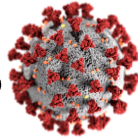


## EVENT DEFINITION FORM

**Event:** Acute liver injury  
**Outcome/covariate:** outcome  
**Version:** 1  
**Status:** final

### Contributing authors

authors	Role	Date
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Leila Belbachir	Medical review	August 22, 2020
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Miriam Sturkenboom	Inclusion of codes used in final report	23-08-2021



## 1. Event definition

The European Association for the study of the Liver defines acute liver failure (ALF) as highly specific and rare syndrome, characterised by an acute abnormality of liver blood tests in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver aetiology, and clinically apparent altered level of consciousness due to hepatic encephalopathy (HE). The condition of patients who develop coagulopathy, but do not have any alteration to their level of consciousness is defined as acute liver injury (ALI).<sup>[1]</sup>

The clinical course of ALF is initiated with a severe ALI. This is characterised by a two- to three times elevation of transaminases (marker of liver damage) associated with impaired liver function, such as jaundice or coagulopathy in a patient without previous chronic disease.<sup>[1]</sup>

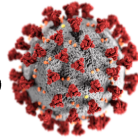
The disturbances to coagulation required to define ALF are determined by a prolongation of International Normalised Ratio (INR), usually >1.5 or a prolongation of prothrombin time (PT).<sup>[2]</sup>

Severe acute liver injury defines a syndrome characterised by markers of liver damage (elevated serum transaminases) and impaired liver function (jaundice and INR >1.5) which usually precedes clinical encephalopathy.<sup>[1]</sup>

Wlodzimirrow et al.<sup>[3]</sup> conducted a systematic review to investigate the explicitness and extent of variability in the used ALF definitions in the ALF prognostic literature. As a result they found 41 different definitions. Pievsky et al.<sup>[4]</sup> gathered in the following table four different definitions that warrant special mention.

*Table 1. Classification systems of acute liver failure ( Modified from <sup>[4]</sup>)*

	<b>Bernuau System<sup>[5]</sup></b>	<b>O'Grady System<sup>[6]</sup></b>	<b>IASL System<sup>[7]</sup></b>	<b>Japanese System<sup>[8]</sup></b>
<b>Definition of ALF</b>	>50% decrease in factor II or V with HE	Severe liver injury with HE without prior liver disease	Severe liver Dysfunction with HE within 4 wk without prior liver disease	INR $\geq$ 1.5 or PT $\leq$ 40% <b>within 8 wk of symptoms</b> without prior liver disease
<b>Requirement for HE</b>	Yes	Yes	Yes	No
<b>Subclasses</b>	Fulminant Subfulminant	Hyperacute Acute Subacute	Hyperacute Fulminant	With hepatic Coma : ✓ Acute ✓ Subacute Without hepatic coma
<b>Duration between symptoms and HE</b>	Fulminant <2 wk Subfulminant 2–12 wk	Hyperacute <1 wk	Hyperacute Fulminant	With hepatic Coma : ✓ Acute <10 d



Acute 1–4 wk  
Subacute 4–12 wk

✓ Subacute 10–56 d  
Without hepatic coma NA

Abbreviations: ALF, acute liver failure; HE, hepatic encephalopathy; IASL, International Association for the Study of the Liver; INR, International Normalized Ratio; NA, not applicable; PT, prothrombin time.

The Catalan Society of Digestology defines ALF as liver injury in the context of acute, but potentially reversible, liver disease affecting a previously healthy liver. However, it also includes other aetiologies in which the condition is the acute manifestation of a chronic liver disease (Wilson's disease, reactivation of hepatitis B virus (HBV) in a non-cirrhotic liver, usually in the context of immunosuppression induced by chemotherapy, acute Budd-Chiari and autoimmune hepatitis) and describes the accepted diagnostic criteria are essentially as follows:<sup>[9]</sup>

- Acute liver disease.
- Reduction of the prothrombin rate below 40% or INR  $\geq 1.5$  as a biological sign of liver failure.
- Less than 28 weeks since onset (24 according to the 1999 definition from the International Association for the Study of the Liver).
- Onset of hepatic encephalopathy (HE) as a clinical sign of liver failure (not considered essential in paediatric patients )
- Previously healthy liver (with the exceptions previously mentioned).

### Drug Induced Liver injury

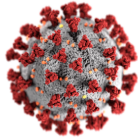
Case definitions for Drug Induced Liver Injury (DILI) include one of the following thresholds:<sup>[10]</sup>

- i)  $\geq 5$  x Upper Limit of normal (ULN) elevation in ALT,
- ii)  $\geq 2$  ULN elevation in Alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of gamma-glutamyltransferase (GGT) in the absence of known bone pathology driving the rise in ALP level),
- iii)  $\geq 3$  x ULN elevation in Alanine Transaminase (ALT) and simultaneous elevation of total bilirubin level (TBL) concentration exceeding 2x ULN.

In patients with abnormal liver tests prior to starting treatment with the implicated drug, ULN is replaced by the mean baseline values obtained prior to DILI onset and increases should be proportionate to this modified baseline.<sup>[10]</sup>

Three patterns of DILI are determined using earliest identified elevation of liver enzymes levels. Initially ALT activity (patients ALT/ULN of ALT) and ALP activity (patients ALP/ULN of ALP) is calculated. Then ALT/ALP ratio (R) is determined:

- Hepatocellular, when there is a 5-fold or higher rise in ALT alone or when the ratio of serum activity ( activity expressed as a multiple of ULN) of ALT to ALP is 5 or more.
- Cholestatic, when there is a 2-fold or higher rise in ALP alone or when the ratio of serum activity of ALT to ALP is 2 or less.
- Mixed, when the ratio of the serum activity of ALT to ALP is between 2 and 5.



## 2. Synonyms / lay terms for the event

Fulminant hepatitis

Fulminant hepatic failure

Fulminant hepatic necrosis

Acute hepatic necrosis

Acute and subacute necrosis of liver

## 3. Laboratory tests that are specific for event

The European Association for the Study of the liver recommends the following laboratory analysis at admission for a patient with suspected ALF/ ALI:<sup>[1]</sup>

### For assessing the severity of the disease:

Prothrombin time (PT), INR or factor V and full coagulation screen including fibrinogen.

Liver blood tests including Lactate dehydrogenase (LDH) and conjugated and unconjugated bilirubin and creatinine kinase

Assessment of renal function:

- urine output: hourly.
- low urea is a marker of severe liver dysfunction.
- creatinine may be difficult to assay in the context of elevated bilirubin.

Arterial blood gas and lactate

Arterial ammonia

### For aetiology:

Toxicology screen in urine and paracetamol serum level

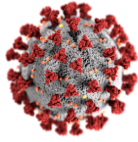
Serological screen for virus infections

- HBsAg, anti-HBc IgM (HBV DNA), delta if positive for HBV
- anti HAV IgM
- anti-HEV IgM
- anti-HSV IgM, anti VZV IgM, CMV, HSV, EBV, parvovirus
- and VZV PCR

Autoimmune markers: ANA, ASMA, anti-soluble liver antigen, globulin profile, ANCA, HLA typing

### For testing for complications:

Lipase or amylase



Laboratory results	Physician progress notes	Brain imaging reports <sup>+</sup>
Alanine aminotransferase*	Diagnoses of:	Diagnoses of:
Alkaline phosphatase*	1. Acute (or fulminant)	1. Acute cerebral ischemia
Alpha-fetoprotein	hepatitis (or liver injury)	2. Acute stroke
Ammonia*	2. Asterixis <sup>‡</sup>	3. Cerebral edema
Anti-kidney liver microsomal type 1 Ab	3. Acute (or fulminant) liver failure	4. Intracranial/cerebral bleed
Anti-mitochondrial Ab	4. Hepatic encephalopathy <sup>†</sup>	5. Intracranial/cerebral mass
Anti-nuclear Ab	5. Jaundice	6. Uncal herniation
Anti-smooth muscle Ab	Drugs to treat encephalopathy <sup>§</sup>	
Aspartate aminotransferase*	Liver transplantation	
Ceruloplasmin	Pre-existing liver disease	
Cytomegalovirus IgG Ab	Suspected SALI etiology	
Ethanol	Use of argatroban, warfarin	
Gamma-glutamyl transpeptidase*	Use of mechanical ventilation	
Hepatitis A IgM, IgG Ab		
Hepatitis B core IgM Ab	<b>Admission history/exam and hospital discharge summaries</b>	
Hepatitis B surface antigen	Diagnoses of:	
Hepatitis C Ab	1. Acute (or fulminant) hepatitis (or liver injury)	
Hepatitis C RNA	2. Asterixis <sup>‡</sup>	
Hepatitis D Ab	3. Acute (or fulminant) liver failure	
Hepatitis E Ab	4. Hepatic encephalopathy <sup>†</sup>	
International normalized ratio*	5. Jaundice	
Total bilirubin*	Pre-existing liver disease	
	Suspected SALI etiology	

Ab = antibody; SALI = severe acute liver injury.

\*Admission and peak results.

<sup>†</sup>Hepatic encephalopathy was recorded if there was a report of altered mentation and a diagnosis was recorded in a physician's note.

<sup>‡</sup>Asterixis was recorded if documented in a physician's physical examination.

<sup>§</sup>Drugs to treat hepatic encephalopathy included lactulose, flumazenil, intravenous mannitol, methylprednisolone, pentobarbital, rifaximin, and thiopental.

+Reports from computed tomography and magnetic resonance imaging studies of the brain.

Figure 1. Data collected from hospital medical records to permit determination of severe acute liver injury and acute liver failure (Re et al.<sup>[11]</sup>)

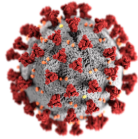
#### 4. Diagnostic tests that are specific for event

Diagnostics test at admission are the following:<sup>[1]</sup>

- Cultures (respiratory, blood, urine).
- Chest X-ray/ECG/liver echography: axial imaging of the abdomen and chest may also be required.
- Cardiac ECG.

The diagnostic evaluation of a patient with suspected ALI/ALF includes a combination of blood testing, imaging, and potentially obtaining a sample of liver tissue via fine-needle aspiration (FNA) or biopsy.<sup>[12]</sup>

- Abdominal ultrasound may provide information regarding hepatic venous disease or underlying Budd-Chiari syndrome.<sup>[13]</sup>
- Liver biopsy.
- Chest x-ray is useful to evaluate for aspiration pneumonia in the vomiting patient.<sup>[13]</sup>
- Head computed tomography (CT) or bedside transcranial Doppler in patient with encephalopathy.
- Bedside echocardiogram to evaluate for CHF causing hepatic congestion and aid in determining fluid status and responsiveness.



## 5. Drugs that are used to treat event

- N-Acetyl cysteine (NAC). Its effectiveness is determined by its antioxidant effect, ability to increase nitric oxide availability, anti-inflammatory action through the nuclear factor kappa B, and vasodilation, which increases peripheral blood flow.<sup>[1]</sup>
- Fresh frozen plasma may be used or, more often, prothrombin (Factor II) in order to limit the increase in the patient's blood volume. To rule out possible nutritional deficiencies, 20-30 mg of vitamin K should be administered.<sup>[9]</sup>
- Antibiotics. Administration of selective digestive decontamination regimens protects these patients from the development of infectious bacterial and fungal complications. A typical empirical regimen is administration of norfloxacin 400 mg/day and nystatin 1 MU every 8 h.<sup>[9]</sup>
- Proton-pump inhibitors.<sup>[9]</sup>
- Lactulose.
- Enema.

## 6. Procedures used specific for event treatment

- Liver transplantation.
- Diet. It is crucial to prevent the loss of muscle mass and to ensure the patient's optimum immune status. Anormal-protein diet is recommended in patients with HE 0-1.<sup>[9]</sup>
- Hydration. Enough to maintain fluid balance considering possible hypovolaemia due to vomiting, poor intake and vasodilation, but also avoiding hypervolemia.<sup>[9]</sup>

## 7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

GP, outpatient specialist, in-hospital, or emergency room.

## 8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA: seek literature for papers that have studied this event, and see how they extracted/measured the event.

### ICD-10CM CODES<sup>[14]</sup>

K72 Hepatic failure, not elsewhere classified

K72.0 Acute and subacute hepatic failure

K72.00 Acute and subacute hepatic failure with-out coma

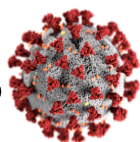
K72.01 Acute and subacute hepatic failure with coma

### Codes used in other EU based studies (not published but reviewed by clinicians)

#### ICD-9

570 Acute and subacute necrosis of liver (Acute hepatic failure; Acute or subacute hepatitis, not specified as infective; Necrosis of liver (acute) (diffuse) (massive) (subacute); Parenchymatous degeneration of liver; Yellow atrophy (liver) (acute) (subacute))

5733 Hepatitis unspecified

**ICD-10**

K71	Toxic liver disease
K710	Toxic liver disease with cholestasis
K711	Toxic liver disease with hepatic necrosis (incl. due to drugs)
K712	Toxic liver disease with acute hepatitis
K717	Toxic liver disease with fibrosis and cirrhosis of liver
K718	Toxic liver disease with other disorders of liver
K719	Toxic liver disease, unspecified
K720	Acute and subacute hepatic failure
K729	Hepatic failure, unspecified
K716	Toxic liver disease with hepatitis, not elsewhere classified

**ICPC**

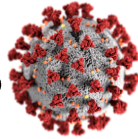
D80	Injury digestive system other (with text searches for liver symptoms of acute nature)
D97	Liver disease NOS

**READ (CPRD version)**

44I4100	Raised serum potassium level
J635.00	Toxic liver disease
J635000	Toxic liver disease with cholestasis
J600z00	Acute necrosis of liver NOS-
J600.00	Acute necrosis of liver
J601.00	Subacute necrosis of liver-
J601z00	Subacute necrosis of liver NOS-
J60z.00	Acute and subacute liver necrosis NOS-
J60..00	Acute and subacute liver necrosis
J635100	Toxic liver disease with hepatic necrosis
J600100	Acute hepatitis - noninfective
J600100	Acute hepatitis - noninfective
J635200	Toxic liver disease with acute hepatitis
J633000	Toxic hepatitis
J635600	Toxic liver disease with fibrosis and cirrhosis of liver
Jyu7000	[X]Toxic liver disease with other disorders of liver
J635X00	Toxic liver disease; unspecified
Jyu7600	[X]Toxic liver disease; unspecified
J635700	Acute hepatic failure due to drugs
J62y.13	Hepatic failure
J625.00	[X] Hepatic failure
J62y.12	Liver failure NOS
J625.11	[X] Liver failure
J601200	Subacute yellow atrophy
J601200	Subacute yellow atrophy
J600000	Acute hepatic failure
J600011	Acute liver failure
J600200	Acute yellow atrophy
J601000	Subacute hepatic failure
J62y.11	Hepatic failure NOS
7L1f.00	Compensation for liver failure
7L1fz00	Compensation for liver failure NOS
J622.00	Hepatic coma
J622.11	Encephalopathy - hepatic
J601100	Subacute hepatitis - noninfective

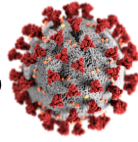
**9. Codes used in ACCESS**

Coding system	Code	Code name	Concept	Concept name	Algorithm
ICD10/CM	K72.91	Hepatic coma NOS	C0019147	Hepatic Coma	Narrow
ICD10/CM	K72	hepatic encephalopathy NOS	C0019151	Hepatic Encephalopathy	Narrow

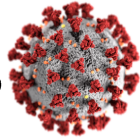


ICD10/CM	K75.9	Inflammatory liver disease, unspecified	C0019158	Hepatitis	Narrow
ICD10/CM	K72.9	Hepatic failure, unspecified	C0085605	Liver Failure	Narrow
ICD10/CM	B17.9	Acute hepatitis NOS	C0267797	Acute hepatitis	Narrow
ICD10/CM	K71.8	Toxic liver disease with other disorders of liver	C0348748	Toxic liver disease with other disorders of liver	possible
ICD10/CM	K71	Toxic liver disease	C0348754	Toxic liver disease	Possible
ICD10/CM	K71.9	Toxic liver disease, unspecified	C0348754	Toxic liver disease	Possible
ICD10/CM	K71.0	Toxic liver disease with cholestasis	C0451707	Toxic liver disease with cholestasis	possible
ICD10/CM	K71.1	Toxic liver disease with hepatic necrosis	C0451708	Toxic liver disease with hepatic necrosis	possible
ICD10/CM	K71.2	Toxic liver disease with acute hepatitis	C0451709	Toxic liver disease with acute hepatitis	possible
ICD10/CM	K71.7	Toxic liver disease with fibrosis and cirrhosis of liver	C0451713	Toxic liver disease with fibrosis and cirrhosis of liver	possible
ICD10/CM	K71.6	Toxic liver disease with hepatitis, not elsewhere classified	C0494782	Toxic liver disease with hepatitis, not elsewhere classified	possible
ICD10/CM	K72	Hepatic failure, not elsewhere classified	C0494783	Hepatic failure, not elsewhere classified	Narrow
ICD10/CM	K72.0	Acute and subacute hepatic failure	C0494784	Acute and subacute hepatic failure	Narrow
ICD10/CM	K71.1	Hepatic failure (acute) (chronic) due to drugs	C2887921	Hepatic failure (acute) (chronic) due to drugs	Narrow
ICD10/CM	K72.01	Acute and subacute hepatic failure with coma	C2887933	Acute and subacute hepatic failure with coma	Narrow
ICD10/CM	K72.0	Acute non-viral hepatitis NOS	C4268643	Acute non-viral hepatitis NOS	Narrow
ICD10/CM	K79.90	Unspecific hepatic failure without coma			Possible
ICD9CM	570	Acute and subacute necrosis of liver	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
ICD9CM	572.2	Hepatic encephalopathy	C0019151	Hepatic Encephalopathy	Narrow
ICD9CM	573.3	Hepatitis, unspecified	C0019158	Hepatitis	Narrow
ICPC2P	D97001	Coma;hepatic	C0019147	Hepatic Coma	Narrow
ICPC2P	D72002	Hepatitis	C0019158	Hepatitis	Narrow
ICPC2P	D97008	Hepatitis	C0019158	Hepatitis	Narrow
ICPC2P	D97007	Failure;hepatic	C0085605	Liver Failure	Narrow
ICPC2P	D72004	Hepatitis;acute	C0267797	Acute hepatitis	Narrow
RCD	J60..	Acute and subacute liver necrosis	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
RCD	J60z.	Acute and subacute liver necrosis NOS	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
RCD	J600.	Acute necrosis of liver	C0001364	Massive Hepatic Necrosis	Narrow

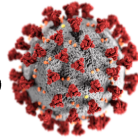




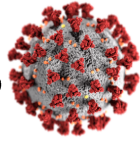
RCD	J6002	Acute yellow atrophy	C0001364	Massive Hepatic Necrosis	Narrow
RCD	J600z	Acute necrosis of liver NOS	C0001364	Massive Hepatic Necrosis	Narrow
RCD	XE0bb	Hepatic coma	C0019147	Hepatic Coma	Narrow
RCD	X0058	Hepatic encephalopathy	C0019151	Hepatic Encephalopathy	Narrow
RCD	J633.	Hepatitis unspecified	C0019158	Hepatitis	Narrow
RCD	J633z	Hepatitis unspecified NOS	C0019158	Hepatitis	Narrow
RCD	X306T	Inflammatory liver disease	C0019158	Hepatitis	Narrow
RCD	J6330	Toxic hepatitis	C0019193	Hepatitis, Toxic	Narrow
RCD	X3076	Hepatic failure	C0085605	Liver Failure	Narrow
RCD	X3077	Liver failure NOS	C0085605	Liver Failure	Narrow
RCD	X3078	Hepatic failure NOS	C0085605	Liver Failure	Narrow
RCD	J6000	Acute hepatic failure	C0162557	Liver Failure, Acute	Narrow
RCD	X3079	Fulminant hepatic failure	C0162557	Liver Failure, Acute	Narrow
RCD	J601.	Subacute necrosis of liver	C0267795	Subacute hepatic necrosis	Narrow
RCD	J601z	Subacute necrosis of liver NOS	C0267795	Subacute hepatic necrosis	Narrow
RCD	XM1Oq	Acute hepatitis	C0267797	Acute hepatitis	Narrow
RCD	Jyu70	[X]Toxic liver dis+o diso/liver	C0348748	Toxic liver disease with other disorders of liver	narrow
RCD	J635.	Toxic liver disease	C0348754	Toxic liver disease	Possible
RCD	Jyu76	[X]Toxic liver disease,unspec	C0348754	Toxic liver disease	Possible
RCD	J6010	Subacute hepatic failure	C0400929	Subacute hepatic failure	Narrow
RCD	J6350	Toxic liver disease with cholestasis	C0451707	Toxic liver disease with cholestasis	Narrow
RCD	J6351	Toxic liver disease with hepatic necrosis	C0451708	Toxic liver disease with hepatic necrosis	Narrow
RCD	J6352	Toxic liver disease with acute hepatitis	C0451709	Toxic liver disease with acute hepatitis	Narrow
RCD	J6356	Toxic liver disease with fibrosis and cirrhosis of liver	C0451713	Toxic liver disease with fibrosis and cirrhosis of liver	Narrow
RCD	J6012	Subacute yellow atrophy	C1304955	Subacute yellow atrophy	Narrow
RCD2	J60..	Acute/subacute liver necrosis	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
RCD2	J60z.	Acute/subacute liver necr.NOS	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
RCD2	J600.	Acute necrosis of liver	C0001364	Massive Hepatic Necrosis	Narrow
RCD2	J6002	Acute yellow atrophy	C0001364	Massive Hepatic Necrosis	Narrow
RCD2	J600z	Acute necrosis of liver NOS	C0001364	Massive Hepatic Necrosis	Narrow
RCD2	J622.	Hepatic coma	C0019147	Hepatic Coma	Narrow
RCD2	J622.	Hepatic coma	C0019151	Hepatic Encephalopathy	Narrow



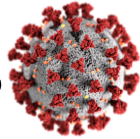
RCD2	J633.	Hepatitis unspecified	C0019158	Hepatitis	Narrow
RCD2	J633z	Hepatitis unspecified NOS	C0019158	Hepatitis	Narrow
RCD2	J6330	Toxic hepatitis	C0019193	Hepatitis, Toxic	Narrow
RCD2	J625.	[X] Hepatic failure	C0085605	Liver Failure	Narrow
RCD2	J62y.	Other chronic liver dis.seque.	C0085605	Liver Failure	Narrow
RCD2	J6000	Acute hepatic failure	C0162557	Liver Failure, Acute	Narrow
RCD2	J601.	Subacute necrosis of liver	C0267795	Subacute hepatic necrosis	Narrow
RCD2	J601z	Subacute necrosis of liver NOS	C0267795	Subacute hepatic necrosis	Narrow
RCD2	Jyu70	[X]Toxc liver dis+o diso/liver	C0348748	Toxic liver disease with other disorders of liver	Narrow
RCD2	J635.	Toxic liver disease	C0348754	Toxic liver disease	Possible
RCD2	Jyu76	[X]Toxic liver disease,unspec	C0348754	Toxic liver disease	Possible
RCD2	J6010	Subacute hepatic failure	C0400929	Subacute hepatic failure	Narrow
RCD2	J6350	Tox liver dis with cholestasis	C0451707	Toxic liver disease with cholestasis	Narrow
RCD2	J6351	Tox liver dis with hep necros	C0451708	Toxic liver disease with hepatic necrosis	Narrow
RCD2	J6352	Tox liver dis + acut hepatitis	C0451709	Toxic liver disease with acute hepatitis	Narrow
RCD2	J6356	Tox liver dis + fibro/cirr liv	C0451713	Toxic liver disease with fibrosis and cirrhosis of liver	Narrow
RCD2	J6012	Subacute yellow atrophy	C1304955	Subacute yellow atrophy	Narrow
SCTSPA	197268000	necrosis hepática aguda y subaguda	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
SCTSPA	13920009	encefalopatía hepática	C0019151	Hepatic Encephalopathy	Narrow
SCTSPA	25072000	necrosis hepática subaguda	C0267797	Acute hepatitis	Narrow
SCTSPA	25072000	atrofia amarilla subaguda del hígado	C2887933	Acute and subacute hepatic failure with coma	Narrow
SCTSPA	29001004	hepatitis	C0019193	Hepatitis, Toxic	Narrow
SCTSPA	33851008	necrosis subaguda	C0348748	Toxic liver disease with other disorders of liver	Narrow
SCTSPA	37871000	hepatitis aguda	C0333502	Subacute necrosis	Narrow
SCTSPA	59927004	insuficiencia hepática	C0494783	Hepatic failure, not elsewhere classified	Narrow
SCTSPA	72836002	coma hepático	C0019151	Hepatic Encephalopathy	Narrow
SCTSPA	73418000	atrofia amarilla aguda del hígado	C0019147	Hepatic Coma	Narrow
SCTSPA	123049003	encefalopatía hepatocerebral - RETIRADO -	C0019151	Hepatic Encephalopathy	Narrow
SCTSPA	128241005	hepatitis	C0019158	Hepatitis	Narrow
SCTSPA	197269008	necrosis aguda de hígado	C0001364	Massive Hepatic Necrosis	Narrow



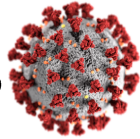
SCTSPA	197270009	insuficiencia hepática aguda	C0162557	Liver Failure, Acute	Narrow
SCTSPA	197272001	atrofia amarilla aguda	C0001364	Massive Hepatic Necrosis	Narrow
SCTSPA	197273006	necrosis hepática aguda, SAI	C0001364	Massive Hepatic Necrosis	Narrow
SCTSPA	197274000	necrosis hepática subaguda	C0267795	Subacute hepatic necrosis	Narrow
SCTSPA	197275004	insuficiencia hepática subaguda	C0451707	Toxic liver disease with cholestasis	Narrow
SCTSPA	197276003	atrofia amarilla subaguda	C1304955	Subacute yellow atrophy	Narrow
SCTSPA	197277007	necrosis hepática subaguda, SAI	C0267795	Subacute hepatic necrosis	Narrow
SCTSPA	197278002	necrosis hepática aguda y subaguda, SAI	C0001364	Massive Hepatic Necrosis	Narrow
SCTSPA	197351001	hepatitis no especificada	C0019158	Hepatitis	Narrow
SCTSPA	197352008	hepatitis tóxica	C0085605	Liver Failure	Narrow
SCTSPA	197353003	hepatitis no especificada, SAI	C0019158	Hepatitis	Narrow
SCTSPA	197354009	hepatopatía tóxica	C0348754	Toxic liver disease	Possible
SCTSPA	197355005	hepatopatía tóxica con colestasis	C0451708	Toxic liver disease with hepatic necrosis	Narrow
SCTSPA	197356006	hepatopatía tóxica con necrosis hepática	C0451709	Toxic liver disease with acute hepatitis	Narrow
SCTSPA	197358007	hepatopatía tóxica con hepatitis aguda	C0451713	Toxic liver disease with fibrosis and cirrhosis of liver	Narrow
SCTSPA	197362001	hepatopatía tóxica con fibrosis y cirrosis hepática	C0494782	Toxic liver disease with hepatitis, not elsewhere classified	Narrow
SCTSPA	197552007	[X]enfermedad tóxica hepática con otros trastornos del hígado	C0348754	Toxic liver disease	Possible
SCTSPA	197558006	[X]enfermedad tóxica hepática, no especificada	C0400929	Subacute hepatic failure	Narrow
SCTSPA	235882007	insuficiencia del hígado, SAI	C0085605	Liver Failure	Narrow
SCTSPA	235883002	insuficiencia hepática, SAI	C0085605	Liver Failure	Narrow
SCTSPA	235884008	insuficiencia hepática fulminante	C0267795	Subacute hepatic necrosis	Narrow
SCTSPA	449902003	encefalopatía portal sistémica	C0019158	Hepatitis	Narrow
SNOMEDCT_US	13920009	Hepatic encephalopathy	C0019151	Hepatic Encephalopathy	Narrow
SNOMEDCT_US	25072000	Subacute hepatic necrosis	C0267795	Subacute hepatic necrosis	Narrow
SNOMEDCT_US	25072000	Subacute yellow atrophy of liver	C1304955	Subacute yellow atrophy	Narrow
SNOMEDCT_US	29001004	Hepatitis	C0019158	Hepatitis	Narrow
SNOMEDCT_US	33851008	Subacute necrosis	C0333502	Subacute necrosis	Narrow
SNOMEDCT_US	37871000	Acute hepatitis	C0267797	Acute hepatitis	Narrow
SNOMEDCT_US	59927004	Hepatic failure	C0085605	Liver Failure	Narrow
SNOMEDCT_US	72445008	Subacute hepatitis - noninfective			narrow



SNOMEDCT_US	72445008	Subacute noninfective hepatitis			narrow
SNOMEDCT_US	72445008	Subacute hepatitis - noninfective			narrow
SNOMEDCT_US	72836002	Hepatic coma	C0019147	Hepatic Coma	Narrow
SNOMEDCT_US	73418000	Acute hepatic necrosis	C0001364	Massive Hepatic Necrosis	Narrow
SNOMEDCT_US	123049003	Hepatocerebral encephalopathy	C0019151	Hepatic Encephalopathy	Narrow
SNOMEDCT_US	128241005	Inflammatory disease of liver	C0019158	Hepatitis	Narrow
SNOMEDCT_US	155808003	Acute/subac. necrosis of liver	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
SNOMEDCT_US	155808003	Acute hepatic failure	C0162557	Liver Failure, Acute	Narrow
SNOMEDCT_US	155820006	Hepatic coma	C0019147	Hepatic Coma	Narrow
SNOMEDCT_US	197268000	Acute and subacute liver necrosis	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
SNOMEDCT_US	197269008	Acute necrosis of liver	C0001364	Massive Hepatic Necrosis	Narrow
SNOMEDCT_US	197270009	Acute hepatic failure	C0162557	Liver Failure, Acute	Narrow
SNOMEDCT_US	197271008	Acute hepatitis - noninfective			narrow
SNOMEDCT_US	197271008	Acute hepatitis - noninfective			narrow
SNOMEDCT_US	197272001	Acute yellow atrophy	C0001364	Massive Hepatic Necrosis	Narrow
SNOMEDCT_US	197273006	Acute necrosis of liver NOS	C0001364	Massive Hepatic Necrosis	Narrow
SNOMEDCT_US	197274000	Subacute hepatic necrosis	C0267795	Subacute hepatic necrosis	Narrow
SNOMEDCT_US	197275004	Subacute hepatic failure	C0400929	Subacute hepatic failure	Narrow
SNOMEDCT_US	197276003	Subacute yellow atrophy	C1304955	Subacute yellow atrophy	Narrow
SNOMEDCT_US	197277007	Subacute necrosis of liver NOS	C0267795	Subacute hepatic necrosis	Narrow
SNOMEDCT_US	197278002	Acute and subacute liver necrosis NOS	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
SNOMEDCT_US	197332007	Hepatic coma	C0019147	Hepatic Coma	Narrow
SNOMEDCT_US	197332007	Encephalopathy - hepatic	C0019151	Hepatic Encephalopathy	Narrow
SNOMEDCT_US	197334008	Hepatic failure	C0085605	Liver Failure	Narrow
SNOMEDCT_US	197335009	Hepatic failure	C0085605	Liver Failure	Narrow
SNOMEDCT_US	197351001	Hepatitis unspecified	C0019158	Hepatitis	Narrow
SNOMEDCT_US	197352008	Toxic hepatitis	C0019193	Hepatitis, Toxic	Narrow
SNOMEDCT_US	197353003	Hepatitis unspecified NOS	C0019158	Hepatitis	Narrow
SNOMEDCT_US	197354009	Toxic liver disease	C0348754	Toxic liver disease	Possible
SNOMEDCT_US	197355005	Toxic liver disease with cholestasis	C0451707	Toxic liver disease with cholestasis	Narrow
SNOMEDCT_US	197356006	Toxic liver disease with hepatic necrosis	C0451708	Toxic liver disease with hepatic necrosis	Narrow



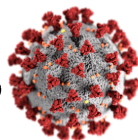
SNOMEDCT_US	197358007	Toxic liver disease with acute hepatitis	C0451709	Toxic liver disease with acute hepatitis	Narrow
SNOMEDCT_US	197359004	Toxic liver disease with chronic persistent hepatitis			possible
SNOMEDCT_US	197360009	Toxic liver disease with chronic lobular hepatitis			possible
SNOMEDCT_US	197361008	Toxic liver disease with chronic active hepatitis			possible
SNOMEDCT_US	197362001	Toxic liver disease with fibrosis and cirrhosis of liver	C0451713	Toxic liver disease with fibrosis and cirrhosis of liver	Narrow
SNOMEDCT_US	197362001	Toxic liver disease with fibrosis and cirrhosis of liver			possible
SNOMEDCT_US	197363006	[X]Toxic liver disease, unspecified	C0348754	Toxic liver disease	Possible
SNOMEDCT_US	197552007	[X]Toxic liver disease with other disorders of liver	C0348748	Toxic liver disease with other disorders of liver	Narrow
SNOMEDCT_US	197558006	[X]Toxic liver disease, unspecified	C0348754	Toxic liver disease	Possible
SNOMEDCT_US	235856003	Subacute necrosis of liver NOS			narrow
SNOMEDCT_US	235856003	LD - Liver disease			possible
SNOMEDCT_US	235856003	Hepatopathy			narrow
SNOMEDCT_US	235856003	Subacute necrosis of liver NOS			narrow
SNOMEDCT_US	235856003	Other sequelae of chronic liver disease			possible
SNOMEDCT_US	235856003	Other liver disorders			possible
SNOMEDCT_US	235856003	Other specified liver disorder			possible
SNOMEDCT_US	235856003	Other specified liver disorder NOS			possible
SNOMEDCT_US	235856003	Liver disorder NOS			possible
SNOMEDCT_US	235856003	[X]Diseases of the liver			possible
SNOMEDCT_US	235856003	[X]Other specified diseases of liver			possible
SNOMEDCT_US	235856003	[X]Liver disorders in infectious and parasitic diseases CE			possible
SNOMEDCT_US	235856003	[X]Liver disorders in other diseases classified elsewhere			possible
SNOMEDCT_US	235856003	Liver anomalies			possible
SNOMEDCT_US	235856003	Liver anomaly, unspecified			possible
SNOMEDCT_US	<b>235862008</b>	<b>Hepatitis due to infection</b>			Narrow
SNOMEDCT_US	235882007	Liver failure NOS	C0085605	Liver Failure	Narrow
SNOMEDCT_US	235883002	Hepatic failure NOS	C0085605	Liver Failure	Narrow



SNOMEDCT_US	235884008	Fulminant hepatic failure	C0162557	Liver Failure, Acute	Narrow
SNOMEDCT_US	266536009	Acute/subac. necrosis of liver	C0001308	Acute and subacute liver necrosis (disorder)	Narrow
SNOMEDCT_US	266536009	Acute hepatic failure	C0162557	Liver Failure, Acute	Narrow
SNOMEDCT_US	413438002	Acute hepatic failure due to drugs			narrow
SNOMEDCT_US	449902003	Portal systemic encephalopathy	C0019151	Hepatic Encephalopathy	Narrow

## 11. Algorithm proposal Exclusion of specific codes (viral hepatitis/other specific causes) & laboratory tests

Concept sets	Concept	Codes
<b>Hepatic_disorders</b>	Hepatic failure	ICD10: K72, K72.0, K72.01, K72.9 ICD9: READ: J6010, J625., J62y., J6000 MEDRA: 10056956, 10016152, 10019663, 10024678, 10000804, 10017469, 10049844 ICPC: D97007
	Hepatic necrosis	ICD10: -- ICD9: 570 READ: J60., J60z., J600., J6002, J600z, J601z, J601. MEDRA: 10000670, 10003695, 10070815, 10042277 ICPC: --
	Hepatic coma	ICD10: K72.91 ICD9: READ: J622. MEDRA: 10010075, 10019644 ICPC: D97001
	Hepatic encephalopathy	ICD10: K72 ICD9: 572.2 READ: J622. MEDRA: 10014630, 10019660 ICPC: --
<b>Hepatitis</b>	Hepatitis	ICD10: K75.9, B17.9 ICD9: 573.3 READ: J633., J633z MEDRA: 10019717, 10019789, 10019790, 10019802, 10029715, 10019727 ICPC: D72002, D97008, D72004
<b>Toxic_liver</b>	Toxic liver	ICD10: K71.8, K71, K71.9, K71.0, K71.1, K71.2, K71.7, K71.6 ICD9: --



		READ: J6330, Jyu70, Jyu76, J635., J6350, J6351, J6352, J6356 MEDRA: 10019795 ICPC: --
<b>Yellow_atrophy</b>	Subacute yellow atrophy	ICD10: -- ICD9: -- READ: J6012 MEDRA: -- ICPC: --

### **Broad & Narrow algorithm:**

- All concept sets = (Hepatic\_disorders, Hepatitis, Toxic\_liver, Yellow\_atrophy) in any provenance, no prior codes
- Index date: first occurrence of any of these concept sets

## **11. Background rates**

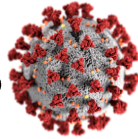
The following search terms were used to extract background rates for ALI/ALF: ("acute liver failure"[MeSH Terms] OR "acute liver injury" [MeSH Terms]) AND ("incidence"[tw]) NOT (Comment[ptyp] OR Editorial[ptyp] OR News[ptyp] OR Newspaper Article[ptyp]) NOT ("animals"[Mesh] NOT "humans"[Mesh]) AND English[lang] Between 2010-2020

The background rates for ALI/ALF obtained through literature review are shown in the link as follows:

*Table 2. References corresponding to the studies included in relation to the background rates.*

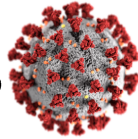
<b>Number</b>	<b>Study reference</b>
1.	Weiler N, Schlotmann A, Schnitzbauer AA, Zeuzem S, Welker M-W. The Epidemiology of Acute Liver Failure. <i>Dtsch Arztebl Int</i> 2020;117(4):43–50.
2	Thanapirom K, Treeprasertsuk S, Soonthornworasiri N, Poovorawan K, Chaiteerakij R, Komolmit P, et al. The incidence, etiologies, outcomes, and predictors of mortality of acute liver failure in Thailand: a population-base study. <i>BMC Gastroenterol</i> 2019;19(1):18.
3	Ho C-M, Lee C-H, Wang J-Y, Lee P-H, Lai H-S, Hu R-H. Nationwide longitudinal analysis of acute liver failure in taiwan. <i>Medicine (Baltimore)</i> 2014;93(4):e35.
4	Bretherick AD, Craig DGN, Masterton G, Bates C, Davidson J, Martin K, et al. Acute liver failure in Scotland between 1992 and 2009; incidence, aetiology and outcome. <i>QJM</i> 2011;104(11):945–56.
5	Warrillow S, Bailey M, Pilcher D, Kazemi A, McArthur C, Young P, et al. Characteristics and outcomes of patients with acute liver failure admitted to Australian and New Zealand intensive care units. <i>Intern Med J</i> 2019;49(7):874–85.

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17. Ho C-M, Lee C-H, Wang J-Y, Lee P-H, Lai H-S, Hu R-H. Nationwide longitudinal analysis of acute liver failure in taiwan. *Medicine (Baltimore)* 2014;93(4):e35.
18. Bretherick AD, Craig DGN, Masterton G, Bates C, Davidson J, Martin K, et al. Acute liver failure in Scotland between 1992 and 2009; incidence, aetiology and outcome. *QJM* 2011;104(11):945–56.
19. Warrillow S, Bailey M, Pilcher D, Kazemi A, McArthur C, Young P, et al. Characteristics and outcomes of patients with acute liver failure admitted to Australian and New Zealand intensive care units. *Intern Med J* 2019;49(7):874–85.