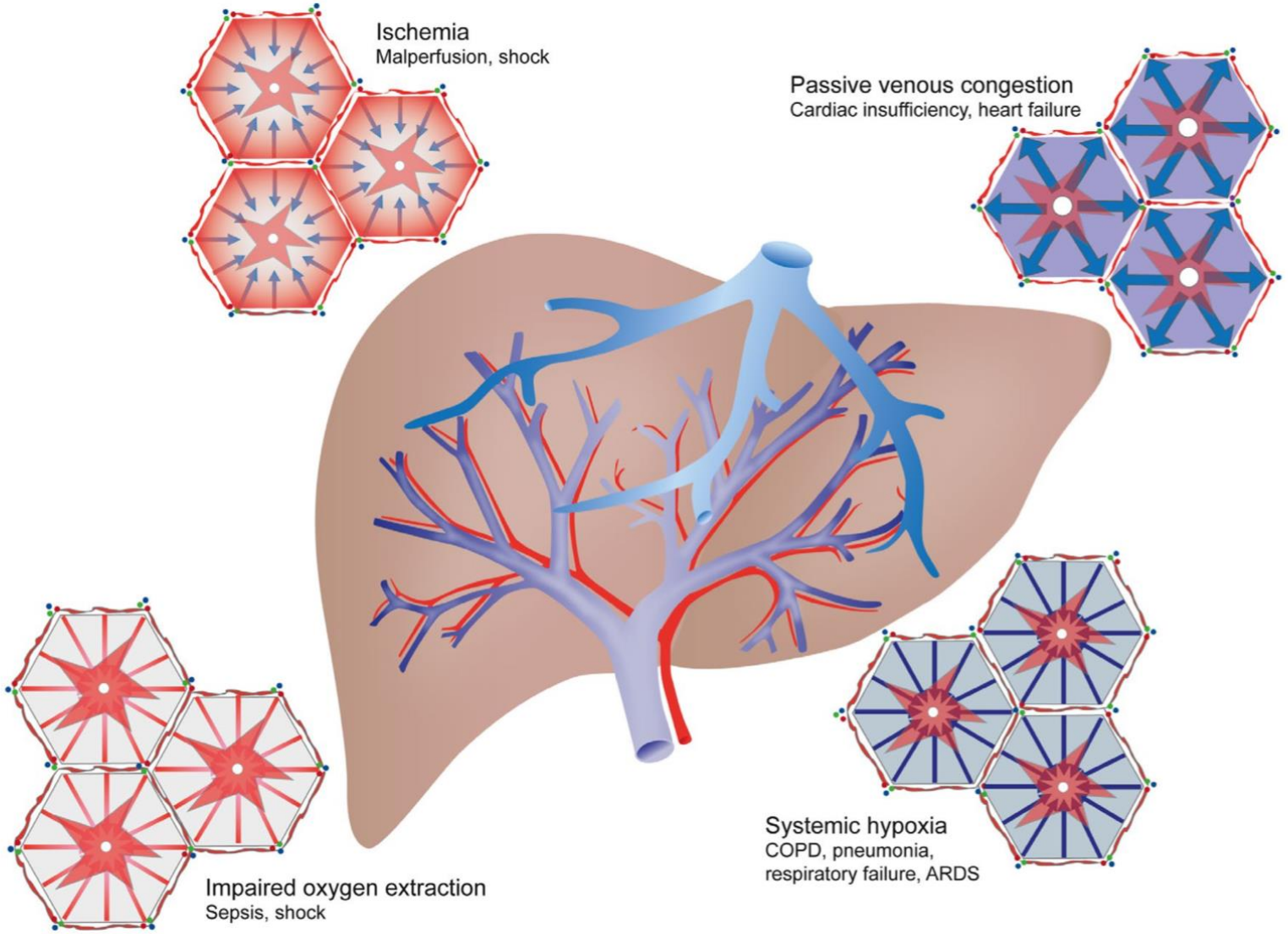
(1) Hypoxic hepatitis,

Ischemic liver damage can occur as a consequence of hypotension, septic chock or prolonged hypoxia in sepsis

Hepatic blood and nutrient flow is depressed in sepsis, might lead to Kupffer cell dysfunction and liver disturbances

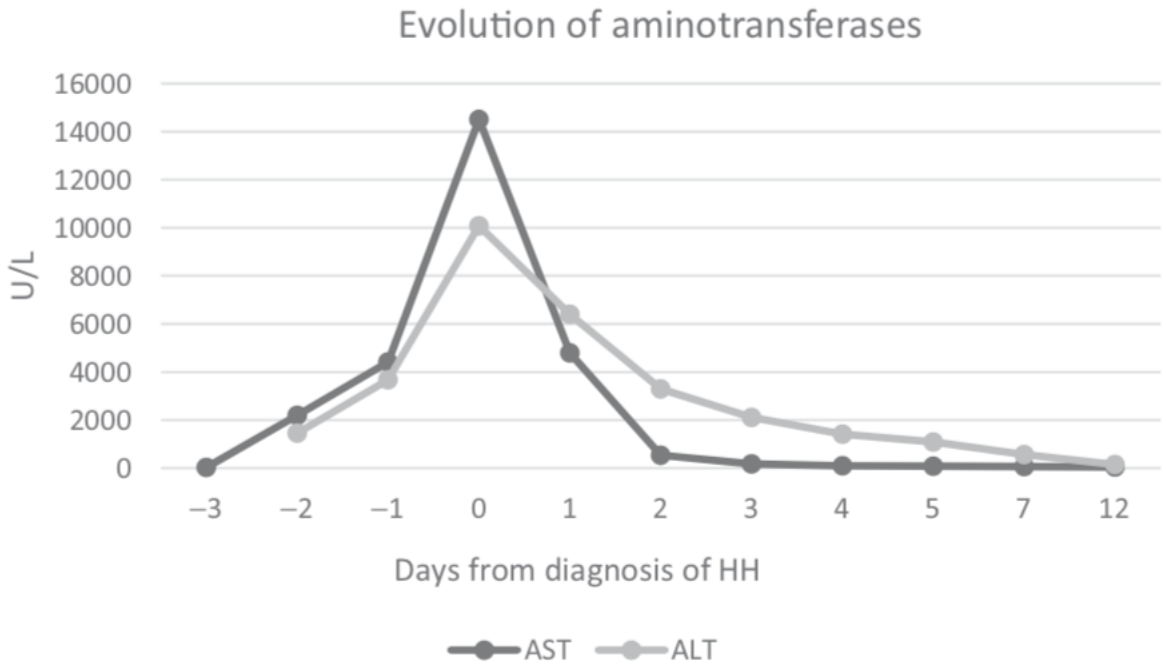
The lack of oxygen, mainly to centrizonal cells and my lead to centrilobular necrosis

Pathophysiological alterations in hypoxic liver injury.



Ischemic hepatitis: hypoxia and sepsis

33 year old woman



(2) Sepsis-induced cholestasis

- The underlying state of endotoxinemia and products released in response to infection appear to play a major role
- Decreased hepatocellular function occurs early in sepsis

This suggests that hepatocellular dysfunction is related to the release of proinflammatory cytokines such as TNF-alpha and Il-6

Endotoxinemia seems to paralyse the hepatocytes and generate the cholestasis of sepsis.

IT IS NOT AN INVASION OF BACTERIA INTO THE LIVER

(2) Sepsis-induced cholestasis

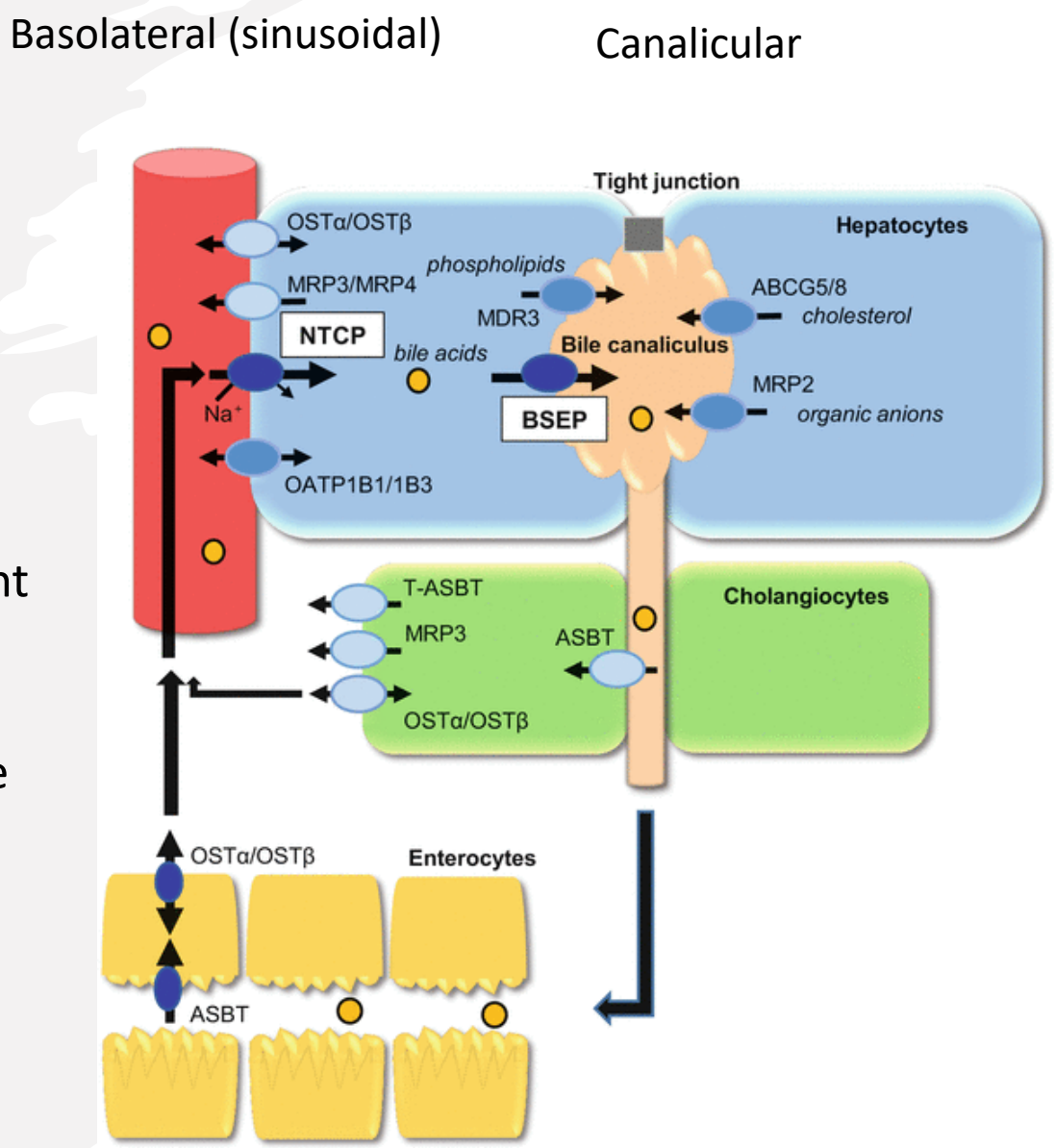
- Several studies have shown a quantitative reduction in bile flow within the isolated perfused livers of rats following LPS or cytokine adminitration
- Immunization with TNF-alpha antibodies blocked endotoxin associated reduction in bile flow and bile salt excretion
- LPS, TNF-alpha and interleukin1-beta have all been shown to mediate these effects

Main mechanisms of cholestasis of sepsis

- **Decreased basolateral transport of bile acids**
  - Inhibition of basolateral membrane Na-K-ATPase activity
  - Decreased basolateral membrane fluidity
  - Down-regulation of transporters
  - Decreased NTCP function
- **Decreased canalicular transport of bile acids**
  - Down-regulations of transporters
  - Decreased BSEP function
  - Decreased MRP2 function

Abnormalities in bile acid formation and flow

- Endotoxinemia does not affect bile acid synthesis, cytosolic transport or permeability of tight junctions
- LPS and cytokines appear to mainly affect hepatocyte uptake and excretion of bile acids
- Endotoxinemia decreases the basolateral and canalicular transport of bile acids



Abnormalities in bile acid formation and flow

- Alterations of hepatic transport and metabolism can occur in the first hours of critical illness
- Several studies have observed endotoxin-induced inhibition of basolateral membrane Na-K-ATPase activity
- Endotoxin may cause decreased function of Na-gradient dependent transporters at the basolateral membrane such as the NTCP
- In a landmark study by Green et al. (Gastroenterology 1996), 16 hours after intraperitoneal adminstration of LPS, both protein expression and functional activity of NTCPs were reduced by >90%

Diagnosis of cholestatic illness in the critically ill patient

- Biliary tract disease: obstruction leading to cholestasis and/or jaundice
- Infection: acute cholangitis
- Liver abscess
- Pylephlebitis
- DILI
- TPN induced cholestasis in chronic cases
- Secondary Sclerosing cholangitis (cholestasis induced by critical illness)

Sepsis associated liver dysfunction

- Sepsis may induce profound changes on the function of the liver due to an uncontrolled systemic inflammatory response and impairments in hepatic microcirculation resulting in changes in the hepatobiliary transport pathways

- Circulating proinflammatory cytokines directly affect the uptake of bilirubin from the systemic circulation and secretion into bile by down- and upregulation of hepatobiliary transporter receptors facilitating a clinically mixed picture of conjugated and unconjugated hyperbilirubinemia

Sepsis-associated liver injury: Incidence, classification and the clinical significance

2013

Haruhiko Kobashi,[1] Junichi Toshimori[1] and Kazuhide Yamamoto[2]

Incidence of sepsis-associated liver injury was 34.7% (156/449)

With 75 cholestatic (48%), 34 hepatocellular (22%) and 47 shock liver (30%) cases.

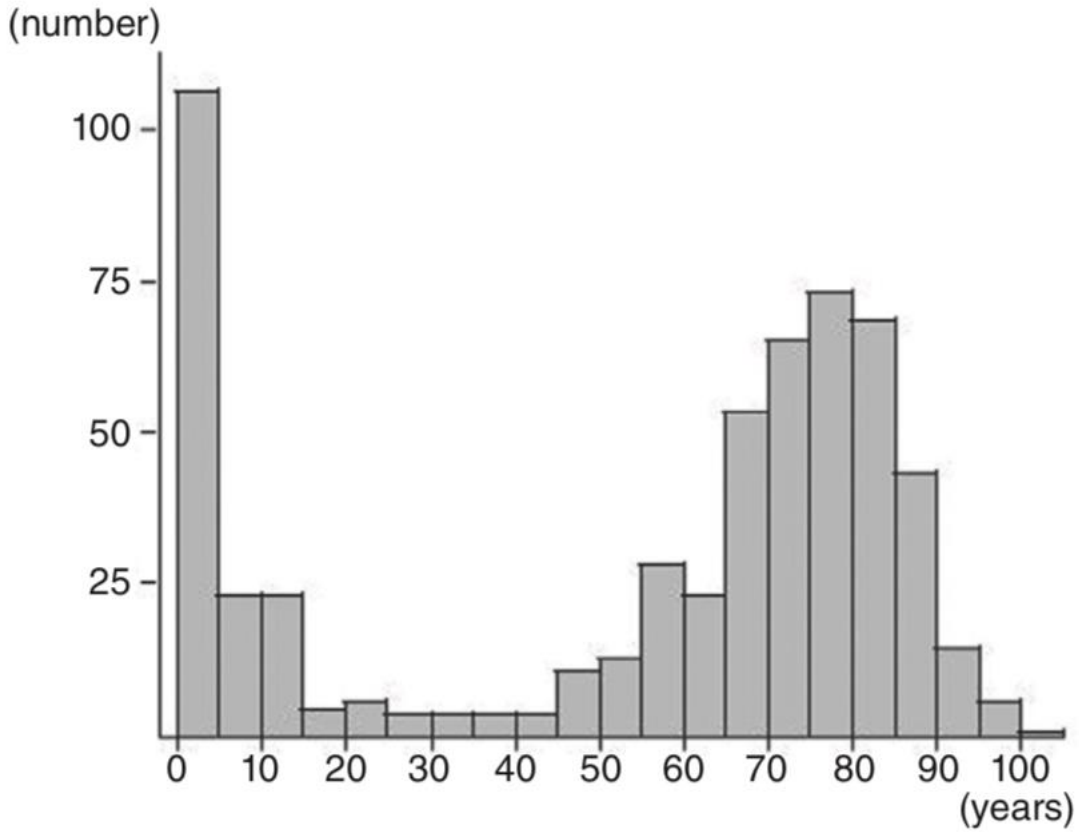
Jaundice was a complication in 25 (33%), six (17.6%) and four (8.5%) patients in each group, respectively.

Mortality was higher in Males (38%) and in the elderly (48%);

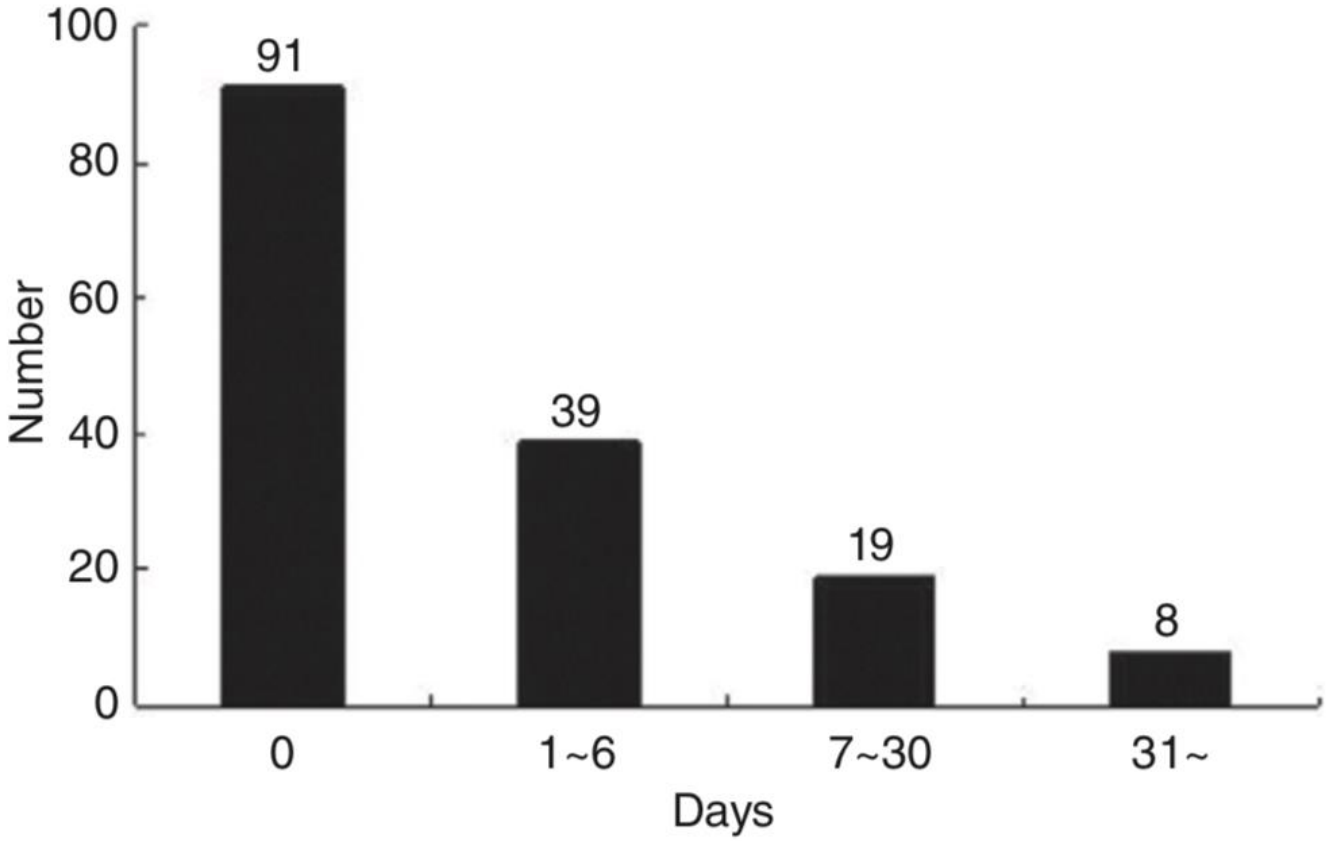
Mortality was 48% in Cholestatic, 38% in hepatocellular and 63% in the shock liver

Higher in patients with elevated liver tests (18%), jaundice (69%) than in those without (45.5%) ($P < 0.0001$).

Age distribution of the all subjects with sepsis



Onset of sepsis-associated liver injury.



Liver INTERNATIONAL

ORIGINAL ARTICLE

Identification of Distinguishing Features of Drug-Induced Liver Injury and Liver Injury Associated With Sepsis

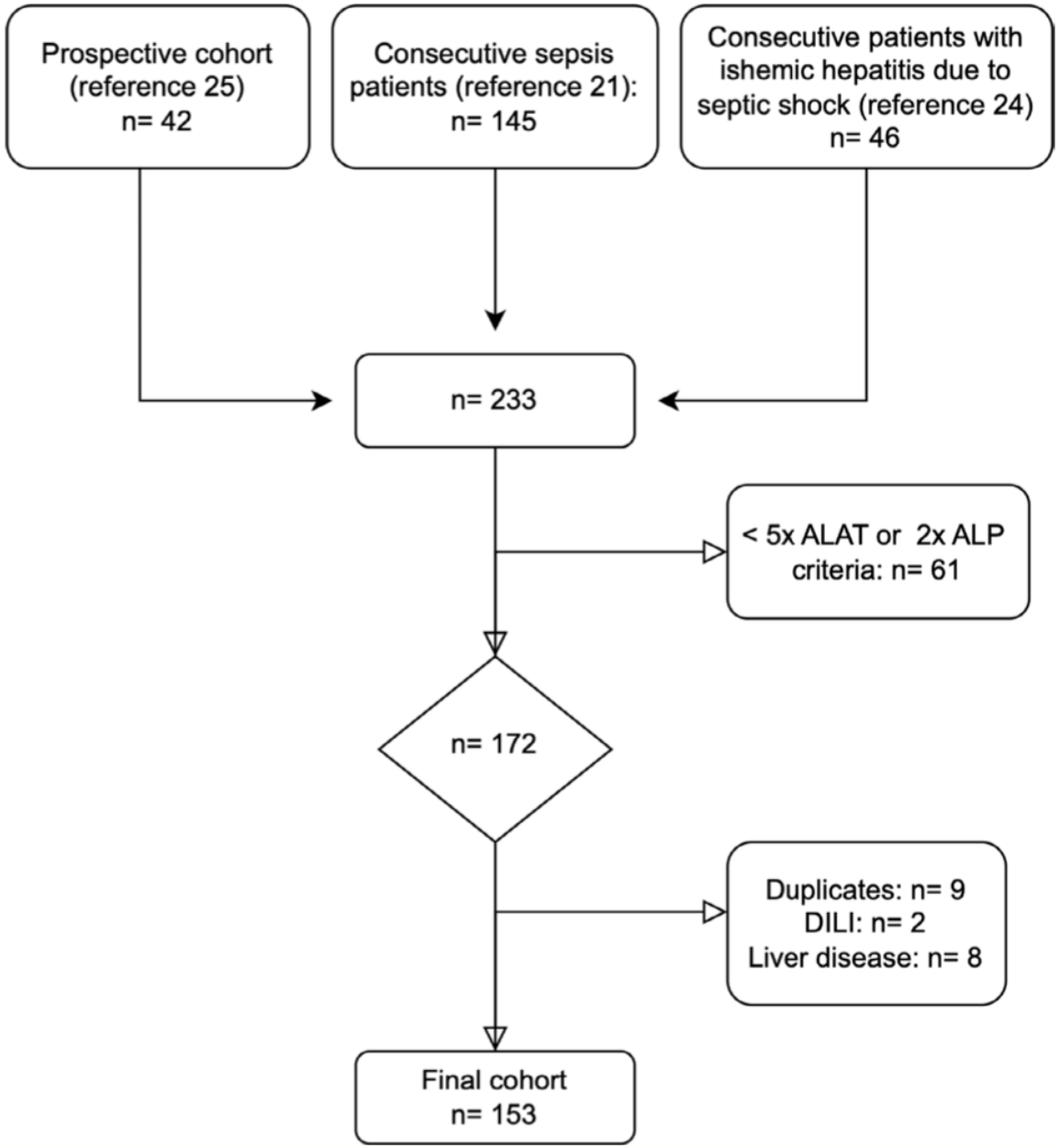
Egill Logason[1] | Sigurdur Sölvi Sigurdarson[1] | Robert A. Björnsson[1] | Edda Vesteinsdottir[2] | Sigurbergur Karason[1,2] | Guruprasad Padur Aithal[3] | Sigrun Helga Lund[4] | Einar Stefan Björnsson[1,5]

Identification of distinguishing features of drug-induced liver injury and liver injury associated with sepsis

- **Background & Aims:** It can be difficult to distinguish between DILI and liver injury associated with sepsis (sepsis induced liver injury, SILI). The aims of the study were to compare clinical and biochemical features between DILI and SILI and identify distinguishing characteristics that might assist in diagnosing these conditions.

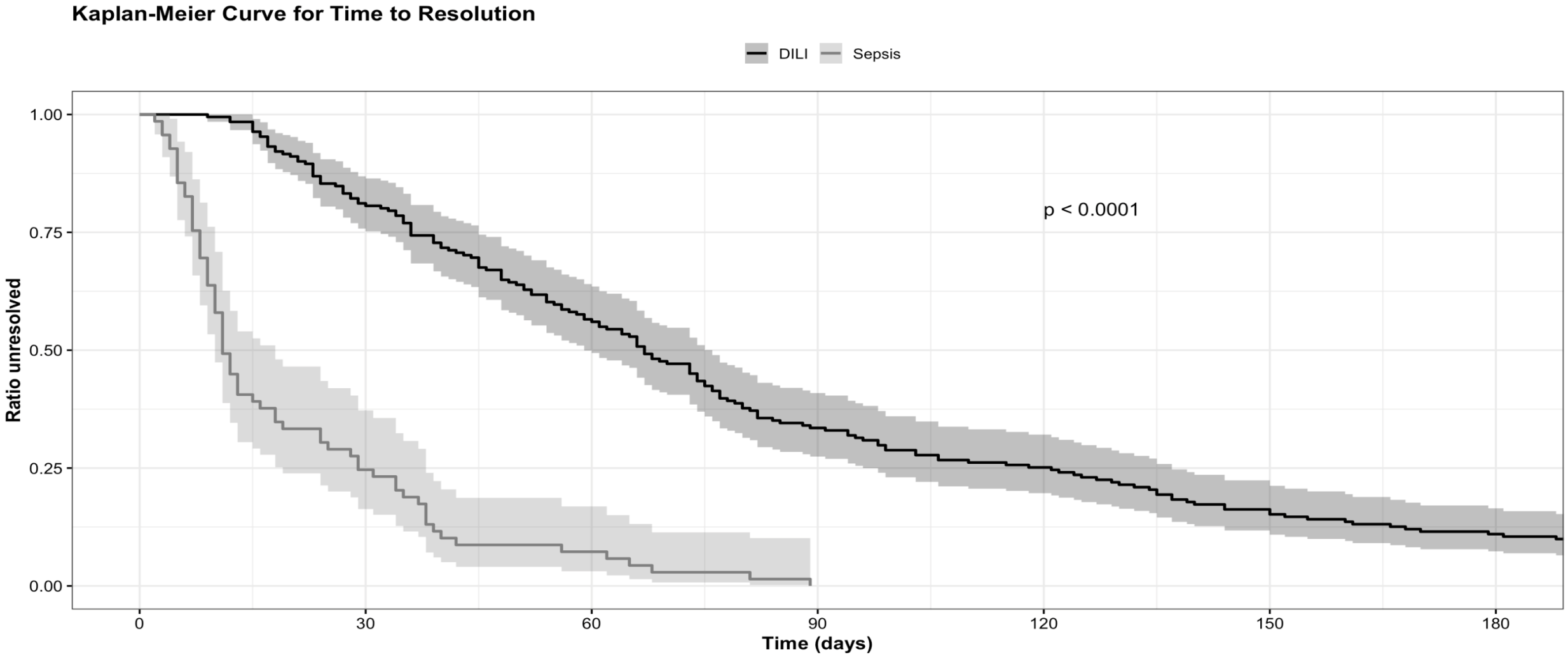
- **Methods:** Retrospective cohorts of all DILI cases diagnosed in Iceland 2009-2024 and SILI 2006-2024 were divided into hepatocellular and Cholestatic (CS/mixed) patterns. Patients had: >5x upper limit of normal (ULN) of ALT and/or >2x ULN in ALP. RUCAM and expert opinion were used in the causality assessment DILI and SILI patient had to fulfill international consensus criteria

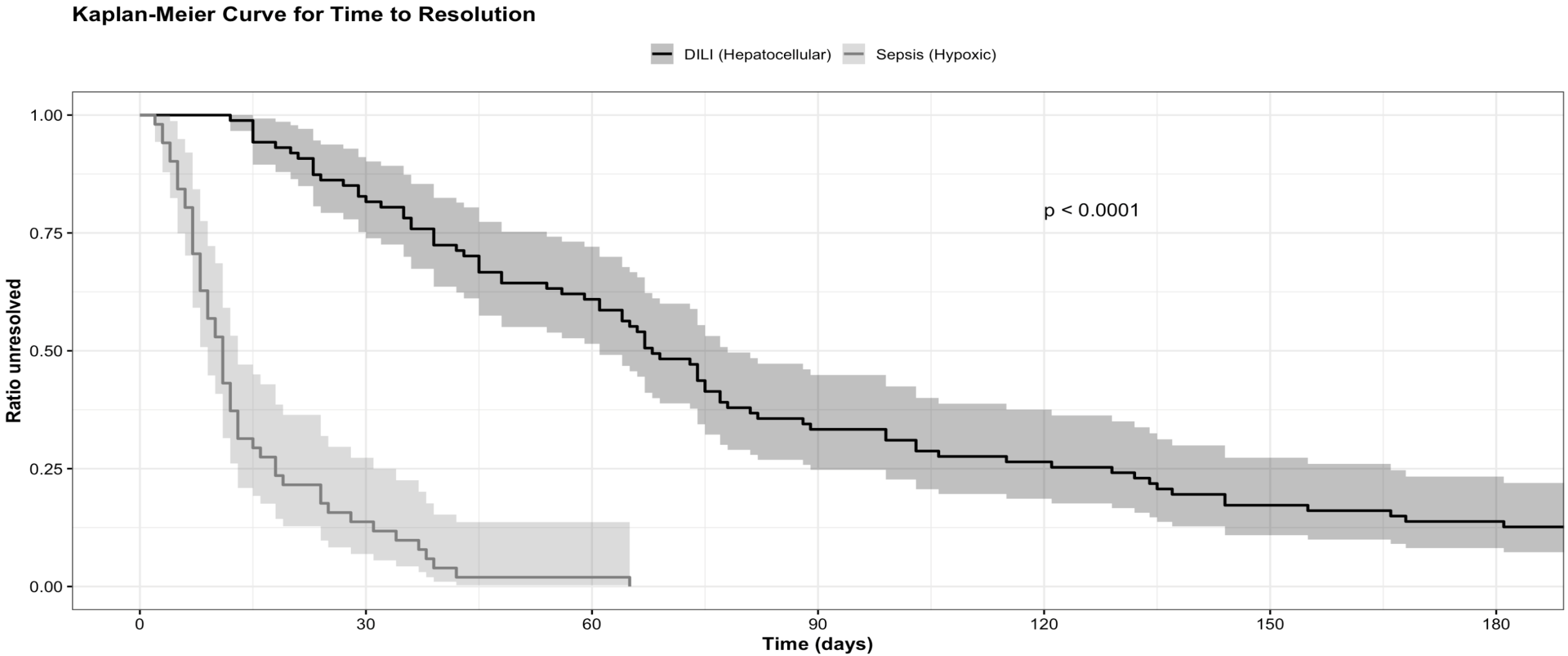
Sepsis patients

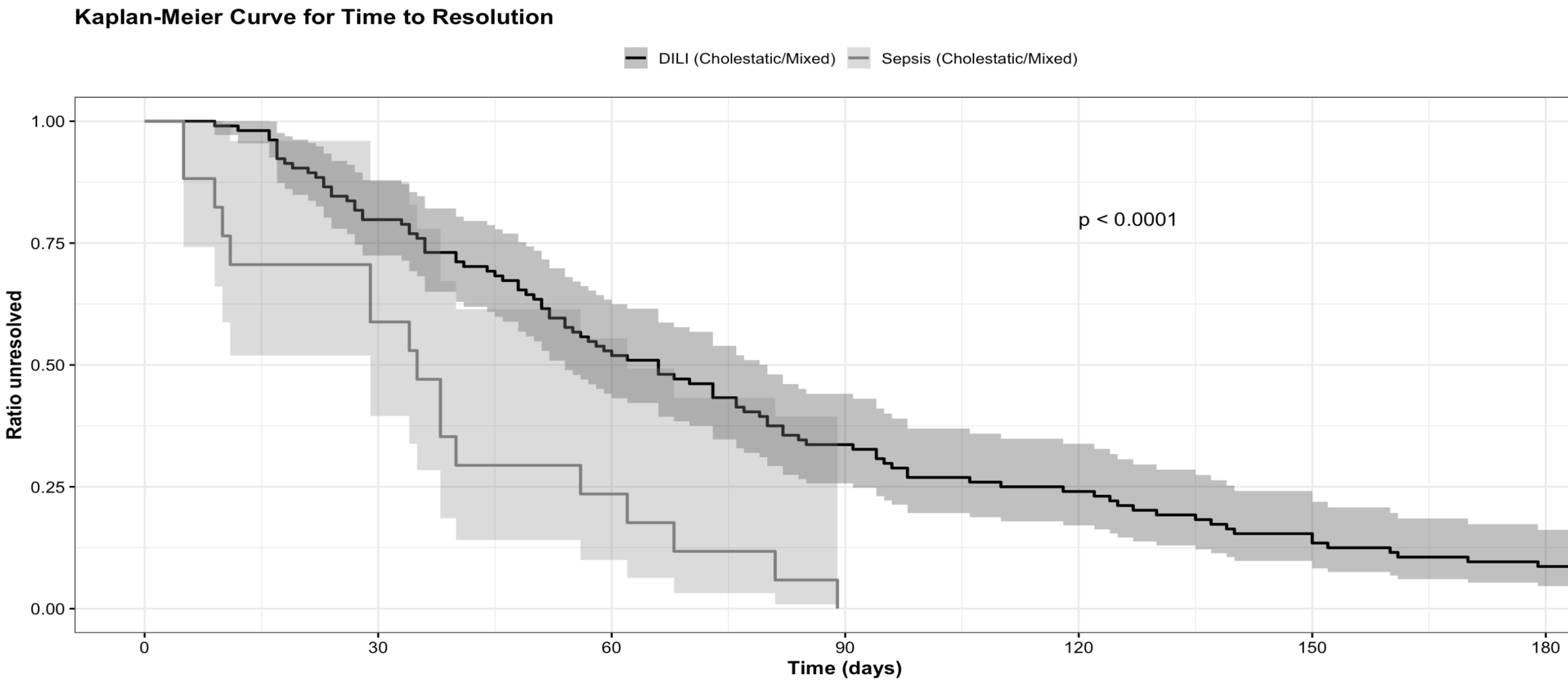


DILI patients

	DILI patients ($n=275$)
Age	59 (43–71), range 16–94
Gender, female (%)	173 (63%)
Onset, days	20 days (8–77)
Most common drugs	
Amoxicillin clavulanate	$n=59$
Multiple drugs	$n=39$
Infliximab	$n=28$
HDS	$n=21$
Statins	$n=9$
TMP/SMP, azathioprine, ceftriaxone	$n=6$
Diclofenac, pembrolizumab, nitrofurantoin	$n=5$
Amoxicillin, cloxacillin, doxycycline, piperacillin/tazobactam	$n=4$
Amiodarone, dicloxacillin, cefazolin	$n=3$
Types of liver injury	
Hepatocellular, *n* (%)	$n=116$ (42%)
Cholestatic, *n* (%)	$n=81$ (29%)
Mixed, *n* (%)	$n=81$ (29%)
Jaundice	$n=93$ (34%)

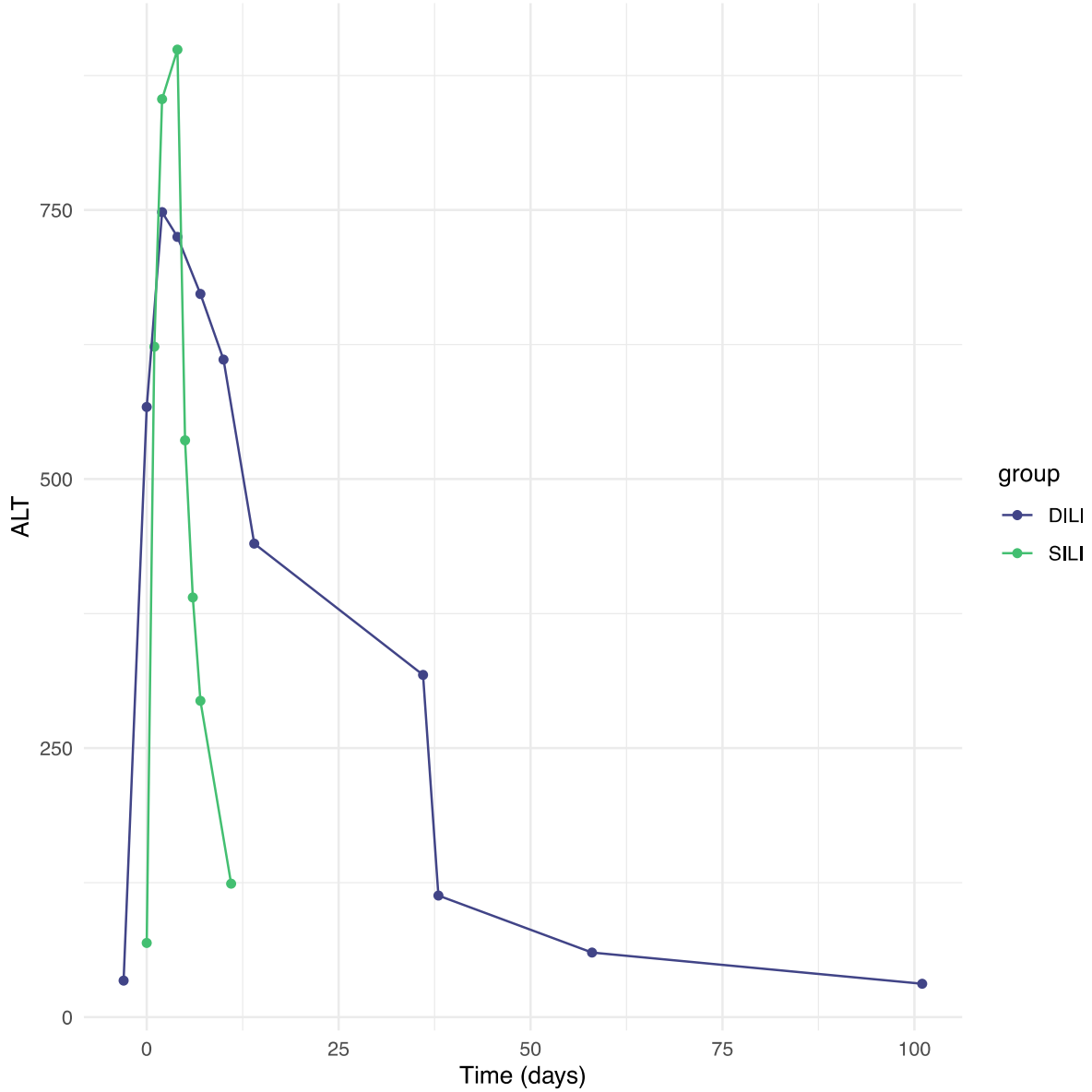

Kaplan-Meier Curve for Time to Resolution
DILI
Sepsis
1.00
0.75
0.50
0.25
0.00
Ratio unresolved
p < 0.0001
0
30
60
90
120
150
180
Time (days)


Kaplan-Meier Curve for Time to Resolution
DILI (Hepatocellular)
Sepsis (Hypoxic)
p < 0.0001
Ratio unresolved
1.00
0.75
0.50
0.25
0.00
0
30
60
90
120
150
180
Time (days)


Kaplan-Meier Curve for Time to Resolution
DILI (Cholestatic/Mixed)
Sepsis (Cholestatic/Mixed)
p < 0.0001
Ratio unresolved
1.00
0.75
0.50
0.25
0.00
0
30
60
90
120
150
180
Time (days)

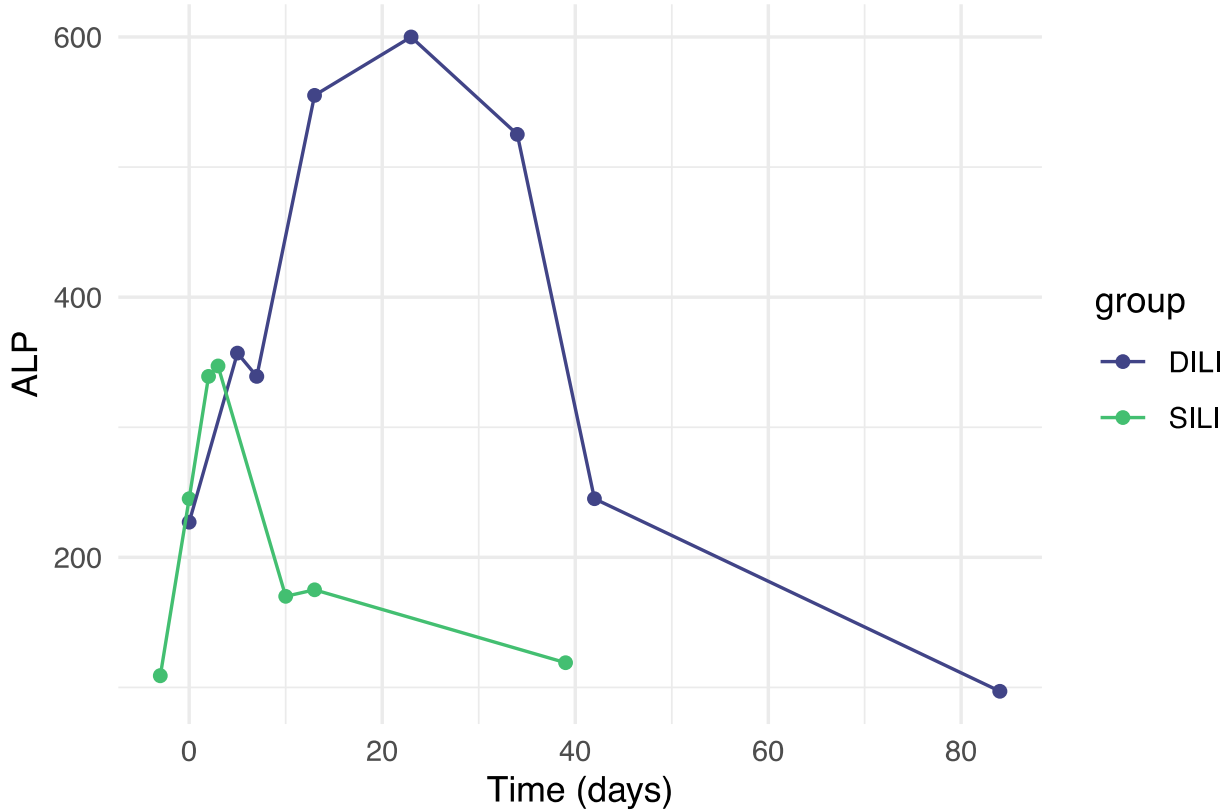
- ALT in a patient with hepatocellular type, hypoxic of sepsis (blue)

- ALT due to infliximab (green)



ALP in a patient with cholestatic type of injury of sepsis (blue)

ALP in a patient with amoxicillin-clavulanate DILI (green)



Independent predictors: Hepatocellular injury

- In patients with hepatocellular liver injury, a longer time to resolution was associated with increased odds of having DILI, with an odds ratio (OR) of 1.225 per day (95% CI, 1.130–1.401).

- Conversely, older age and higher maximal AST levels were asso-ciated with decreased odds of having DILI, with an OR of 0.277 (95% CI, 0.104–0.530) for every 10 years of age and an OR of 0.782(95% CI, 0.660–0.877) per 100- unit increase in AST. The model showed excellent discrimination, with an AUC (area under the curve) of 0.987.

Independent predictors: Cholestatic injury

- Female gender was associated with significantly increased odds of DILI, with an odds ratio (OR) of 5.999 (95% CI, 1.427–31.791).
- Among laboratory values, higher ALP at onset (OR 3.197, 95% CI, 1.647–7.480) and maximal ALT levels (OR1.872, 95% CI, 1.202–3.261) were also associated with increased odds of DILI.
- The model had strong discriminatory performance, with an AUC of 0.944.

Conclusions

- Marked elevation of AST and rapid resolution with a HC pattern of liver injury favours the diagnosis of SILI.

- Cholestatic/mixed SILI also resolved rapidly in contrast to CS/mixed DILI that was associated with markers of more pronounced liver injury.