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A Systematic Review on Prognostic Indicators of Acute Liver Failure and Their Predictive Value for Poor Outcome

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Authors' contributions

All authors made substantial contributions to the study design and methods. Authors KAW, SE and RAFMC performed the literature search, evaluated studies, extracted data and analyzed data and interpreted the results. Authors KAW and RAFMC drafted the manuscript. Authors KAW, SE, AAH, MN and RAFMC were involved in revising the final manuscript, read and approved the final manuscript.

Review Article

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ABSTRACT

Aims: To systematically identify and summarize prognostic indicators in patients with acute liver failure and to evaluate their predictive value. To analyse a wide spectrum of indicators used worldwide for prediction of outcome in patients with acute liver failure as a starting point for a better prognostic index.
Methodology: Online databases MEDLINE® (1950-2014) and EMBASE® (1980-2014) were searched and studies published up to 01 January 2014 were considered. Articles were included if they reported original data from a clinical trial or observational study on patients with diagnosis of acute liver failure or fulminant hepatic failure and if one of their main objectives was evaluating prognostic indicators of acute liver failure outcome. Of 1835 identified studies 119 were included for detailed analysis.

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Results: Based on 289 selected indicators and their effect on patient outcome following 8 categories were formed: general markers (n=32), bio-markers (n=131), hemodynamic (n=14), liver function tests (n=7), imaging/morphology (n=15), scoring systems (n=53), time intervals (n=17), and treatments (n=20). The most frequently reported indicators were: bilirubin, age creatinine, coagulopathy expressed by prothrombin time or INR and hepatic encephalopathy.
Conclusion: This review provides a large amount of information, including the extensive list of worldwide used indicators to predict outcome in patients with acute liver failure. There is large heterogeneity in prognostic indicators of acute liver failure, methods of measurement, complexity of calculation and threshold values. Based on this large list of indicators we suggest that an ideal prognostic index should preferentially be based on pathophysiological aspects and has to be applied in a dynamic way. Future studies on acute liver failure can profit from this inventory.

Keywords: Acute liver failure; fulminant hepatic failure; prognosis; predictive indicators; acute liver injury.

1. INTRODUCTION

Acute liver failure (ALF) is a syndrome with a high mortality up to 80% depending on the aetiology and the clinical experience of the reference center [1]. An early and exact assessment of the severity of ALF together with a prediction of its further development is critical in order to determine the further management of the patient. Spontaneous recovery occurs in a minority of patients with ALF. In most cases the only life saving treatment for ALF is liver transplantation (LT) with a 1 year survival of >70%. The timely identification of patients with spontaneous recovery helps prevent LT and also the need for lifelong immunosuppressive therapy. Distinguishing patients requiring LT from those who will survive receiving only intensive medical care remains challenging. This distinction is also important in light of the worldwide shortage of liver donors.

The critical decision for LT should be informed by the likelihood of spontaneous recovery, and many criteria for predicting this likelihood have been suggested. However, these criteria are not universally accepted.

Most commonly used prognostic models (Appendix Table 1) like KCC (the King's College Criteria), Clichy criteria and MELD (Model of End-Stage Liver Disease) have shown inconsistent sensitivity and specificity. Prior reviews on paracetamol-induced ALF reported for KCC a pooled sensitivity of 58.2% and specificity of 94.6% [2] and a sensitivity range of 67%-100% and specificity range of 52%-98% [3]. Meta-analysis [4] of KCC for non-paracetamol-induced ALF reported pooled sensitivity of 68% (ranging from 13% to 96%) and specificity of 82% (ranging from 36% to 100%). Sensitivity and specificity of Clichy Criteria ranged between 58 and 86% and 56 to 100% respectively [5-8]. MELD, primarily designed to estimate mortality of cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt [9], was later applied to patients with end-stage chronic liver disease [10] and used for organ allocation in patients awaiting LT [11]. Since 2003 [3] MELD is used to predict prognosis in ALF patients [12]. Recently MELD received increasing attention and is applied as predictor for ALF patients and some studies report its superiority to KCC [12]. Reported sensitivity and specificity of MELD ranges, respectively, from 54 to 96.5% and 54 to 88% [13-22].

There is consequently a need for a better prognostic index. At present no specific biomarker or set of biomarkers have been shown with sufficient sensitivity and specificity. In order to create a better prognostic index one needs to have a better understanding of the used

prognostic indicators such as commonly used scoring systems as well as single predictor variables.

The aim of this review is to provide a solid starting point for the future studies on development of a better prognostic index for ALF by identifying and summarizing previously employed prognostic indicators in terms of mortality and morbidity in patients with ALF and to assess the possibility of performing meta-analysis of the clinical studies on prognostic indicators for ALF.

2. MATERIALS AND METHODS

The following databases were searched: Ovid Embase(R) (1980 to 2014), Ovid MEDLINE(R) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1950 to 2014) for journal articles based on keywords in title, abstract and MeSH terms, using the following query: (prognosis OR prognostic OR predict*) AND (acute liver failure OR fulminant hepatic failure OR acute liver injury OR acute hepatic failure OR (acute on chronic AND liver failure)). The asterisk "*" indicates the wildcard that may stand for any combination of characters (including nothing), so predict* stands also for "prediction" etc. "Liver failure" and "prognosis" were MeSH terms. All duplicate articles were removed and only English-language articles were included. The final search considered studies published up to 01 January 2014. Articles were included if they reported original data from a clinical trial or observational study on patients with diagnosis of ALF or Fulminant Hepatic Failure (FHF), and if one of their main objectives was evaluating prognostic indicators of ALF outcome. We allowed search to any synonym of ALF definition without limiting search a priori and without predefining any explicit definition. Two reviewers independently screened the titles and abstracts. In the first step conference abstracts and papers, reviews, comments and case studies were excluded. Then, based on titles and abstracts studies were excluded that focused on animal models, pediatric population, hepatitis and other diseases, or studies that only evaluated therapeutic options (e.g. LT, supportive devices etc). Discrepancies between the 2 reviewers were resolved by consensus involving a third reviewer. Fig. 1 shows the search flowchart. The initial two reviewers then extracted prognostic indicators of ALF. Discrepancies between them were again resolved by consensus involving the third reviewer.

A study's statistical approach was classified as "univariate analysis", when association was investigated between indicators and outcomes without adjusting for other possible confounders. Alternately, when association between an indicator and outcome was adjusted for other possible confounders, the approach was classified as "multivariate analysis". Association was presented when the study reported the statistical significance level.

Where possible, the association with mortality at admission was reported. An indicator could have positive (+) or negative (-) association when it was significantly associated with mortality. "Positive association" was used when the indicator was higher in non-survivors or tended to increase together with mortality. "Negative association" was used when the indicator was lower in non-survivors or tended to increase when mortality decreased (protective indicator). "No association" was used when the indicator was not significantly associated with mortality. If no other time point was reported, the admission values of indicators were analyzed in the studies. Indicators were either continuous or categorical.

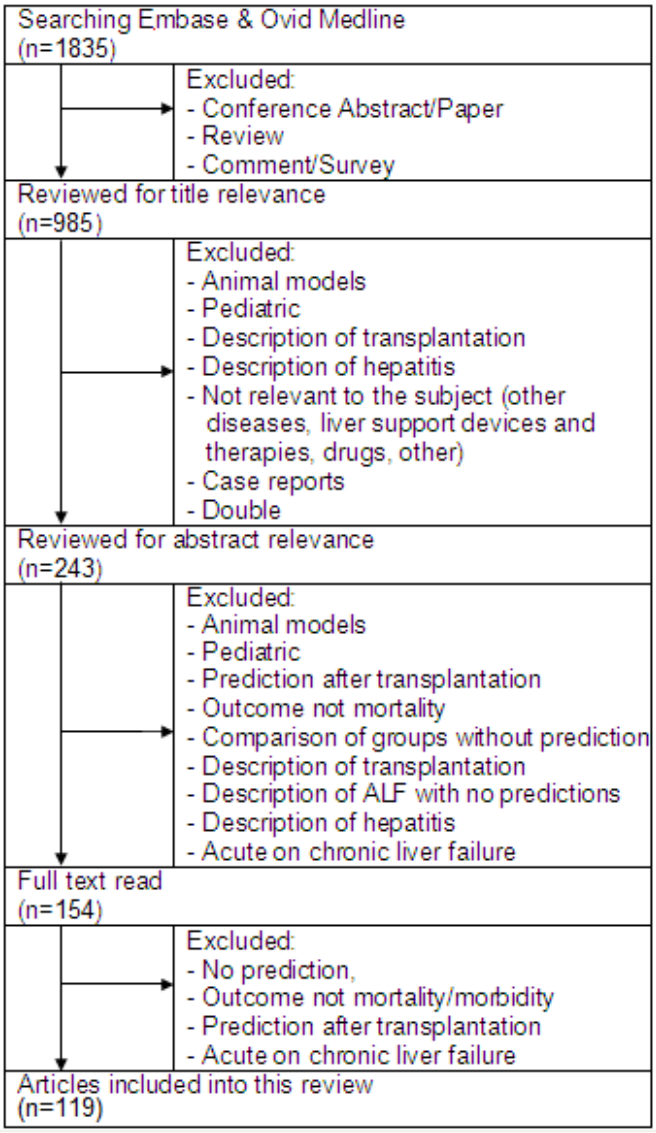

Fig. 1. Search flowchart

The indicators were divided into 8 categories: General markers, bio-markers, hemodynamics, liver function tests, imaging/morphology, scoring systems, time intervals, and treatment. “General markers” were indicators falling outside the 7 specific categories. “Bio-marker” was defined as a measurable compound or molecule used as an indicator of biological state. “Hemodynamics” was defined as flow, pressure or vascular resistance for systemic or portal circulation. “Liver function test” was defined as any clinical assay designed to give information about the quantitative functional capacity of the patient's liver. “Imaging/morphology” was defined as features of liver biopsy, ultrasound or CT-scan. “Scoring system” was defined as any composite mathematical algorithm used for assessment and prediction of development of disease. “Treatment” was defined as any therapeutic plan.

3. RESULT

Searching the online databases resulted in 1835 articles. Initial screening of titles and abstracts resulted in 154 articles for full text review, of which 119 articles were retained.

Table 2 in the appendix shows the characteristic of the final studies: a total of 13743 patients were included, with the largest study including 698 patients. Among the 105 studies where gender was reported 58.8% of patients were female. In 14 studies (1390 patients) gender was not reported.

The most common etiology was viral, particularly hepatitis A and B virus, followed by paracetamol and other drug overdoses, and then autoimmune hepatitis. Etiology of disease was not reported in 7 studies.

Among the studies reporting survival versus non-survival (defined as death or as combined outcome death or LT) related to etiology, the most often reported etiology was paracetamol, followed by hepatitis A and B virus. Table 1 presents the number and percentage of survived patients in 10 the most often reported etiologies. Survival was highest in patients with paracetamol overdosis and lowest in Wilson's disease. Top 10 etiologies constitute 4115 patients, of which 53.4% survived with medical treatment only.
Survival

Table 1. Patients' survival according to etiology

Etiology	No. of studies	Total included no.of patients	No. of patients with etiology	%	Outcome			
					Survival	%	Non survival	%
APAP	32	3728	2580	69.2	1603	62.1	977	37.9
HBV	26	1764	458	26.0	143	31.2	315	68.8
HAV	21	1627	140	8.6	69	49.3	71	50.7
NANB	9	673	356	52.9	112	31.5	244	68.5
HEV	7	710	251	35.4	148	59.0	103	41.0
AIH	7	1310	82	6.3	17	20.7	65	79.3
Halothane	7	194	31	16.0	10	32.3	21	67.7
ATT	6	985	105	10.7	35	33.3	70	66.7
WD	6	1129	26	2.3	1	3.8	25	96.2
Ischemic	5	669	86	12.9	61	70.9	25	29.1

AIH = autoimmune hepatitis; APAP = paracetamol; ATT = Antituberculosis therapy; Halothane = halothane hepatitis; HAV, HBV, HEV = hepatitis A, B, E virus; NANB = non-A non-B hepatitis; WD = Wilson's disease

Sixty-six studies performed univariate and 53 multivariate analysis. Twenty-nine percent of all studies were prospective, 28% retrospective, and 43% did not provide an indication of the design.

Two and eighty-nine and ninety different indicators and their effect on patient outcome were extracted from the studies and divided into 8 categories: 32 general markers, 131 bio-markers, 14 hemodynamics, 7 liver function tests, 15 imaging/morphology, 53 scoring systems, 17 time intervals, and 20 treatments. Seventy indicators were encountered only once in the studies.

A short summary presenting the "top3" of the most often studied indicators within each category is shown in Table 2. Table 3 in appendix presents the full list of all extracted indicators together with their association with mortality and morbidity, as the result of either univariate or multivariate statistical analysis and, if reported, their intervals or cut-off values.

Notably, some studies performed separate analysis for specific subgroups of patients, such as patients with paracetamol overdosis (POD) and non paracetamol (nPOD) etiology or different outcomes such as survival versus death with or without LT (for example ref.1).

Remarkable findings for the most often studies within each category are:

General Markers (n=32): The most often studied general marker was age. One study [23] found a positive association with mortality in nPOD patients, while for POD patients no association with mortality was found. The majority of studies did not find an association between age and mortality on univariate analysis. Thirteen studies found a positive association with mortality on multivariate analysis and 11 did not. Age was considered as categorical variable in 15 studies with 8 different cut-off points, where 40 years was reported most often (4 times).

The second most often studied general marker of ALF was hepatic encephalopathy (HE). One study [24] found a positive association both on univariate analysis and on multivariate analysis only at 10-20 days following the onset of HE, while at onset of HE this association was not found. Seventeen studies showed a positive association with mortality on multivariate analyses in at least one time point in the course of the disease or in one subgroup of patients (e.g. POD on nPOD), while 11 studies did not find an association with mortality. One study [25] out of those 17 demonstrated a positive association with mortality on multivariate analysis only for a value on days 4, 8, 15 but not at admission. One study [26] found a positive association with mortality on multivariate analysis in POD and not in the nPOD subgroup.

Bio-markers (n=131): The most commonly studied bio-marker was total bilirubin. Some studies [20,23,27-30] considered either different time points during the course of disease or different subgroups of patients and showed mixed-results (positive or negative or no association with mortality). One study [30] found a negative association with mortality on univariate analysis considering only subgroup of POD patients. A positive association with mortality on multivariate analysis was found in 17 studies in at least one time point during the course of the disease or in one subgroup of patient. One study [25] of those 17 showed a positive association with mortality for a value at day 4 of HE, but not at admission nor for a value on days 8 and 15 of HE. One study [26] found a positive association on multivariate analysis in the nPOD subgroup and not in the POD subgroup of patients. One study [30] found a positive association with mortality for a peak value during the stay in hospital only in nPOD subgroup of patients, while in the POD subgroup a negative association was found. No association between bilirubin and mortality on multivariate analysis was showed in 8 studies. Bilirubin was considered as categorical variable in 21 studies with different cut-off points, most often 15mg/dL (5 times)

Table 2. Top 3 of the most often studied indicators within each category

	Indicator	Univariate analysis	Multivariate analysis
General markers	Age 60 studies	19 studies+ass. 31 studies no ass.	13 studies+ass. 11 studies no ass.
	Hepatic encephalopathy (HE) 49 studies	24 studies+ass. 16 studies no ass 1 study ass. but direction NR	17 studies+ass. 11 studies no ass. 1 study ass. but direction NR
	Sex/gender 47 studies	2 studies+ass. 1 study–ass. 38 studies no ass.	1 study+ass. 1 study–ass. 7 studies no ass.
Bio-markers	Bilirubin total 68 studies	32 studies+ass. 1 study–ass. 35 studies no ass.	17 studies+ass. 1 study –ass. 8 studies no ass.
	Coagulopathy PT 47 studies INR 36 studies	37 studies+ass 11 studies–ass. 1 study ass. but direction NR 31 studies no ass.	19 studies+ass. 4 studies–ass. 1 study ass. but direction NR 10 studies no ass.
	Creatinine 52 studies	18 studies+ass. 1 study–ass. 1 study ass. but direction NR 32 studies no ass.	4 studies+ass. 1 study ass. but direction NR 9 studies no ass.
Hemo-dynamics	Cerebral edema 11 studies	9 studies+ass.	3 studies+ass. 4 studies no ass.
	Heart rate 6 studies	4 studies+ass. 3 studies no ass.	1 study+ass. 3 study no ass.
	ICP (Intracranial pressure) 2 studies	2 studies+ass.	1 study+ass.
Liver function tests	Galactose elimination capacity (GEC) 4 studies	2 studies–ass. 2 studies no ass.	1 study–ass.
Morphology / Histology	Caspase activity / apoptose activity (M-30) 4 studies	1 study–ass. 2 studies+ass. 1 study no ass.	1 study+ass. 1 study no ass.
	Liver volume 4 studies	3 studies–ass. 2 studies no ass.	2 study–ass.
Scoring systems	KCC 33 studies	5 studies+ass. 5 studies no ass.	2 studies+ass. 1 study no ass.
	MELD 25 studies	16 studies+ass. 6 studies no ass.	6 studies+ass. 1 study no ass.
	APACHE II 9 studies	5 studies+ass. 1 study no ass.	3 studies+ass.
Intervals	Interval jaundice to HE 16 studies	8 studies+ass. 7 studies no ass.	3 studies+ass. 2 studies no ass.
	Interval onset of symptoms to HE 4 studies	1 study+ass. 2 studies no ass.	1 study+ass. 1 study no ass.
	Interval onset of symptoms to diagnosis 3 studies	2 studies no ass.	1 study no ass.

Table 2 Continued…….

Treatments	Ventilation / intubation 6 studies	6 studies+ass.
	Hemodialysis 4 studies	4 studies no ass.
	Steroids / corticosteroids 4 studies	4 studies no ass.

+ass. = significant positive association with mortality (lower/less in survivors, higher/more in non-survivors); – ass. = significant negative association with mortality (higher/more in survivors, lower/less in non-survivors); no ass. = no significant association with mortality
Studies reporting mixed results (+/-/no association) are counted each time.
NR = association with mortality not reported

The second most commonly studied bio-marker was coagulation measured by prothrombin time (PT) in seconds (s) or as prothrombin activity (%) and/or INR. One study [20] showed a positive association on univariate analysis only at 1 to 6 days after the onset of HE. One study [27] found this association in POD subgroup of patients and not in nPOD. One study [1] found this association comparing survived versus died patients, but not comparing survived versus died+LT patients. In one study [29] this association was found when PT was considered as categorical variable with a cut-off point of 50 seconds and not for 100 seconds. One study [13] demonstrated a positive association with mortality at admission as well as at the date of the highest levels of M65 (epitope of cytokeratin 18 released from destroyed cells). A negative association between coagulopathy and mortality on univariate analysis was found in 11 studies of which 4 studies [6,24,31,32] showed it in some time points, but no association in other time points. A positive association of PT with mortality on multivariate analysis was reported in 12 studies and 7 studies reported a positive association of INR and 9 studies showed no association. A negative association with mortality on multivariate analysis was showed in 4 studies, of which one study [24] found this association only at 10-20 days after onset of HE.

Twenty-nine studies described also other alternative clotting related bio-markers, such as: Antithrombin III, factor II,V,VII,VIII, fibrinogen degradation products, fibrinogen, hepaplastin, platelets, activated partial prothrombin time and thromboplastin time.

Hemodynamics (n=14): The most common studied was cerebral edema (CE), a consequence of increased intracranial pressure. Univariate analysis was performed by 9 studies and all of them found CE positively associated with mortality. Three [14,33,34] out of those 9 studies showed a positive association with mortality also on multivariate analysis but two [35,36] out of those 9 studies did not. Two other studies [37,38] also did not find an association with mortality on multivariate analysis.

The second most common studied indicator was heart rate (HR). One study [39] found a positive association only at the onset of HE, but not at admission. One study [38] found a positive association for tachycardia only on univariate but not on multivariate analysis. One study found a positive association with mortality on multivariate analysis but 3 studies did not.

Liver function tests (n=7): The most common test was galactose elimination capacity (GEC). A negative association with mortality on univariate analysis was found by 2 studies, of which one [40] also did so on multivariate analysis for a value measured within 200 hours after acetaminophen ingestion.

The other 6 tests in this category were studied only once.

Imaging/histology (n=15): The most often studied was caspase activity=apoptose activity (M30). A positive association with mortality on univariate analysis was found in one study [13] at the date of the highest levels of M65 (epitope of cytokeratin 18 released from destroyed cells) but not at admission. A positive association with mortality on multivariate analysis was found in one study [41] for log value on day 3, but for value on day 3 no association with mortality was found.

The second commonly studied indicator was liver volume expressed as standard liver volume (SLV) or ratio of estimated liver volume (ELV/SLV). Three studies found a negative association with mortality in univariate analysis, of which 2 studies [24,42] also in multivariate analysis. Liver volume was considered as categorical variable in 4 studies with different cut-off points.

Scoring systems (n=53): The KCC was the most commonly studied scoring system. A positive associations with mortality on multivariate analysis was found in 2 studies, of which one [8] found this association only when comparing survivors with deceased patients, but no association was found when transplanted patients were also included.

The MELD score was the second most commonly studied. A positive association with mortality on univariate analysis was found in one study [20] but only at 1 to 6 days after the onset of HE and not at the onset of HE. Six studies showed a positive association with mortality on multivariate analysis and one did not. The MELD score in 11 studies was considered as categorical variable with different cut-off points, where a cut-off point of 30 was reported most often (5 times).

Modifications of the KCC and MELD were found in only single studies.

Time intervals (n=17): The most often studied was the interval from the onset of jaundice to onset of HE. Three studies found a positive association with mortality in multivariate analysis and two did not. Thirteen studies considered it as a categorical variable with different cut-off of points, of which 1 week was most often considered.

The second most often studied was interval from onset of symptoms to HE. One study [38] found a positive association with mortality on multivariate analysis and one other [30] did not, but this study considered only nPOD subgroup of patients.

Treatments (20): The most often reported was artificial ventilation/ intubation and all studies performed only univariate analysis and found a positive association with mortality.

The second most often reported were both steroid therapy and hemodialysis. All studies performed only univariate analysis but none of them found associations with mortality.

4. DISCUSSION

To our knowledge this is first systematic review exclusively dedicated to prognostic indicators for patients with ALF. Prior reviews on ALF are much more limited in the number of included studies (14 studies [2]), inclusion criteria and in the search terms (only “acute liver failure” and “prognosis” [3]) compared to our study.

In this review we identified, categorized and listed prognostic indicators used for prediction of outcome in patients with ALF as used in 119 studies. One of our goals at the start of the review was to present the results in a meta-analytic way. However, due to the large heterogeneity of the findings (definitions, etiologies, case mix, and outcomes) we were forced to turn to the descriptive way. The differences in methods of indicators' measurement and the complexity of calculation of indicators (e.g. calculation mean, median, peak, threshold values) hamper the comparability among the studies and hinder performing such quantitative analysis. Although meta-analysis is theoretically possible, the results will not be meaningful.

In our former review [43] we reported that there is a wide diversity in ALF definitions used in the literature. However, the exact implications of the differences in ALF definitions on performance of prognostic markers are unknown yet. In our other review [44] we identified, characterized and assessed the quality of newly developed prognostic models of mortality for ALF patients and provided recommendations for future research on prediction models for ALF. This review is another part of the research on ALF.

The strength of our study is its extensiveness. We summarized a large number of indicators used worldwide to predict outcome in patients with ALF. This study provides a good overview of both the commonly used indicators (like bilirubin, age, HE, PT, INR, creatinine) as well as less frequent indicators. In addition, our analysis covered a great heterogeneity of patients with ALF (or FHF) due to many different etiologies such as viral, acetaminophen overdose, autoimmune hepatitis, halothane hepatitis, Amanita phalloides toxicity, Wilson's disease and others. A limitation of our search is that we only addressed studies in which the prognostic effect of indicators formed a main objective; we may consequently have missed studies with a more limited focus on prediction. Our study may be limited by publication bias of studies on ALF outcome evaluation.

The categories of indicators are more or less subjective, but are helpful to find a way in the large variety.

On the whole, many studies did not motivate their choice for a specific subset of indicators. The majorities of the studies were retrospective, and if the kind of the study was not reported one can assume it was retrospective, making the study limited in validity due to a lack of control in the quality of the available data.

In some studies it was not clear why the indicators that were not associated with mortality on univariate analysis were taken to the further multivariate analysis (e.g. logistic regression). In addition it was often unclear which indicators were considered as continuous and which as categorical. Also the reason to convert the continuous indicators to categorical was often not given. Furthermore the reasoning behind a certain threshold value of an indicator was not always clearly explained.

Studies reported association with mortality comparing the group of survivors and the group of non-survivors. Non-survivors mostly consist of patients who died, but in some studies non-survivors comprised deaths and transplanted patients (LT) as one outcome group. Associations found in such studies are questionable. Adding LT patients to "non-survivors" caused that the association with mortality reached significance. For example, one study [28] reported no association with mortality for bilirubin when comparing survivors with "non-survivors", but extending this group with LT patients made bilirubin positively associated with mortality. To avoid such inaccuracy we advise to perform a separate analysis to compare the

transplantation patients' characteristics to the death group. When the groups are similar one can consider forming the group with the combined outcome of "non-survivors".

In some cases mixed results were found when comparing the results, i.e. either positive or negative or no association with mortality. It remains intriguing why the direction of the association in various studies was incompatible, e.g. 2 studies [21,35] reported positive association with mortality for male sex but 1 study [6] a negative association, but those studies can not be directly compared because of the differences in the etiology of included patients: viral in [21,35] and non-viral in [6].

Indicators designed to measure the same underlying concept differed among the studies. For example coagulopathy which plays a crucial role in assessing of liver's damage has been expressed by PT or INR. Of note, there are different thresholds for PT and INR values. A comparison of studies becomes then difficult, and even more difficult when in some studies PT is expressed as percentage of normal and in other as prolongation (in seconds). PT values depend on baseline values and measurement methods. However, there is large variation in laboratory assays, mainly due to the source of the used thromboplastin. For this reason INR seems to be more appropriate. However, there is no uniform standardization of measuring coagulopathy in ALF patients.

Notably, in the majority of studies a value of an indicator was measured in one time point. A. recent study [36] proposes an innovative dynamic approach for development of a prognostic model based on early changes (during first 3 days of hospitalisation) in values of variables. Since ALF is a dynamic process and admission values of prognostic variables change over time during the clinical course of the patient, such approach seems to be the right direction for future research on prediction of ALF outcome [45].

In our systematic review we extracted a very large number of variables used for prediction in ALF. We suggest that next to the most often used indicators like age, HE, bilirubin, creatinine and coagulopathy, which are already part of the most commonly accepted scoring systems such as KCC, MELD and Clichy criteria, the variables involved in the pathophysiology of ALF should be used for prediction of ALF like e.g. plasma ammonia, a contributing factor to hepatic encephalopathy, plasma lactate, representing disturbance of metabolic homeostasis and IL6/IL10 as biomarkers of the inflammatory response. In addition, we believe that incorporating promising variables involved in the pathophysiology of ALF to the dynamic approach might be a valuable step forward in predicting ALF outcome.

5. CONCLUSIONS

When comparing results of various studies one must consider differences in case-mix, in aetiology, therapies, power of the analysis, and outcome measures. The variability in the prognostic indicators of ALF and their threshold values hamper the comparability among the studies. In general, no indicator appears to be conclusive in multivariate analysis. There is still a clear need to define the best combination of prognostic indicators for ALF, which should be tested in a large prospective study of ALF patients with different aetiologies. Our unique inventarisation provides the perfect starting point for development of ALF prognostic index of clinical importance.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX 1

Table 1. Models to predict prognosis in ALF

<table>
<tr><td colspan="2">King’s College Criteria</td></tr>
<tr><td>Acetaminophen-related ALF</td><td>Nonacetaminophen-related ALF</td></tr>
<tr><td>• pH < 7.3</td><td>• Prothrombin time > 100s (INR >6.5)</td></tr>
<tr><td>or</td><td>Or any three of the following:</td></tr>
<tr><td>• Prothrombin time > 100s (INR >6.5)
• Creatinine >300µmol/L</td><td rowspan="4">• Age < 10 or > 40 years
• Etiology non-A,non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
• Jaundice to encephalopathy time > 7 days
• Prothrombin time > 50s (INR >3.5)
• Bilirubin >300µmol/L</td></tr>
<tr><td>with</td></tr>
<tr><td>• Encephalopathy grade 3 or 4</td></tr>
<tr><td colspan="2">Clichy Criteria</td></tr>
<tr><td colspan="2">Hepatic encephalopathy grade 3-4 and factor V level:
• < 20% of normal in patients < 30 years of age; or
• < 30% of normal in patients > 30 years of age.</td></tr>
<tr><td colspan="2">Model for End-Stage Liver Disease (MELD)</td></tr>
<tr><td colspan="2">MELD = 3.78×ln(Bilirubin[mg/dL]) +11.2×ln(INR) + 9.57×ln(Creatinine[mg/dL]) + 6.43</td></tr>
</table>

APPENDIX 2

Table 2. Study characteristics

Study	Materials / methods [no. of patients (no. of female), mean/median age (range of age); model; outcome]*	Etiology (number of patients)
Bala et al. 2013, India [46]	24 patients (7F); med age 30 (18-56); multi; survl vs death	HAV 2, HBV 5, HEV 10, HAV+HEV 2, indeterminate (absence of virus A/B/C/E 5)
Lock et al. 2013, Germany [47]	12 patients (6F); med age 49 (11-72); uni; survl vs death+LT	viral (2), toxic (3), cryptogenic (7)
Manka et al. 2013, Germany[48]	108 patients (69F); mean age 43.4 (NR); uni; survl vs death and survl vs death+LT	indeterminate (24), miscellaneous (21; WD, Amanita, Epstein-Barr), drug (24), APAP (17), HBV (18), HAV (4)
Zhao et al. 2013, China [49]	177 patients (85F); m. age NR (NR); multi; survl vs death	indeterminate (52), herbs (30), APAP (21), HBV (11), antibiotics (11), ischemic (6), extrahepatic malignancy metastasis (5), ATT (5), antineoplastic chemotherapy (5), HEV (5), alcoholism (4), severe infection of biliary tract (3), poisonous chemical agents (3), Amanita (3), drug (3), phenprocoumon (2), HAV (2), cytomegalovirus (1), Epstein–Barr (1), pregnancy (2), Budd-Chiari (1), heat stroke (1)
Audimooolam et al. 2012, UK [50]	218 patients (115F); med age 36 (16-90); multi; survl vs death	APAP (NR), hypoxic hepatitis (NR), viral (NR), drugs (cocaine (7), ecstasy (5)), AIH (NR), indeterminate (NR)
Cholongitas et al. 2012, UK [51]	125 patients (73F); med age 38 (NR); multi; survl vs death+LT	APAP (125)
Etogo-Asse et al. 2012, UK [52]	89 patients (44F); med age 34 (27-48); multi; survl vs death+LT	APAP (51), drug (12; Ecstasy (4), Cocaine (1), Cyprotene (1), Minoxycycline (1), Flucloxacillin (1), Valerian (1), Venlafaxine (1), Sulfasalasine (1) anti-retroviral drug (1)), pregnancy (6), HBV (3), HAV (2), WD (2), auto-immune (2), ischemic (1), Leptospirosis (1), unknown (9)
Hadem et al. 2012, Germany[53]	37 patients (29F); med age 34 (NR); multi; survl vs death+LT	APAP (4), viral (12), non-APAP toxic (5), indeterminate (12), others (4)
Kumar et al. 2012, India [36]	cohort1: 244 patients (130F); med age 25 (13-76); cohort2: 136 patients (85F); med age 26 (13-68); multi; survl vs death	cohort1: HEV (120), HBV (21), HAV (3), ATT (5), other (94) cohort2: HEV (41), HBV (21), HAV (4), ATT (7), other (63)

Kumar et al. 2012, India [54]	295 patients (163F); med age 25 (12-76); multi; survl vs death	HEV (135), dual acute viral infection (31), HBV (31), HAV (6), ATT (7), other (78)
Naiki et al. 2012, Japan [38]	cohort1: 421 patients (202F); mean age 48.6 (NR); cohort2: 231 patients (111F); med age 54.7 (NR); multi; survl vs death	cohort1: HAV (33), HBV (178), HCV (8), other virus (3), AIH (26), drug (35), undetermined (132), no record (6) cohort2: HAV (15), HBV (100), HCV (3), other virus (5), AIH (23), drug (33), undetermined (49), no record (3)
Nakayama et al. 2012, Japan [55]	698 patients (351F), mean age 47 (NR); multi; survl or death	HBV (271), indeterminate (90), drug (65), AIH (48), HAV (45), HCV (10) HEV (3), other viral (6), unknown (3)
Ohnishi et al. 2012, Japan [56]	37 patients (22F); m. age NR (16-73); multi; survl vs death+LT	HBV (14), AIH (9), drug (5), HAV (3), indeterminate (6)
Rutherford et al. 2012, USA [41]	cohort 1: 250 patients (156F), med age 40 (17-78); cohort2: 250 patients (170F); med age 42 (18-87); multi; survl vs death+LT	cohort1: APAP (75), drug (56), indeterminate (33), HBV (20), AIH (26), shock (16), other (24) cohort2: APAP (121), drug (43), indeterminate (23), HBV (9), AIH (22), shock (17), other (26)
Shaikh et al. 2012, Pakistan [57]	76 patients (27F); mean age 24.6 (NR); uni; survl vs death	HEV (9), HBV (37), HDV (14), HELP (11), ATT (5)
Taylor et al. 2012, USA [58]	51 patients (32F); mean age 50 (NR); multi; survl vs death+LT	ischemic (51)
Ajmera et al. 2011, USA [59]	29 patients (14F); med age 48 (21-72); uni; survl vs death+LT	HAV (29)
Bretherick et al. 2011, UK [60]	514 patients (249F), mean age 39.7 (NR); multi; survl vs death+LT	NR
Khandelwal et al. 2011, USA [61]	309 patients (205F), m. age NR (NR); uni; survl vs death	APAP (199), indeterminate (110)
Bechmann et al. 2010, Germany[13]	68 patients (36F), mean age 42.7 (NR); uni; survl vs death+LT	HBV (13), drug (21; APAP 9), CHF (8), HAV (3), HBV/HDV (2), Amanita (2), undetermined (13), others (6)
Berry et al. 2010, UK [62]	51 patients (NR), m. age NR (NR); multi; survl vs death+LT	APAP (34), SH (4), HBV (3), AIH (2), HAV (1), Budd-Chiari (1), drug (1), ATT (1), Epstein–Barr (1), WD (1), Amanita (1), ecstasy (1)
Gregory et al. 2010, USA [63]	113 patients (76F), m. age NR (17-62); multi; survl vs death+LT	APAP (113)

Kumar et al. 2010, India [18]	85 patients (56F), m. age NR (13-80); multi; survl vs death	ATT (70), ATT + viral (15)
Strnad et al. 2010, USA [64]	344 patients (224F), mean age 39.4 (NR); uni; survl vs death+LT	APAP (167), indeterminate (44), drug (39), viral (32), AIH (23), rare etiology (20), ischemic (19)
Canbay et al. 2009, Germany[65]	134 patients (84F), mean age 41, med age 38 (NR); multi; survl vs death+LT	indeterminate (28), APAP (22), drugs (22), HBV (18), phenprocoumon (9), HAV (8), HSV (2), HCV (1), HDV (1), Epstein-Barr (1), miscellaneous (22; AIH (3), Budd-Chari, ischemic, cancer, WD, pregnancy)
Karvellas et al. 2009, Canada [66]	206 patients (119F), m. age NR (NR); multi; survl vs death	APAP (105), seronegative/undefined (47), fatty liver/HELLP (15), drug (12), HBV (10), Budd-Chiari (9), ischemia (4)
Merle et al. 2009, Germany [67]	25 patients (19F), mean age 42.1 (18-80); uni; survl vs death+LT	toxic (15; APAP 11), cryptogenic (4), viral (4), ischemic (2)
Singhal et al. 2009, India [68]	37 patients (20F), m. age NR (12->40); uni; survl vs death	HEV (15), no aetiology (10), HBV (4), Epstein–Barr (3), co-infection (3), HAV (1), HCV (1)
Yamagishi et al. 2009, Japan [42]	30 patients (16F), m. age NR (19-83); multi; survl vs death+LT	HBV (10), drug (7), unknown (7), AIH (3), HAV (2), HEV (1)
Hadem et al. 2008, Germany[15]	102 patients (72F), med age 38 (16-74); multi; survl vs death+LT	indeterminate (21), HBV (18), APAP (16), Budd-Chiari (9), phenprocoumon (7), IDR (5), Amanita (5), WD (5), other (5), HAV (4), ischemic (“shock liver”) (4), halothane (3)
Koskinas et al. 2008, Greece [69]	40 patients (28F), mean age 37.4 (15-84); uni; survl vs death+LT	HBV (21), drug (APAP, cyproterone acetate, gold salts; 4), poisoning (Amanita, Teucrium polium; 6), unknown (5), ischemic (2), WD (1), AIH (1)
Kotoh et al. 2008, Japan [17]	33 patients (15F), mean age 43.7 (NR); uni; survl vs death+LT	HBV (13), unknown (9), HAV (6), drugs other than APAP (3), WD (2)
Volkmann et al. 2008, Germany[70]	70 patients (52F), mean age 43 (16-77); uni; survl vs death+LT	cryptogenic (22), drug or Amanita (12), viral (11), APAP (9), Budd-Chiari (7), WD (5), mixed poisoning (3), AIH (1)
Zheng et al. 2008, China [71]	25 patients (7F), m. age NR (NR); uni; survl vs death	HEV (16), unknown (7), AIH (2)
Antoniades et al. 2007, UK [72]	61 patients (39F), med age 32(IQR 18-64); multi; survl vs death+LT	APAP (41), viral (6), unknown (6), drug (2), Budd-Chiari (2), AIH (2), WD (1), Amanita (1)

Choi et al. 2007, Korea [5]	43 patients (28F), mean age 37 (10-75); uni; survl vs death+LT	APAP (16), indeterminate (11), drugs (5), HBV (3), HAV (2), ischemia (2), heat stroke (1), AIH (1), WD (1), HELLP (1)
Dhiman et al. 2007, India [14]	144 patients (82F), mean age 31.7 (12-82); multi; survl vs death	viral (144)
Escudie et al. 2007, France [6]	27 patients (13F), mean age 48 (NR); uni; survl vs death+LT	Amanita (27)
Katoonizadeh et al. 2007, Belgium [16]	99 patients (59F), mean age 42 (16-72); multi; survl vs death	cryptogenic (38), viral (29), drugs (20), AIH (4), FLoP (2), ischemic (2), WD (1), Budd-Chiari (1), HELLP (1), Amanita (1)
Miyake et al. 2007, Japan [73]	31 patients (16F), med age 45 (20-74); multi; survl vs death	HBV (31)
Miyake et al. 2007, Japan [74]	104 patients (62F), med age 48 (16-81); multi; survl vs dearh	HBV (32), HAV (7), HCV (2), AIH (11), drugs (16), FLoP (1), AIH (2), indeterminate (30)
Møller et al. 2007, USA [75]	100 patients (74F), med age 39 (NR); uni; survl vs death	APAP (29), other (29), indeterminate (24), drug (18)
Mudawi et al. 2007, Sudan [37]	37 patients (16F), mean age 38 (19-75); multi; survl vs death	SH (14), HBV (8), malaria (3), AIH (3), HEV (2), ATT (2), lymphomatous infiltration (2), FLoP (1), Budd-Chiari (1), ketoconazole (1)
Okumoto et al. 2007, Japan [76]	26 patients (14F), mean age 49.9 (NR); uni; survl vs death	unknown (19), HBV (5), AIH (2)
Parekh et al. 2007, USA [77]	187 patients (122F), med age39 (15-81); uni; survl vs death	APAP (80), indeterminate (41), other (21), ischemia/shock (19), HBV (14), HAV (12)
Rutherford et al. 2007, USA [78]	67 patients (40F), med age 39 (17-76); uni; survl vs death+LT	APAP (17), viral (16), indeterminate (16), drug (12), WD (6)
Schiodt et al. 2007, USA [79]	252 patients (183F), med age 38 (15-78); uni; survl vs death+LT	APAP (110), indeterminate (40), IDR (38), HBV (15), ischemic (12), others (12), AIH (9), HAV (7), WD (4), pregnancy (3), Budd-Chiari (2)
Schmidt et al. 2007, Denmark [20]	124 patients (NR), m. age NR (NR); uni; survl vs death+LT	APAP (124)

Yantorno et al. 2007, Argentinia [8]	64 patients (NR), med age 35 (18-65); multi; survl vs death, survl vs death+LT	indeterminate (19), AIH (12), drug (11), HAV (8), HBV (7), pregnancy (5), WD (2)
Antoniades et al. 2006, UK [80]	50 patients (35F), med age 33 (22-42); uni; survl vs death+LT	APAP (50)
Arai et al. 2006, Japan [81]	43 patients (23F), mean age 37.4 (NR); uni; survl vs death	viral (23), non-viral (20)
Bhatia et al. 2006, India [33]	80 patients (51F), med age 25 (14-72); multi; survl vs death	viral (65; HEV (35)), no evident cause (10), ATT (5)
Gagliardi et al. 2006, Italy [82]	23 patients (9F), mean age 35 (NR); uni; survl vs death	HBV (12), ecstasy (3), unknown (3), APAP (2), cocaine (1), leptospirosis (1), peripartum (1)
Lin et al. 2006, Japan [83]	16 patients (5F), mean age 48.1 (21-69); uni; survl vs death	HBV (8), NANBNC (5), drug (2), AIH (1)
Peláez-Luna et al. 2006, Mexico [19]	58 patients (41F); mean age 37 (NR); multi; survl vs death	NR
Rutherford et al. 2006, USA [84]	573 patients (379F), m. age NR (NR); multi; survl vs death+LT	APAP (264), indeterminate (86), viral (65), drug (63), other (44), AIH (35), WD (12), FLoP (4)
Saxena et al. 2006, India [85]	22 patients (NR), m. age NR (18-55); uni; survl vs death	HEV (6), undetermined (5), HBV (4), HAV (2), HAV+HEV (2), FLoP (1), sepsis + cerebral malaria(1), ATT (1)
Schiodt et al. 2006, USA [86]	206 patients (150F), med age 39 (15-78); uni; survl vs death+LT	APAP (80), indeterminate (33), IDR (31), HBV (15), ischemic (12), AIH (10), HAV (9), WD (5), other (pregnancy, Budd-Chiari, malignancy, giant-cell hepatitis; 11),
Schmidt et al. 2006, Denmark[39]	101 patients (69F), med age 49 (12-75); multi; survl vs death	APAP (101)
Taurá et al. 2006, Spain [87]	63 patients (37F), mean age 32.7 (NR); multi; survl vs death	cryptogenic (NANBNC) (32), viral (18), MAOi (3), Rifampin+Isoniacid (2), Isoflurane (1), α-Metildopa (1), metabolic disease (4), NR (2)
Taylor et al. 2006, USA [21]	29 patients (14F), mean age 48 (21-72); multi; survl vs death+LT	HAV (29)

Zaman et al. 2006, Ireland [22]	72 patients (50F), m. age NR (NR); uni; survl vs death+LT	APAP (72)
Aggarwal et al. 2005, USA [88]	26 patients (18F), mean age 38 (range14-64); uni; survl vs death	APAP (10), viral (9), unknown (5), postpartum (1), halothane (1)
Dabos et al. 2005, UK [89]	cohort1: 97 patients (47F), mean age 36.2 (NR); cohort2: 85 patients (44F), mean age 35.7 (NR); multi; survl vs death+LT	cohort1: APAP (97), cohort2: APAP (85)
Hiraoka et al. 2005, Japan [90]	21 patients (13F), mean age 47.6 (8-73); uni; survl vs death	HBV (12), unknown (NANBNC) (5), HCV (2), drug (2)
MacQuillan et al. 2005, UK [27]	83 patients (48F), mean age 37.8 (17-65); multi; survl vs death	APAP (56), SH (12), drugs (6), viral (5), indeterminate (3), veno-occlusive disease (1)
Miyake et al. 2005, UK [25]	cohort1: 80 patients(47F), med age 45.5 (16-78); cohort2: 26 patients (16F), med age 61.0 (range19-81); multi; survl vs death+LT	cohort1: HBV (27), indeterminate (24), drug (15), AIH (6), HAV (5), HCV (2), FLoP (1) cohort2: HBV (7), indeterminate (10), AIH (4), HAV (2), drug (1), ischemic (2)
Schiødt et al. 2005, USA [26]	182 patients (134F), med age 38 (15-78); uni; survl vs death+LT	APAP (76), indeterminate (31), IDR (26), ischemic (11), HBV (11), HAV (8), other (8), AIH (6), pregnancy (5)
Yamagishi et al. 2005, Japan [31]	24 patients (10F), mean age 38.1 (19-61) survivors, mean age 46.3 (22-69) died; uni; survl vs death+LT	HBV (9), drug other than APAP (5), unknown (5), AIH (2), HAV (2), HEV (1)
Christensen et al. 1984, Denmark[91]	33 patients (19F), med age 30 (17-72); multi; survl vs death	HBV (15), halothane (8), disulfiram (3), NANB (2), FLoP (2), APAP (1), sulfamethoxazole+ thrimethoprim (1), radiotherapy+vincistine (1)
Dabos et al. 2004, UK [1]	59 patients (37F), m. age NR (NR); multi; survl vs death and survl vs death+LT	non-A-E (15), drug (14), AIH (7), unknown (7), Budd-Chiari (5), WD (5), HBV (3), FLoP (2), lymphoma (1)
Kremers et al. 2004, USA [11]	388 patients (270F), m. age NR (19-73); multi; survl vs death	non-APAP (312), APAP (76)
Schmidt et al. 2004, Denmark[40]	220 patients (143F), med age 39 (IQR 26-48); multi; survl vs death+LT	APAP (220)
Sato et al. 2004, Japan [92]	6 patients (2F), mean age 49.8 (NR); uni; survl vs death	congestive heart failure or portal venous gas or postoperative disseminated intravascular coagulation (6)

Tsuchiya et al. 2004, Japan [93]	32 patiente (18F), mean age 41.6 (NR); multi; survl vs death+LT	NANBNC (15), HBV (13), HAV (3), HCV (1)
Baquerizo et al. 2003, USA [94]	112 patients (69F), med age 28 (1-71); multi; survl vs death+LT	APAP (36), viral (11), other (65)
Khuroo et al. 2003, India [35]	180 patients (111F), mean age 31.1 (4-65); multi; survl vs death	HEV (79), non-A-E (56), HBV (25), HCV (13), HAV (4), HDV (2), drugs (1)
Ohmori et al. 2003, Japan [95]	22 patients (12F), mean age 54.0 (NR); uni; survl vs death	ecalazine hydrochlorine (8), halothane (6), pyridinol carbamate (3), isoniazid (3), benzbromarone (1), MAOI (1)
Chung et al. 2003, USA [28]	38 patients (30F), mean age 34 (15-56); uni, survl vs death and survl vs death+LT	APAP (14), viral (8), cryptogenic liver disease (8), AIH (3), drug (3), hea shock (1), WD (1)
Sakurai et al. 2003, Japan [96]	31 patients (15F), med age 28.5 (1-65); uni; mild atrophy vs severe atrophy	SH (20), HBV (8), HAV (1), AIH (1), drug (1)
Bernal et al. 2002, UK [97]	cohort1:103 patients (51F); med age 35 (16–60); cohort2: 107 patients (65F), med age 36 (16-78); multi; survl vs death+LT	cohort1: APAP (103) cohort2: APAP (107)
Hakozaki et a. 2002, Japan [98]	43 patients (14F), mean age 36 (21-59); uni; survl vs death	HBV (43)
Yumoto et al. 2002, Japan [99]	20 patients (12F), mean age 36 (NR); uni; survl vs death+LT	HBV (11), drug (4), HAV (2), non-A (2), HCV (1)
Chawla et al. 2001, India [100]	29 patients (14F), mean age 28 (NR), multi; survl vs death	NR
Shakil et al. 2000, USA [101]	177 patients (112F), mean age 39 (13-76); uni; survl vs death	viral (55), indeterminate (49), APAP (33), drug (21), miscellaneous (19)
Shakil et al. 2000, USA [102]	177 patients (112F), mean age 39 (13-76); uni; survl vs death	indeterminate (49), APAP (33), HBV (33), IDR (21), HAV (13), HSV (6), organic solvents (3), AIH (3), HDV (2), eclampsia (2), ischemic necrosis (2), lymphoma (2), hepatic metastases (2), mushroom (2), WD (2), Epstein-Barr (1), Budd-Chiari (1)
Deasy et al.1999, UK [103]	18 patients (12F), mean age 29 (16-47); uni; survl vs death+LT	APAP (17), HBV (1)

Carraro et al. 1998, Italy [32]	34 patients (NR), m. age NR (NR); uni; survl vs death	HBV (19), Amanita (7), other (4), NNB (3), HAV (1)
Dhiman et al. 1998, India [104]	204 patients (106F), mean age 28.5 (1-75); multi; survl vs death	viral (186), drug (15), WD (1), Budd-Chiari (1), malignant infiltration (1)
Mitchell et al. 1998, UK [105]	102 patients (58F), med age 28 (15-64); uni; survl vs death+LT	NR
Anand et al.1997, UK [106]	145 patients (85F), med age 31 (18-84); multi; survl vs death	APAP (120), drug (8), NANB (7), HAV (3), HBV (2), Epstein Barr (1), Budd-Chiari (1), WD (1), ischemic necrosis (1), FLoP (1)
Schiodt et al. 1997, Denmark [107]	79 patients (48F), mean age 38 (9-76); uni; organ failure	HBV (24), APAP (22), NANB (7), halothane (5), IDR (5), other (HAV, shock liver, AlcH, unknown; 16),
Acharya et al. 1996, India [34]	423 patients (223F), mean age 29.5 (range7-80); multi; survl vs death	NANB (264), HBV (117), ATT (19), HDV (16), HAV (7)
Huo et al.1996, China [108]	61 patients (9F), m. age NR (14-83); multi; survl vs death	HBV (6), HBV+HDV (15), HBV+HBV (14), HBV+ drug (8), HBV+HCV (5), HBV+HCV+ HDV (1), HCV (2), undetermined (4), HEV (1), CMV (1) danazol (1), exposed to CCl4 (1), halothane (1), INH/RIF(1)
Izumi et al. 1996, UK [109]	110 patients (NR), m. age NR (NR); uni; survl vs death	APAP (88), NANB (11), HAV (3), HBV (3), IDR (3), HCV (1), WD (1)
Schiodt et al. 1996, USA [23]	77 patients (47F), mean age 37 (16-76); uni; survl vs death	HBV (24), APAP (18), NANB (8), halothane (8) , IDR (5), other (HAV, shock liver, AlcH, WD, unknown; 14),
Acharya et al.1995, India [110]	69 patients (30F), m. age NR (NR); uni; survl vs death	NANB (41), HBV (21), HDV coinfection and superinfection (5), ATT (2)
Jain et al.1995, India [111]	21 patients (8F), mean age 31.05 (16-45); uni; survl vs death	NANB (15), HBV (5), HAV (1)
Lee et al. 1995, USA [112]	47 patients (NR), m.age NR (NR), uni; survl vs death	APAP (39), HBV (3), NANB (2), HAV(2), FLoP (1)
Yamasaki et al.1995, Japan[113]	26 patients (8F), m. age NR (7-80); uni; survl vs death	NANB (9), HBV (8), halothane (4), HAV (4), valproic acid (1)

Sekiyama et al. 1994, Japan [24]	19 patients (9F), med age 49 (22-78); multi; survl vs death	HCV (8), HBV (7), NANBNC (2), HAV (1), NR (1)
Pauwels et al. 1993, France [7]	81 patients (NR), mean age 31 (11-60), uni; survl vs death	HBV (44), indeterminate (25), drug (7), HAV (3), HBV+HDV (2)
Frohburg et al. 1992, Germany[29]	33 patients (23F), med age 30 (16-55); uni; survl vs death	HBV (22), NANB (6), HAV (3), Amanita (1), APAP (1)
Pereira et al. 1992, UK [114]	27 patients (16F), m. age NR (NR); uni; survl vs death+LT	APAP (22), NANB (5)
Nagel et al. 1991, UK [115]	16 patients (NR), m. age NR (NR); uni; survl vs death	APAP (8), NANB (5), HBV (2), HAV (1)
Saibara et al. 1991, Japan [116]	19 patients (7F), mean age 48.1 (7-80); uni; survl vs death	NANB (7), HBV (6), halothane (4), HAV (1), valproic acid (1)
Harrison et al. 1990, UK [117]	150 patients (94F), mean age 29.8 (14-62); uni; survl vs death+LT	APAP (150)
Scaiola et al.1990, UK [118]	28 patients (NR), m. age NR (NR); uni; survl vs death	APAP (22), NANB (4), HBV (1), HAV (1)
Anand et al. 1989, India [119]	30 patients (12F), mean age 30.9 (14-65); uni; survl vs death	viral (30)
Nandi et al. 1989, India [120]	22 patients (12F), mean age 31.2 (NR); uni; survl vs death	NANB (15), HBV (7)
O'Grady et al. 1989, UK [30]	cohort1: 588 patients (NR), m. age NR (NR); cohort2: 175 patients (NR), m. age NR (NR); multi; survl vs death	cohort1: APAP (310), HBV (79), NANB (79), presumed viral with incomplete serology (38), HAV (37), halothane (34), IDR (11) cohort2: APAP (121), NANB (30), HBV (10), HAV (5), IDR (5), halothane (3), Epstein-Barr (1)
Tandon et al. 1986, India [121]	145 patients (80F), m. age NR (12-82); uni; survl vs death	NANB (84), HBV (52), HAV (9)
Bihari et al. 1985, UK [122]	32 patients (23F), m. age NR (16-58); uni; survl vs death	APAP (22), viral (9), drug (cotrimoxazole) (1)

Gazzard et al. 1976, UK [123]	12 patients (NR), m. age NR (16-62); uni; survl vs death	AH (10), FLoP (1), halothane (1)
Horak et al.1976, Austria [124]	14 patients (10F), m. age NR (17-53); multi; survl vs death	APAP (10), HBV (2), HAV (1), isoniazid + rifampicin (1)
Murray-Lyon et al. 1976, UK [125]	64 patients (50F), m. age NR (15-64); uni; survl vs death	APAP (24), HAV (15), halothane (10), HBV(8), drug (4), FLoP (2), Amanita (1)
Ranek et al. 1976,Denmark[126]	25 patients (16F), m. age NR (17-69); uni; survl vs death	HAV (12), HBV (7), halothane (5), drug (1)
Dymock et al. 1975, UK [127]	12 patients (11F), m. age NR (8-71); uni; survl vs death	viral (6), APAP (3), halothane (3)
Scotto et al. 1973, France [128]	38 patients (NR), m. age NR (NR); uni; survl vs death	NR

- *if the studies reported values as % we recalculated into the numbers to assure homogeneity of the presented data*
- *m. age = mean or median age; med. age = median age; age and range considered NR if the study did not report mean or median age and range for all patients; IQR = interquartile range*
- *NR = not reported in the study; uni/multi = univariate/multivariate analysis*
- *AH = acute hepatitis; AIH = autoimmune hepatitis; AlcH = alcoholic hepatitis; Amanita = Amanita phalloides; APAP = acetaminophen, paracetamol; ATT = Antituberculosis therapy; Budd–Chiari = Budd–Chiari syndrome; drug = any drug causing ALF not mentioned separately; Epstein–Barr = Epstein–Barr virus; FLoP = fatty liver of pregnancy; halothane = halothane hepatitis; HAV, HBV, HCV, HDV, HEV = hepatitis A, B, C, D, E virus; HELLP = HELLP syndrome; HSV = herpes simplex virus; IDR = idiosyncratic drug reaction; MAOI = monoamine oxidase inhibitors; NANB = non-A non-B hepatiti; PSC = primary sclerosing cholangitis; PBC = primary biliary cirrhosis; SH = seronegative hepatitis; viral = viral hepatitis; WD = Wilson's disease*

APPENDIX

Table 3. Extracted indicators

	Indicator	Univariate analysis	Multivariate analysis	NR	Note
General markers	Age 60 studies	19 studies +ass [17], (cont. and cat.) [14], (at onset of HE) [16], (cont. and cat.) [73], (cat.) [74, 33, 22, 27], (cont. and cat.) [35, 49, 36, 54], (survl vs death and survl vs death+LT) [28], (cont. and cat.) [34, 108], (in nPOD subgroup) [23], (in POD and nPOD subgroups) [30], (surv vs death and surv vs death+LT) [48, 38] 31 studies no ass. [13, 18, 47, 50, 51, 53, 56, 58, 65, 67, 68], (cont. and cat.) [42, 15, 69, 6, 76, 19, 84, 21], (cont. and cat.) [31, 91, 94, 95, 98, 100, 102], (cat.) [104], (in POD and nPOD subgroups) [106], (in POD subgroup) [23], (in nPOD subgroup) [29, 116]	13 studies +ass. [54], (survl vs death, survl vs death+LT) [66], [14, 49, 38, 73, 74, 91, 35, 104, 34, 108], (in all patients and in nPOD subgroup) [30] 11 studies no ass. [50, 36], (cont. and cat.) [41, 63, 42, 37, 33, 84, 25], (in POD and nPOD subgroups) [26], (in nPOD subgroup) [11]	3 studies [64, 93], [110]	cut-off <11 or >40yr [42, 37, 31, 30], ≥ 50yr [14], >45yr [73, 25], >40yr [41, 74, 37, 35, 34], <30years [33], >50yr [104], >43 years [108], <10 or >40years [29]
	APAP dose	no ass. [63]	no ass. [63]		cut-off 10g, 20g 30g, 40g, 50g [63]
	APAP dose to body weight ratio		no ass. [63]		
	Ascites 6 studies	3 studies +ass. [17, 100, 101], 3 studies no ass. [14, 68, 104]			
	Bacteraemia		no ass. (survl vs death+LT) [66]	(survl vs death) [66]	
	BMI / Obesity / Body weight 5 studies	2 studies +ass. [65], (cont. and cat.) [84] 3 studies no ass. [13], (survl vs death, survl vs death+LT) [48, 91]	+ass. [84] no ass. [65]		cut-off ≥30 [84]
	Convulsion	no ass.[38]			
	Diabetes history 2 studies	2 studies no ass. [58, 84]			
	Etiology 30 studies	87 studies +ass. (indeterminate vs POD) [61, 18] (ATT vs HEV), (at onset of HE) [16] (HBV, cryptogenic, drug), [84] (all patients and drug vs POD,	5 studies +ass. [84] (drug vs POD, indeterminate vs POD), [25] (HBV or indeterminate vs others), [91] (NANB, halothane	3 studies [64, 93], [110]	

		indeterminate vs POD, viral vs POD), [27] (POD vs nPOD), [94] (POD, virus vs other), [35] (HEV vs others), [54] 15 studies no ass. (POD) [59], [49], [53], [36], (viral) [56], [42] (viral or non-viral, HBV or non-HBV, cryptogenic or drug), [69] (HBV or other), [17] (HAV, HBV, drug, WD, unknown), [74] (viral), [84] (other (shock liver, mushroom toxicity, autoimmune hepatitis, WD, acute fatty liver of pregnancy, Budd Chiari syndrome) vs POD), [31] (cryptogenic or drug/toxin), [91] (HBV, NANB, halothane hepatitis, disulfram hepatitis, fatty liver of pregnancy), [106] (nPOD), [34] (HAV, HBV, HDV, NANB, ATT), [29], [116]	hepatitis, disulfram hepatitis, HBV), [35] (HEV vs others), [30] (POD, HBV, drug, NANB) 5 studies no ass. [50], (POD vs non-POD, POD+drug vs other, POD+HAV+shock vs other) [41], [42] (viral or non-viral), [84] (other (shock liver, mushroom toxicity, autoimmune hepatitis, WD, acute fatty liver of pregnancy, Budd Chiari syndrome) vs POD), [25] (HBV or indeterminate vs others; on day4,8,15)		
	Flapping tremor	no ass. [38]			
	Gastrointestinal bleeding 4 studies	1 study ass. but direction NR (peak in POD subgroup) [106] 4 studies no ass. [35], (peak in nPOD subgroup) [106], (during ICU stay) [51], [36]	no ass. (peak in POD and nPOD subgroups) [106]		
	Heart disease	no ass. [58]			
	HAV genotype	no ass. (1B vs 1A) [59]			
	HAV PCR	–ass. [59]			
	HBV 5 studies	+ass. (HBV carrier) [38] 2 studies no ass. (of HbsAg) [14], [104] no ass. (of HBeAg) [98] no ass. (of IgM-positive HBcAb) [98]	no ass. (HBV carrier) [38]	of HBsAg [121]	
	Hepatic encephalopathy (HE) 49 studies	24 studies +ass. (grade >II) [49], [50], [56], [63], (grade III-IV) [18], [15], [17], [72], (grade III-IV) [16], (grade II-IV) [76], (in POD subgroup) [80], (grade III-IV) [33], [22], [94], (cont. and cat. I,II vs III,IV) [35], (grade 0-II vs III-IV) [97], (grade III-IV) [102], (grade III-IV) [104], [34], (at 10-20 days after onset of HE) [24], (in POD subgroup) [30], [36], [54], (grade III-IV) [58] 16 studies no ass. (grade III-IV) [56], [42], [69], (grade III-IV) [14], (grade III-IV) [73], (grade III-IV) [74], (grade III-IV at adm and at 3	17 studies +ass. (grade >II) [49], [50], (dynamic change or grade >II) [36], [54], (adm and grade III and IV) [41], (adm both to hospital and to LTU) [60], (grade III-IV) [18], (peak in both survl vs death, survl vs death+LT) [66], (grade III-IV) [14], (grade III-IV) [37], (grade III-IV on day4,8,15) [25], (peak in POD subgroup) [26], [91], [35], (grade III-IV) [34], (at 10-20	4 studies [62], (cont. and cat. grade III-IV) [110], (grade III-IV in POD group) [114], [121]	

		weeks) [21, 91, 98, 100], (in POD and nPOD subgroup) [106], (grade III-IV) [108], (in POD and nPOD subgroups) [23], (at onset of HE) [24, 29], (PSE) [116] 1 study ass. but direction NR (peak in POD and nPOD subgroups) [106]	days after onset of HE) [24, 30] 1 study ass. but direction NR (peak in POD subgroup) [106] 11 studies no ass. (grade II) [41, 42], (grade III-IV) [74], (grade III-IV) [33, 87], (grade III-IV) [25], (adm in POD and nPOD, peak in nPOD subgroup) [26, 97], (grade III-IV) [104], (peak in nPOD subgroup) [106], (at onset of HE) [24]		
	Hepatic odor	no ass. [38]			
	Hypertension	no ass. [58]			
	Infection 8 studies	3 studies +ass. [87, 34, 110] 1 study ass. but direction NR (peak in POD and nPOD subgroups) [106] 3 studies no ass. [69, 29, 36]	3 studies +ass. [37, 87, 34] no ass. (peak in POD and nPOD subgroups) [106]		
	MOF	no ass. [73]			
	Pneumonia	+ass. (during ICU stay) [51]			aspiration pneumonia
	Pregnancy 4 studies	2 studies no ass. [18, 35]	–ass. [91]	[121]	
	Pulse	no ass. [58]			
	Race/ethnicity 7 studies	3 study +ass. (African American vs white, other races vs white) [84], (caucasian) [27], (Hispanic vs white and Hispanic vs Asian/black) [94] 3 studies no ass. [84, 21, 58]	2 studies no ass. (white) [63], (African American vs white, other races vs white) [84]	[64]	
	Renal failure 6 studies	+ass. [73] 4 studies no ass. (survl vs death+LT) [28, 36, 58, 69]	no ass. [35]		
	Respiratory disfunction 2 studies	+ass.(respiratory distress syndrome) [73] no ass.(respiratory failure) [69]			
	Seizure	+ass. [36]			
	Sepsis 2 studies	no ass.(at onset of HE) [39]	no ass. [35]		
	Sex/gender 47 studies	2 study +ass. (male) [21], (male) [35] – ass. (male) [6]	+ass. (male) [84] –ass. (male) [91]	3 studies [65, 93, 110]	

		38 studies no ass. [13, 14, 15, 17, 18, 22], (in nPOD subgroup) [11], (in POD and nPOD subgroups) [106, 27, 29, 47, 49, 50, 51, 53, 36, 54, 38, 56, 58, 67, 68, 42, 69, 73, 74, 76, 84, 91, 94, 95, 98, 100, 104, 34, 108, 116, 121,]	7 studies no ass. [25, 35, 50, 41, 63, 73, 74]		
	Sites of tuberculosis	no ass. [18]			pleuropulmonary, abdominal, disseminated, lymph node, others
	SIRS 5 studies	3 studies +ass [73, 74], (adm and at onset of HE) [39]	4 studies +ass. [73, 74, 39], (adm, day4,8) [25] 2 studies no ass. (survl vs death and survl vs death+LT) [66], (on day15) [25]		
	Temperature/ fever 4 studies	2 studies +ass. (adm and at onset of HE) [39, 97] 2 studies no ass. [38, 73]			cut-off >38℃ or <36℃ [39, 73] ≥ 37.5°C [38]
	Type of disease	+ass. [38]	no ass. [38]		acute,subacute, late onset
Bio-markers	Acetate 2 studies	–ass. [89] no ass. [46]	–ass. [89]		
	Acetoacetate	no ass. [46]			
	Acetone	no ass. [46]			
	Activin A	+ass. [83]			
	Adhesion molecules	+ass. [56]	+ass. [56]		sPECAM-1; cut-off ≥650ng/ml
		no ass. [56]			sICAM-3
		no ass. [56]			sE-selectin
		-ass. [56]	-ass. [56]		sICAM-1; cut-off ≤1.750ng/ml
		no ass. [56]			sP-selectin
		no ass. [56]			sVCAM-1
	AFP (alpha fetoprotein) 9 studies	2 studies +ass. [86], (on day0 of peak transaminases) [32] 5 studies –ass. (on day2,3,4,5 of peak transaminases) [32], (peak, cont. and cat.) [108, 111], (peak) [113], (after HE of grade IV) [125] 4 studies no ass. (in POD and nPOD		2 studies [82], (declining on day5 and day10) [111]	cut-off 15ng/ml [96]; 11ng/ml on day3 of peak transaminases [32]; 400ng/mL[108]. 50ng/ml [111, 125]

		subgroups and on day3 in all patients and in POD and nPOD subgroups) [86], (at onset of HE in patients with mild atrophy vs sever atrophy) [96], (on day1 of peak transaminases) [32, 38]			
	AFP ratio day3/ day1	–ass. (in all patients and in POD and nPOD subgroups) [86]			cut-off <1 [86]
	AFP-L3 (isoform of alpha-fetoprotein)	–ass. (at onset of HE in patient with mild atrophy vs sever atrophy) [96]			cut-off 10% [96]
	AKBR (arterial ketone body ratio) 3 studies	3 studies –ass. (on 3rd day of HE ≥ II) [113], (on 24h and 48h of adm) [116;116, 118] no ass. [116]			cut-off <0.6 [113] <0.4 [116]
	Alanine 3 studies	2 studies –ass. [89], (survl vs death and survl vs death+LT) [1] 1 study +ass. [46]	–ass. [89] no ass. [1]		
	Albumin 21 studies	6 studies –ass. [17, 38, 33, 19, 89], (survl vs death and survl vs death+LT) [1] 14 studies no ass. [18, 14, 46, 49, 50, 51, 36, 54, 82, 91, 98, 100], (cat.) [104], (nadir) [108]	3 studies –ass. [91, 1, 38] 4 studies no ass. [33, 19, 25, 50]		cut-off >3g/dl [33, 25, 104]
	ALP (Alkaline phosphatase) 20 studies	4 studies +ass. [15], (surv vs death) [48, 58, 60] 2 studies –ass. (peak) [65, 21] 16 studies no ass. (peak) [13, 46], (surv vs death+LT) [48, 49, 36, 54], (at adm to LTU) [60, 18, 68, 17, 14, 91, 35, 100], (peak) [29] (adm and peak in both POD and nPOD subgroups) [30]	–ass. (peak) [65] 2 studies +ass. (at adm to LTU) [60, 91]		
	ALT (Alanine transaminase) 44 studies	7 studies –ass. (at adm to LTU) [60, 42, 15], (cont. and cat.) [21], (adm and peak) [31], (survl vs death+LT) [48, 38] +ass. (peak in week3 in uni test and adm in uni. Cox a.) [58] 35 studies no ass. [18], (peak) [13, 46, 47], (survl vs death) [48, 49, 53, 36, 54, 56, 58, 60], (peak) [65, 67, 68, 69, 17, 14], (adm and peak) [6], (cont. and cat.) [73, 74, 76, 85], (peak) [21, 91, 35], (peak) [95], (at onset of HE in patient with mild atrophy vs sever	–ass. [60] +ass. [58] 5 studies no ass. [38, 41, 63, 42, 73],	3 studies [82, 93, 110]	cut-off >2000IU/L [73]; >1000IU/L [74]; <2600IU/L [21]; >10×normal [104] 200, 340, 460, 600 KU/dl [110]

		atrophy) [96, 98, 100], (peak) [32], (cat.) [104], (peak) [108], (adm and peak in both POD and nPOD subgroups) [23], (peak) [29]			
	Ammonia 13 studies	7 studies +ass. [15, 49, 50, 36, 54, 38, 33] 5 studies no ass. [42, 31], (peak) [29], (cat. adm, 24hr and 48hr of adm) [116, 126]	6 studies +ass. [49, 50], (dynamic change) [36], (dynamic change) [54, 38, 33] no ass. [42]		cut-off <124mmol/l [33]; <70g [116] 123µmol/l [36] ≥122µmol/l [54]
	Ammonium			[82]	
	Amylase	no ass. [35]			
	Angiopoietin-2	no ass. [53]	no ass. [53]		
	AST (Aspartate transaminase) 37 studies	–ass. [15] 3 studies +ass. (of pattern of biphasic increase) [6], (in nPOD subgroup) [30, 38] 33 studies no ass. (peak) [13, 18, 46, 47], (surv vs death, surv vs death+LT) [48, 49, 50, 53, 36, 54, 56], (adm and peak in week3) [58], (peak) [65, 67, 68, 17, 72, 14], (adm and peak) [6, 76], (in POD subgroup) [80, 85], (adm and peak) [21], (peak) [95, 98, 100], (peak) [32], (at onset of HE and 10-20 days after onset of HE) [24], (peak) [29], (in POD group) [114], (cat. adm, 24hr and 48hr of adm) [116], (both adm and peak in POD subgroup and peak in nPOD subgroup) [30, 126]	3 studies no ass. (at onset of HE and 10-20 days after onset of HE) [24], (both adm and peak) [50, 38]	2 studies [62, 82]	cut-off <35IU/L [116]
	AST/ALT ratio	no ass. (peak) [108]			
	BCAA branched chain amino acids (isoleucine, leucine, valine)	+ass. [46]			
	Bicarbonate 4 studies	2 studies –ass. [19] 3 studies no ass. [58, 33, 89]	2 studies no ass. [33, 19]		cut-off ≤20 [33]
	Bile acids	+ass. (day14 of onset of HE grade IV) [124] no ass. (at onset of HE grade IV) [124]			
	Cholic acid conjugated total 2 studies	–ass. [91] –ass. (24-36hr after onset of HE grade IV) [124]			cut-off <1.09%/kg [91]

	Cholic acid glycine conjugation	–ass. [91]	–ass. [91]		cut-off <0.52%/kg [91]
	Cholic acid sulphate conjugation	no ass. [91]			
	Cholic acid taurine conjugation	no ass. [91]	–ass. [91]		
	Glycolithocholic acid	no ass. [91]			
	Glycolithocholic acid sulphate	no ass. [91]	–ass. [91]		
	Bilirubin = B.T.= bilirubin total 68 studies	27 studies +ass. (survl vs death+LT) [48], [58], (adm both to hospital and to LTU) [60], [18], (cont. anc cat.) [42], [15], [69], (cont. anc cat.) [14], (at onset of HE) [16], (at day+2 till day+6 of HE) [20], [33], [19], [27], (cont. at day0 and day5 of ALS and cat.) [31], [91], (survl vs death and survl vs death+LT) [1], [94], (peak) [95], (survl vs death+LT) [28], [100], [102], (cat.) [104], (cat.) [34], (peak) [108], (both adm and peak in nPOD subgroup) [23], (cat.) [29], (both adm and peak in nPOD subgroup [30], [50], [53], [36], [54], [38] -ass. (both adm and peak in POD subgroup) [30] 35 studies no ass. (adm and at peak of M65) [13], [46], [47], (survl vs death) [48], [49], [51], [56], (peak in week3) [58] (peak) [65], [67], [68], [17], [72], [6], (cont. and cat.) [73], (cat.) [74], [76], (at onset of HE and on day+1 of HE) [20], [82], [85], (adm and peak) [21], [22], (in POD and nPOD subgroups) [27], [35], (survl vs death) [28], (at onset of HE in patient with mild atrophy vs sever atrophy) [96], [98], [99], (both adm and peak in both POD and nPOD subgroups) [106], (both adm and peak in POD subgroup) [23], (at onset of HE and 10-20 days after onset of HE) [24], (cat. in nPOD subgroup) [29], (in POD group) [114], (cat. adm, 24hr and 48hr of adm) [116], [126],	17 studies +ass. (adm both to hospital and LTU) [60], [18], [42], [15], [19], (in nPOD subgroup) [27], (on day4) [25], (in nPOD subgroup) [26], [1], [94], [34], (peak) [108], (both adm and peak in nPOD subgroup) [30], [50], [36], [38], [41] –ass. (peak in POD subgroup) [30] 8 studies no ass. [62], [14], [37], [33], (adm and on day8,15) [25], (in POD subgroup) [26], [104], (at onset of HE and 10-20 days after onset of HE) [24]	4 studies (of Δ value=difference in values from day 0 to day1 after the onset of HE) [20], [93], [110], [121]	cut-off ≥10.8mg/dL [18]; >17mg/dl [42], [31]; >140µmol/dl [15]; ≥20.0mg/dL [14], [104]. >15 mg/dl [25], [36], [73], [74], [34]; >18mg/dL [37] <15mg/dl [33] >384µmol/l [91] <10mg/dl [94] <13mg/dL [94] >23mg/dL [108] 6.6, 8.2, 10.4, 14.8mg% [110]; >300µmol/l [29], [30]; >320µmol/L [29]; <160µmol/L [29]; <1.0mg/dl [116] >20mg% [121]

	B.D.= bilirubin direct 6 studies	+ass. (survl vs death+LT) [48] 6 studies no ass. [17], [46], (survl vs death) [48], [38], [68], [85]			
	B. T/D = bilirubin total/direct ratio 5 studies	2 studies +ass. (cat.) [73], (on day5 of ALS) [31] 4 studies no ass. [68], (cont.) [73], (cat.) [74], (at day0 of ALS) [31]	2 studies +ass. [73], (adm and day4,8) [25] no ass. (on day15) [25]		cut-off >2.0 [73], [74], [25]
	B. D/T = bilirubin direct/total ratio 4 studies	3 studies –ass. [38], [56], (at onset of HE in patient with mild atrophy vs sever atrophy) [96] no ass. (at onset of HE and 10-20 days after onset of HE) [24]	2 studies -ass. [38], [56] no ass. (at onset of HE and 10-20 days after onset of HE) [24]		
	Blood gas 3 studies	no ass. [35]			PaO_2, pcO_2,O_2 saturation %
			no ass. [87]		VACO2 veno/ arterial gradient of PCO2
		no ass. [50]	no ass. [50]		SVO2 central venous saturation
		-ass. [50]	-ass. [50]		pO2 partial pressure of oxygen
		+ass. [50]	+ass. [50]		FiO2 fraction of inspired oxygen
	Blood group 2 studies	2 studies no ass. (O) [91], (ABO) [94]	–ass. [91]		
	BUN (Blood urea nitrogen) 3 studies	+ass. [68] no ass. [49]		[82]	
	C-reactive protein	no ass. [53]			
	Calcium 2 studies	–ass. [89] no ass. (survl death+LT) [28]	–ass. [89]		
	sCD163 (soluble) 2 studies	+ass. (on day3 and peak) [75] no ass. [75]		[90]	cut-off >26mg/l [75], 600 ng/ml [90]
	CD40	+ass. [71]			
	Cephalin time			[127]	
	Chloride Cl^-	no ass. [49]			
	Cholesterol 2 studies	–ass. (within 24h of adm) [52], (nadir) [108]			cut-off 1–5mMol/L [52]
	Citrate	no ass. [46]			
	Citrulline	no ass. (survl vs death and survl vs death+LT) [1]	no ass. [1]		
	CK-18 total	+ass. [70]			

	(Cytokeratin-18)				
	CK creatinine kinase	no ass. [50]	no ass. [50]		
	Creatinine 52 studies	18 studies +ass. (at peak of M65) [13], (survl vs death, survl vs death+LT) [48], (adm both to hospital and to LTU) [60], (peak) [65, 68], (cont and cat) [14], (at onset of HE) [16], (at day+2 till day+6 of HE) [20, 19], (adm/cont. and peak) [21, 22], (cont. and cat.) [102], (peak) [108], (POD group) [23], (cat.) [29], (in POD group) [114], (both adm and peak in POD subgroup) [30, 54] –ass. (peak in nPOD subgroup) [30] 1 study ass. but direction NR (both adm and peak in POD subgroup) [106] 32 studies no ass. [13, 18, 47, 49, 51, 56, 67, 15, 69, 17, 72, 6], (cont. and cat.) [73], (cat.) [74], (at onset of HE and day+1 of HE) [20], (in POD subgroup) [80, 85], (at onset of HE) [39], (cat.) [21, 89], (in all patients and POD and nPOD subgroups) [27, 91, 94], (survl vs death and survl vs death+LT) [28, 98], (cat.) [104], (both adm and peak in nPOD subgroup) [106], (in nPOD subgroup and peak in both POD and nPOD subgroups) [23], (in nPOD subgroup) [30, 50, 36], (adm and peak in week3) [58]	4 studies +ass. (adm both to hospital and to LTU) [60], (peak) [65, 14], (in POD subgroup) [30] 1 study ass. but direction NR (in POD subgroup) [106] 9 studies no ass. [62, 73, 37, 19, 25], (in POD and nPOD subgroups) [26], (peak in POD subgroup) [106, 50, 41]	2 studies (of Δ value (difference in values from day0 to day+1 of HE) [20, 82]	cut-off ≥1.5mg/dL [14]; >106 µmol/L (3 days or more after ingestion) [6] >2.0 mg/dl [73, 74]; >1.2mg/dl[37] >2.0mg/dl [21, 25] <2.5mg/dl[94] >1.5mg/dl[102] ≥3.0mg/dl[104] >110µmol/L [29]; >300µmol/L [30]
	D-dimers	no ass. (survl vs death and survl vs death+LT) [1]	no ass. [1]		
	Disseminated intravascular coagulation	+ass. [73]			
	Erythrocyte sedimentation rate (ESR)	no ass. [68]			
	Fibronectin 2 studies	2 studies no ass.(adm, +1day, +2days, +3days, +4days) [110, 119] –ass.(changes in levels on 1st-2nd day, 2nd-3rd day, 3rd-4th day, 4th-5th day) [110]			cut-off 12, 18.8, 30, 56 (µg/ml) [110]
	Follistatin	+ass. [83]			

	Follistatin/ activin A ratio (F/A ratio)	–ass. [83]			
	Formate	no ass. [46]			
	Gamma-glutamyl transferase (GGT, γ-GTP) 5 studies	–ass. (peak) [65] 4 studies no ass. (peak) [13], [17], (survl vs death and survl vs death+LT) [48], [95]	–ass. (peak) [65]		
	Gc globulin (Actin-free) Af-Gc 6 studies	6 studies –ass. (in all patients and POD subgroup) [72], (adm and on day3) [79], (in all patients and nPOD subgroup) [26], (total and free) [107], (in all patients and in nPOD subgroup) [23], (Af-Gc, total, and percentage of Gc complexed with actin at up to day4) [112] 4 studies no ass. (in nPOD subgroup) [72], (in POD subgroup) [26], (in POD subgroup and complexed) [23], (Af-Gc, total, and percentage of Gc complexed with actin) [112]	–ass. (in nPOD subgroup) [26] 2 studies no ass. [72], (in POD subgroup) [26]		cut-off 46.5mg/L [72], 40 mg/L [79], 80mg/L [26]; 120 mg/L (total Gc globulin) [107]; 100ml/L [23]. 34µg/mL [112]
	Glucose / Hypoglycaemia 5 studies	5 studies no ass. [49], [68], [69], [91], (peak) [29]	+ass. [91]		
	Glutamate	no asa. [46]			
	GLDH(Glutamate dehydrogenase)	no ass. (peak) [13]			
	Glutamine 3 studies	2 studies +ass. [46], [85]	+ass. [46]	[89]	
	Glycine	+ass. (survl vs death) [1] no ass. (survl vs death+LT) [1]	no ass. [1]		
	GST (Glutathione S-Transferase-Alpha)	no ass. (peak) [13]			
	G-CSF (Granulocyte colony stimulating factor	no ass. [76]			
	H+	no ass. [89]			^{1}H-NMR of plasma
	HDL	+ass. (within 24h of adm) [52]	no ass. [52]		cut-off >1mMol/L [52]

	Hematocrit	+ass. [19]	no ass. [19]		
	Hemoglobin 16 studies	4 studies –ass (adm both to hospital and to LTU) [60, 15, 89, 19] 11 studies no ass. [68, 14, 6, 76, 21, 35, 49, 36, 54, 56, 58]	2 studies –ass. (adm to LTU) [60, 89] 3 studies no ass. [60, 19, 25]		cut-off ≤10g/dl [25]
	HGF (Hepatocyte growth factor) 3 studies	+ass. [38], [76], (on day3) [78]	+ass. [38]		
	Histidine 3 studies	–ass. (survl vs death+LT) [1] +ass. [46] no ass. (survl vs death) [1]	+ass. [46] no ass. [1]	[89]	
	HLA-DR (%)	–ass. (in POD subgroup) [80]			cut-off ≤15% [80]
	Total HLA-DR–positive monocytes	–ass. (in POD subgroup) [80]			cut-off <0.035 [80]
	HLA-DR MFI	–ass. (in POD subgroup) [80]			cut-off <52 [80]
	IFN-γ Interferon γ	+ass. (in POD subgroup) [80]			
	IL-10 Interleukin 10 3 studies	2 studies +ass. (in all patients and in POD subgroup) [62], (in POD subgroup) [80] –ass. [99]	+ass. [62]		cut-off >130.5 [62]
	IL-18 Interleukin 18	no ass. [99]			
	IL-4 Interleukin 4 2 studies	+ass. (in POD subgroup) [80] no ass. [99]			
	IL-6 Interleukin 6 3 studies	–ass. [70] 2 studies +ass. (in all patients and in POD subgroup) [62], (in POD subgroup) [80]	no ass. [62]		cut-off >72 [62]
	Keratin K8/K18 variants	+ass. [64] no ass. (K8 R341H, K8 G434S, A333A/A338A variants) [64]	+ass. (in white subgroup and K8 R341H variant) [64] no ass. (in all patients and POD subgroup) [64]		
	Lactate 17 studies	17 studies +ass. [15], (adm and 4h, 8h, 12h) [51, 53, 72, 6, 50], (in POD subgroup) [80], (adm and at onset of HE [39, 89], (in all patients and POD subgroup at adm, 4hr,	10 studies +ass. [50], (at 12h) [51], (survl vs death, survl vs death+LT) [66, 15, 72], (at onset of HE) [39, 89], (at 12hr both in		cut-off >3.5 mmol/L [15, 39, 97] <3mmol/L [39, 97]; >4mmol/L [39],

		8hr, 12hr and in nPOD subgroup at 4hr, 12hr) [27], (survl vs death and survl vs death+LT) [1], (adm and after fluid resuscitation) [97] 4 studies no ass. [49], [87], (in nPOD subgroup at adm and 8hr) [27], [35]	nPOD and POD subgroups) [27], [1], (adm and after fluid resuscitation) [97] no ass. [62]		3.3mmol/L [51], 4.7mmol/L (at 12h) [51]
	Hyperlactatemia+ Metabolic acidosis	+ass. [122]			
	LDH Lactate dehydrogenase 2 studies	+ ass. [49] no ass. [17]			
	LDL	no ass. (within 24h of adm) [52]			cut-off 1-3mMol/L [52]
	LECT2	–ass. (peak) [92]			
	Leucine 2 studies	+ass. (survl vs death+LT) [1] no ass. (survl vs death) [1]	no ass. [1]	[89]	
	Leukocytes 2 studies	+ass. [19] no ass. [91]	+ass. [91] no ass. [19]		
	Lysine	+ass. [46]	+ass. [46]		
	Magnesium	no ass. (survl vs death+LT) [28] +ass. (survl vs death) [28]			
	Mean arterial pressure (MAP) 6 studies	3 studies –ass. [19], [50], [97] 3 studies no ass. [58], [72], (in POD subgroup) [80]	-ass. [50] 2 studies no ass. [19], [97]		
	Methionine	no ass. [46]			
	MBL gene mutation	+ass. [98]			mannose-binding lectin
	MBL in serum concentration	–ass. [98]			mannose-binding lectin
	Monocyte count total	–ass. (in POD subgroup) [80]			
	Osteopontin (OPN)	no ass. (cont. and cat.) [81] +ass. (cat at ≥30 days of adm) [81]			cut-off >2.580 log_{10},ng/ml [81]
	pH 27 studies	10 studies –ass. [51], [72], (in POD subgroup) [80], [33], (at onset of HE) [39], (survl vs death) [28], (cat.) [97], (in POD subgroup) [114], (in POD and nPOD subgroups) [30], [54] 1 study ass. but direction NR (both adm	3 studies –ass. [33], [97], (in POD subgroup) [30] 1 study ass. but direction NR (peak in POD subgroup) [106] 4 studies no ass. (AV pH) [87], (in POD and nPOD subgroups)	3 studies [5], [62], [109]	cut-off <7.3 [5], [97], [106], [109], [114], [30], ≤7.40 [33], <7.25 [106], <7.1 [106]

		and peak in POD subgroup) [106] 13 studies no ass. [69], [6], (adm and nadir) [21], (in all patients and POD and nPOD subgroups) [27], [35], (survl vs death+LT) [28], [102], (both adm and peak in nPOD subgroup) [106], (peak) [29], [49], [50], [36], (adm and peak in week3) [58]	[26], (in POD subgroup) [106], [50]		AV pH = arterial/mixed venous gradient of pH
	Phenylalanine 2 studies	+ass. [46] –ass. [89]	+ass. [46] –ass. [89]		
	Phosphate 6 studies	2 studies +ass. [27], [58] 5 studies no ass. (adm and at peak of M65) [13], [21], [89], (in POD and nPOD subgroups) [27], [51]	+ass. [58]		
	Phosphorus 3 studies	2 studies +ass. [94], (nadir in survl vs death+LT) [28] no ass. (nadir in survl vs death) [28]	2 studies +ass. (cat.) [41], [94]		cut-off ≥3.7mg/dL [41] <2.5, 2.5-5, >4.2, >5mg/dL [94]; ≥1,≥2.5mg/dL [28]
	Potassium 6 studies	+ass. (adm both to hospital and to LTU) [60] 1 study ass. but direction NR (both adm and peak in POD subgroup) [106] 5 studies no ass. [49], [51], [91], [35], (both adm and peak in nPOD subgroup) [106]	2 studies +ass. (adm to LTU) [60], [91] 1 study ass. but direction NR (peak in POD subgroup) [106] 2 studies no ass (in POD subgroup) [106], [60]		cut-off >5.5 mol/l [106]
	Prealbumin	no ass. [111]		(rising on day5 and 10) [111]	
	Pyruvate 3 studies	2 studies –ass. [89], (survl vs death and survl vs death+LT) [1] no ass. [46]	2 studies –ass. [89], [1]		
	Respiratory rate/ Tachypnea 2 studies	+ass. [19] no ass. [73]	no ass. [19]		cut-off >20 breaths/minute or PaCO2 <43 Kpa [73]
	sCD154	+ass. [71]			serum-soluble immunoactivating molecules
	sFasL 2 studies	+ass. [78] no ass. [68]			
	Sodium 15 studies	+ass. [89], 12 studies no ass. (adm both to hospital and to LTU) [60], [15], [14], [35], (both adm and peak in both POD and nPOD	no ass. [41]	[121]	cut-off <119mEq/liter [121]

		subgroups) [106], [29], (both adm and peak in both POD and nPOD subgroups) [30], (survl vs death, survl vs death+LT) [48], [49], [51], [36], [54]			
	Stem Cell Factor (SCF)	–ass. [76]			hematopoietic growth factor
	Thrombopoietin (TPO)	–ass. [76]			hematopoietic growth factor
	TNF gene polymorphism			[93]	poor prognosis related to higher frequencies of positions 1031C and 863A in the TNF-α promoter region, and higher frequencies of the B2 allele of the TNF-gene[93]
	TNF-alpha TNF-α 5 studies	2 studies +ass. [78], [80] –ass. [70] 2 studies no ass. (in all patients and in POD subgroup) [62], [68]	no ass. [62]		cut-off >98.5 [62]
	Triglyceride	no ass. (within 24h of adm) [52]			cut-off 0.5-2mMol/L
	Troponin 2 studies	2 studies +ass. [50], [77]	no ass. [50]		cut-off >0.1ng/ml[77]
	Tyrosine	+ass. [46]	+ass. [46]		
	Urea = Carbamide 9 studies	–ass. (peak in nPOD subgroup)[30] 9 studies no ass. [60], [18], [91] (both adm and peak in both POD and nPOD subgroups) [106], (in nPOD subgroup and both adm and peak in POD subgroup) [30], [50], [51], [36], [54]	2 studies +ass. [91], (adm to LTU) [60] 2 studies no ass. [50], [60]		
	Urine glutamine /creatinine ratio	no ass. [85]			
	Urine urea /creatinine ratio	+ass. [85]			
	Valine 2 studies	+ass. (survl vs death and survl vs death+LT) [1]	+ass. [1]	[89]	
	WBC (White blood cell count) 24 studies	6 studies +ass. (adm both to hospital and to LTU) [60], [15], (at onset of HE) [39], (peak) [21], [97], (in POD and nPOD subgroups) [30]	+ass. [60] 1 study ass. but direction NR (peak in POD subgroup) [106] 2 studies no ass. (adm to LTU)	[62]	cut-off >12×10^3/mm^3 or <4×10^3/mm^3 [73], [39]; <4000/mm^3 or >18,000/mm^3 [104] >20×10^9 per liter [106]

		1 study ass. but direction NR (peak in POD subgroup) [106] 20 studies no ass. [46, 49, 51, 36, 54, 38, 56, 58, 68, 14, 73, 76, 39, 21, 35], (peak) [95], (cat.) [104], (in POD subgroup and in both adm and peak in nPOD group) [106], (peak) [108], (peak in POD and nPOD subgroups) [30]	[60, 97]		
	Zinc	–ass. (in serum) on days1,4,7[120] +ass. (in urine) on days1,4,7 [120]			
	Coagulopathy				
	ATIII antithrombin III 2 studies	+ass. [38] no ass. [82]	no ass. [38]		
	Factor II	no ass. (adm and within 36hr of onset of HE grade IV) [123]			
	Factor V 8 studies	4 studies –ass. (nadir) [6], (in all patients and POD subgroup) [109], [114], (at 1st and 2nd biopsy) [128] 3 studies no ass. [15], [82], (adm and within 36hr of onset of HE grade IV)[123]		[127]	cut-off <20%, <10% [109], [114]
	Factor VII 2 studies	no ass. (adm and within 36hr of onset of HE grade IV) [123]		[127]	cut-off <9% [123], [127]
	Factor VIII	+ass. (in POD group) [114]			
	Factor VIII/V ratio	+ass. (in POD group) [114]			cut-off >30 [114]
	Fibrin degradation products (FDP)			[127]	
	Fibrinogen 2 studies	no ass. (cat. adm, 24hr and 48hr of adm) [116]		[127]	cut-off 200-400mg/dl[116] 150mg%[127]
	Hepaplastin test 3 studies	+ass. [38] 2 studies no ass. [98], (cat. adm, 24hr and 48hr of adm) [116]	no ass. [38]		cut-off >70% [116]
	INR (International Normalized Ratio) 36 studies	19 studies +ass. (adm and peak of M65) [13], (survl vs death, survl vs death+LT) [48], [49, 50, 51, 36, 54], (peak) [65, 67, 15, 17, 72], (at onset of HE) [16], (at day+1 till day+6 of HE) [20], (in POD subgroup) [80, 19, 22, 89, 97]	7 studies +ass. [49, 50], (dynamic change) [36, 41, 62], (peak) [65, 72] 5 studies no ass. [42, 19, 89], (in POD and nPOD subgroups) [26, 97]	5 studies [5], (of Δ value=difference from day 0 to day 1 after the onset of HE) [20, 82, 109],	cut-off >3.5 [42, 31]; >5 [36, 69]. >6.5 [5, 109]; >-0.3 for Δ value (difference from day

		11 studies no ass. (adm and peak in week3) [58], [47], (cont. and cat.) [42], (cat >5) [69], (adm and nadir) [6], (at onset of HE) [20], (at onset of HE) [39], (adm and peak) [21], [31], [28], (in POD group) [114]		[127]	0 to day 1 after the onset of HE) [20]
	Platelets 22 studies	6 studies –ass. (on day15) [25], (nadir in POD subgroup) [30], (adm to LTU) [60] 1 study ass. but direction NR (peak in POD subgroup) [106], [49], [38], [56] 16 studies no ass. [51], [53], [54], [58], [60], [17], (survl vs death, survl vs death+LT) [48], [6], (cont. and cat.) [73], (cat.) [74], [76], [21], [35], (in POD subgroup and in both adm and peak in nPOD subgroup) [106], (cat. adm, 24hr and 48hr of adm) [116], (in POD and nPOD subgroups and nadir in nPOD subgroup) [30]	3 studies –ass. [38], (adm to LTU) [60], [62] 3 studies no ass. (adm and day4,8) [25], (peak in POD subgroup) [106], [56]	[127]	cut-off <100×10^3/mm^3 [73] <80×10^3/mm^3 [74] ≤10×10^{3}mm^3 [25] range 12-41× 10^{3}mm^3 [116]
	PT (s) (Prothrombin time) 47 studies	19 studies +ass. [51], (adm both to hospital and to LTU) [60], [18], [68], (cont and cat) [14], [33], [19], [85], (in POD subgroup) [27], (survl vs death) [1], (cont. and cat.) [35], [100], (cat.) [104], (cat.) [34], (peak) [108], (cat.>50s in nPOD subgroup) [29], (on day4) [114], (cat. peak, rise on day4, (rise from day3 to day4 with PT fell between those days) [117], (both adm and peak in both POD and nPOD subgroups)[30] 1 study ass. but direction NR (both adm and peak in POD subgroup and peak in nPOD subgroups) [106] 12 studies no ass. [46], [69], (in all patients and nPOD subgroup) [27], (survl vs death+LT) [1], [94], (at onset of HE in patient with mild atrophy vs sever atrophy) [96], [102], (in nPOD subgroup) [106], (both adm and peak in both POD and nPOD subgroups) [23], (cat.>100s in nPOD subgroup) [29], (cat. adm, 24hr and 48hr of adm) [116], (rising value from day1	12 studies +ass. [51], (adm to LTU) [60], [18], [14], [37], [1], [94], [35], [104], [34], (peak) [108], (peak in POD subgroup and adm and peak in nPOD subgroup) [30] 1 study ass. but direction NR (peak in POD and nPOD subgroups) [106] 3 studies no ass. [60], [33], [19] Expressed in %: 4 studies –ass. [38], [74], [91], (at 10-20 days after onset of HE) [24] 3 studies no ass. [73], [25], (at onset of HE) [24]	3 studies [93], [110], [114]	cut-off ≥26s [18]; ≥35s [14]; <10% [6], [25]; ≤10% [73], [74]; ≥25s [37], [33], [34]; <20s [94]; 22.5s[94]; ≥30s [35]; 19% (on 3rd day after peak transminases) [32]; >100s [104], [30]; >75s [106]; >130s [106]; >19s [108]; 10s,16s, 26s, 60s [110]; <15% [29]; >50s [29]; >100s [29]; > 180s [114]; <11s [116]; ≥180 [117];

		to day3 after overdosis) [117] Expressed in %: 11 studies –ass. (nadir) [6], [53], [38], (cat.) [74], [76], (on day5 of ALS) [31], (on days1,2,3,4,5,6 of peak transaminases) [32], (at 10-20days after onset of HE) [24], (cat.) [29], [49], [56] 12 studies no ass. (per 1% increase) [56], (cont. and cat.) [42], [15], [6], (cont. and cat.) [73], (on day0 of ALS) [31], [91], (peak) [95], [98], (on day 0 of peak transaminases) [32], (at onset of HE) [24], [126]			130-179 [117]; 90-129 [117]; <90 [117]; >50s [30];
	aPTT(Activated partial thromboplastin time 2 studies	+ass. [51] no ass. [82]			
	Thromboplastin time	–ass. (at 1st and 2nd biopsy) [128]			cut-off ≤10% [128]
Hemodynamics	Cardiac index(CI)	no ass. [50]	no ass. [50]		
	Central venous pressure (CVP)	+ass. [50]	+ass. [50]		
	Cerebral edema 11 studies	9 studies +ass. [18], [14], [36], [38], [54], [73], [33], [35], [34]	3 studies +ass. [14], [33], [34] 4 studies no ass. [37], [35], [36], [38]	[110]	
	Hemodynamic instability	no ass. [69]			
	Heart rate 6 studies	4 studies +ass. [19], (tachycardia) [38], (at onset of HE) [39], [73] 3 studies no ass. [39], [50], (arrhythmia) [58]	+ ass. [50] 3 studies no ass. [19],(tachycardia)[38], (arrhythmia) [58]		cut-off >90 beats/min [39], [73]
	Hepatic artery resistance index (HARI)	+ass. (adm and peak) [103]			
	Hypotension	no ass. [6]			
	ICP (Intracranial pressure) 2 studies	2 studies +ass. [88], [104]	+ass. [104]		cut-off >25 mmHg [88]
	Intrathoracic blood volume index (ITBVI)	no ass. [50]	no ass. [50]		

	ICP + CBF changes defined as different phases of disease*	+ass. [88] (increase in died, decrease or no change in survivors)			cutoff <30 (low aCBF) and ≥30 (high aCBF).
	Portal vein flow	no ass. [103]			
	Portal vein time average velocity (TAV)	no ass. [103]			
	Portal vein hemodynamics	no ass. [100]			portal vein diameter; portal flow velocity; cross sectional area; portal blood flow rate
	Pedal oedema	no ass. [68]			
Liver function tests	Antipyrin clearance	no ass. [91]			
	Caffeine clearance	no ass. [115]			
	Cholinesterase	no ass. [49]			
	Galactose elimination capacity (GEC) 4 studies	2 studies –ass. (in all patients cat., in patients with HE cont.; within 200hr postoverdose) [40], (either shortly after adm or at onset of HE) [126] 2 studies no ass. [91], [115]	–ass. (in patients with HE; measured within 200hr postoverdose) [40]	both GEC measured within 72hr and after 72hr post-overdose [40]	cut-off <10, <12, <15.5, <16.5 µmol/min/kg [40], ≤2.3mg/kg per min [115] < 12.8 µmol/ min/kg [126]
	LiMAx test	-ass. [47]			
	Plasma disappearance rate of indocyanine green	–ass. [67]			cut-off ≤ 6.3%/min [67]
	Plasma phenazone clearance	no ass. [91]			
Imaging/morphology	Caspase activity /apoptose activity / M-30 4 studies	– ass. [70] 2 studies +ass. (at peak of M65) [13], [78] no ass. [13]	+ass. (log value on day3) [41] no ass. (on day3 and changes on day1,2,3) [41]		in serum and biopts (measured both caspase-generated CK-18 neoepitope and caspase-3/caspase-7 activity) [70], [78] cut-off caspase-generated CK-18 fragments: 6712 U/L; caspase-3/7 activity: 9276 RLU [70]
	Cell death M65	+ ass. (adm and peak) [13]	no ass. (on day3 and log value		cut-off

	epitope		on day3 and changes on dat 1,2,3) [41]		>12316.5 U/L
	M-65 and M-30		no ass. (ratio M-65/M-30 and M65-M30 and logM65-M30) [41]		
	Diffuse low hepatic density	no ass. [101]			
	Disappearance of liver dullness	+ass. [38]	no ass. [38]		
	Hepatocyte volume (%)	–ass. (at 1st and 2nd biopsy) [128]			cut-off <35% [128]
	Heterogeneity of liver	no ass. [101]			
	Liver atrophy	+ass. [38]	+ass. [38]		
	Liver size in percussion space	–ass. (cont. and cat.) [34]			cut-off <2 [34]
	Liver span	–ass. [68]			cut-off ≤4cm [68]
	Liver volume SLV: standard liver volume 3 studies	–ass. (at onset of HE and 10-20 days after onset of HE) [24] 2 studies no ass. [42], [101]	–ass. (at onset of HE and 10-20 days after onset of HE) [24]		SLV [ml] = 706.2 × BSA [m2] + 2.4; cut-off <1000ml [101], <656ml [24]
	ELV/SLV ratio	2 studies –ass. (cont and cat) [42], (cont and cat, at day0 and day5 of ALS) [31]	–ass. [42]		cut-off <0.80,<0.90,<0.85,<0.75,<0.70 [42], [31]
	Portal vein cross-sectional area	no ass. [103]			
	Parenchymal necrosis (%)	+ass. [101]			cut-off >50% [101]
	Spleen length	no ass. [103]			
Scoring systems	ALF in-hospital mortality score ALFIHMS			[19]	0.714+0.02(TB) +0.03(APACHE II score) × 10 cut-off >15 [19]
	ALFED model			[36]	dynamic changes over 3 days of: HE>II, INR, ammonia, bilirubin [36]
	ALFSG		+ass. [41]		HE,INR,bilirubin, phosphorus
	ALFSG Index			[21]	creatinine > 2.0 mg/dL, ALT < 2600 IU/L, intubation, pressors
	Algorithms through decision			(at onset of HE and at	

	tree analysis			5 days later) [55]	
	ALT-LDH index	no ass. [17]			serum ALT/ (serum LDH -median of normal LDH range) cut-off >3.0 [17]
	APACHE II 9 studies	5 studies +ass. [67], (in POD subgroup) [80], [19], [50], [51] no ass. [72]	3 studies +ass. (survl vs death, survl vs death+LT) [66], [19], [50]	2 studies [82], [105]	cut-off >15 [105] 12 [51] 11 (at 12h) [51]
	Any 2 indicators	+ass. [29]			bilirubin > 320µmol/L bilirubin<160 or >320µmol/L creatinine > 110 µmol/L PT<15% interval jaundice-HE >7days
	Any 3 indicators			[14]	age≥50, jaundice-HE interval 7 days, HE grade 3 or 4, presence of CE, PT≥35s, creatinine ≥1.5
	Any 3 indicators	+ass. (in nPOD subgroup) [29]			age<10 or >40yr, unfavorable etiology, interval jaundice -HE >7days PT>50s PT>100s bilirubin > 320µmol/L
	Any 1, 2, 3 or 4 of indicators			[35]	age>40yr, HE >2, PT>30s, non-E cause
	BiLE score (Bilirubin–Lactate–Etiology score) 2 studies	2 studies +ass. (cont and cat) [15], (fulfilled and points) [53]	+ass. [15]		bilirubin (µmol/L)/100 + lactate (mmol/L) +4 (in case of indeterminate ALF, Budd-Chiari syndrome, or phenprocoumon toxicity) -2 (in case of APAP toxicity) +0 (in case of any other ALF etiology) cut-off ≥6.9 [15]
	Biochemical model			[1]	0.5×(albumin [g/L])-2×(lactate[mmol/L])-36× (valine [mmol/L])-38× (pyruvate [mmol/L])
	Biochemical model			[89]	(400×pyruvate (mmols/L)+(50×phenylalanine(mmols/L)-4×hemoglobin (g/dL)

	Composite multivariate model (bilirubin, lactate, INR, HE)		+ ass. [50]		
	Charlson score	no ass. (cont. and cat. 1-2 vs 0 and >2 vs 0) [84]	no ass. (1-2 vs 0 and >2 vs 0) [84]		comorbidity index
	Clichy criteria 5 studies		no ass. (survl vs death and survl vs death+LT) [8]	4 studies [5, 6, 16, 7]	
	Factor V< 20% + HE gr. I-IV			[109]	
	Factor V< 10% + HE gr. I-IV			[109]	
	Factor V< 20% + HE gr. III-IV			[109]	
	Ganzert's Criteria			[6]	decrease in PT below or equal to 25% of normal between day 3 and 10 after ingestion + creatinine ≥106 Imol/L
	Glasgow Coma Score	–ass. [19]	no ass.[19]		
	KCC 33 studies	5 studies +ass. [67, 15], (at onset of HE) [39], [36, 57] 5 studies no ass. (adm and peak) [13, 18], [31, 47, 53]	2 studies +ass. (survl vs death) [8], (at onset of HE) [39] no ass. (survl vs death+LT) [8]	22 studies [5, 14, 6, 16, 79, 20, 19, 21, 22, 89, 26, 1, 40, 28, 97, 105, 109, 23, 7, 51, 52, 41]	
	KCC + actin-free Gc-globulin <40mg/L			[79]	
	KCC+HDL			[52]	
	KCC modified			[39]	KCC + arterial lactate concentration >3.0 mmol/L after adequate fluid resuscitation
	KCC + serum			[28]	

	Phosphorus ≥ 2.5 mg/dL				
	KCC + either lactate criteria			[97]	lactate crit.: adm value >3.5mmol/L, value after fluid resuscitation >3.0mmol/L [97]
	KCC + postresuscitation lactate>3mmol/L			[97]	
	KCC + time to GEC measurement ≤72hr or >72hr			[40]	
	KCC + HE or GEC<10 µmol/min/kg + HE			[40]	
	HE + GEC <10µmol/min/kg or HE + GEC <12µmol/min/kg			[40]	
	KCC+ HE + GEC >10µmol/min/kg <16.5µmol/min/kg	+ass. [40]			
	pH < 7.30 or INR > 6.5, creatinine > 300 µmol/L, HE III or IV			[109]	
	Either of lactate criteria			[97]	lactate crit.: adm value >3.5mmol/L, value after fluid resuscitation >3.0mmol/
	MELD 25 studies	16 studies +ass. (adm and peak) [13, 14, 18], (survl vs death, survl vs death+LT) [48, 50, 36, 57, 64, 65, 67, 15, 17, 16], (on day+1 till day+7 of HE) [20], (survl vs death) [8, 84] 6 studies no ass. [47], (cont nad cat) [42, 69], (at onset of HE) [20, 21], (in POD subgroup) [11]	6 studies +ass. [65, 15], (survl vs death and survl vs death+LT) [8, 84], (in nPOD subgroup) [11, 50] no ass. [42]	5 studies [19],(ΔMELD= difference from day 0 to 1 after the onset of HE) [20, 21;22, 51, 41]	cut-off >25.5 [13], >25 [19], >33 [18], ≥30 [42, 8], ≥32 [15], <30 [17], <35(day3)[17] ≥33 [14], >30 [16, 22], >35 [36, 16], >33 (day+1 of HE) [20, 57], >32 (day of HE) [20], (adm and 12h) [51];

					≥35 [21]; >-0.4(ΔMELD = difference from day0 to 1 after the onset of HE [20]
	MELD≥33 + presence of CE			[14]	
	MELD≥33 + age≥50			[14]	
	MELD≥33 + jaundice-HE interval			[14]	
	MELD-Na	+ass. (survl vs death, survl vs death+LT) [48]			MELD−Na− [0.025×MELD× (140−Na)] +140
	M-MELD	+ass. (adm and peak) [13]			10 × (0.957 LnCreatinine[mg/dl] + 0.378 Ln_{M65} [U/µl] + 1.12 Ln_{INR} + 0.643); cut-off >53.5 [13]
	Novel scoring system			[38]	cut-off ≥5 interval onset of disease to HE, PT, bilirubin T, ratio bilirubin D/T, platelet, presence of liver antrophy
	SAPS-III 3 studies	2 studies +ass. [15], [50] no ass. [53]	2 studies +ass. [15], [50]		
	SOFA 6 studies	5 studies +ass. [72], (adm and at onset of HE) [39], [50], [51], [53]	3 studies +ass. [72], [39], [50] no ass. [62]		cut-off >8 [39], >12 (at onset of HE) [39] 12 (adm and at 12h) [51]
	SOFA + Lactate 12h			[51]	
	SOFA subscore Respiratory	+ass. (at onset of HE) [39] no ass. [39]			
	SOFA subscore Hepatic	no ass. (adm and at onset of HE) [39]			
	SOFA subscore Coagulation	+ass. (adm and at onset of HE) [39]			
	SOFA subscore Cardiovascular	+ass. (adm and at onset of HE) [39]			
	SOFA subscore Neurologic	no ass. (adm and at onset of HE) [39]			
	Renal SOFA	+ass. (adm and at onset of HE) [39]			

	subscore				
	UKELD	+ass. (survl vs death, survl vs death+LT) [48]			{(5.395×ln(INR))+(1.485×ln(creatinine [µmol/l])) +(3.13×ln(bilirubin T [µmol/l])) - 81.565 × ln(Sodium[mmol/l]))} + 435
	Z index	+ass. [42]			-2.6213 - [0.15234 x TB (mg/dl)] + [4.5734 x CTLV/SLV]
Time intervals	Duration of HE	no ass. [29]			
	Duration of history	no ass. [91]	+ass. [91]		
	Duration of ICU stay	no ass.[51]			
	Duration of jaundice	+ass. (cont and cat) [14]	no ass. [14]		cut-off >5.5days [14]
	Duration of (C)HDF	no ass. [31]			
	Duration of PE	no ass. [31]			
	Interval ATT to ALF	no ass. [18]			
	Interval admission to lowest PT index	+ass. [6]			
	Interval ingestion /drug administration to admission 2 studies	no ass. [6] +ass. [95]			
	Interval ingestion to diarrhea	+ass. [6]			cut-off <8hr [6]
	Interval onset of symptoms to diagnosis 3 studies	2 studies no ass. (cont and cat) [73], (cat.) [74]	2 studies no ass. [73], [25]		cut-off ≤7days [73], [74], [25]
	Interval onset of symptoms to icterus	no ass. [34]			
	Interval hospital admission to study enrollment 2 studies	2 studies no ass. [21], [58]			

	Interval jaundice (icterus) to HE 16 studies	8 studies +ass. [42], (cont and cat) [14], (cat.) [87], [31], (cat.) [102], (cat.) [104], (in all patients and nPOD subgroup) [29], [30] 7 studies no ass. [18], (cat.) [16], (in nPOD subgroup) [106], [36], [54], [34], (cat.) [108]	3 studies +ass. [14], [104], (in nPOD subgroup) [30] 2 studies no ass. [42], [37]		cut-off >1week [42], [14], [16], [31], [102], [104], [106], [29], [30], >28days [37], [87], [108] 0-7, 8-14, 15-21, 22-28 days [34]
	Interval onset of symptoms to HE 4 studies	+ass. [38] 2 studies no ass. [49], [34]	+ass. [38] no ass. (in nPOD subgroup) [30]		cut-off 0-7, 8-14,15-21, 22-28 days [34]
	Interval onset of symptoms to study enrolment 2 studies	2 studies no ass. (cont and cat) [21], [58]			cut-off >21 days [21]
	Pre-HE period 2 studies	2 studies +ass. (cont and cat) [35], [42]	2 studies no ass. [35], [42]		cut-off ≤7days [35]
Treatments	Extracorporal perfusion via baboon livers	no ass. [29]			
	Fresh frozen plasma infusion 3 studies	3 studies no ass. [14], [104], [126]			
	Hemodiafiltra-tion 3 studies	3 studies no ass. [42], [73], [74]			
	Hemofiltration 2 studies	2 studies +ass. [50], (during ICU stay)[51]	no ass. [50]		
	Exchange transfusion	no ass. [126]			
	Hemodialysis 4 studies	4 studies no ass. (adm and at week3) [21], [29], (adm and at week3) [58], [94]			
	Hemoperfusion	no ass. [29]			
	Inotropic support 2 studies	2 studies +ass. [50], (ad mand during ICU stay) [51]	+ass. [50]		
	Inspiratory oxygen concentration %	+ass. [51]	+ass. [51]		
	Lamivudine and / or interferon 2 studies	2 studies no ass. [42], [73]			

	N-acetylcysteine 2 studies	2 studies no ass. (in POD subgroup) [106], (peak in week3) [58]			
	Norepinephrine =Noradrenaline 2 studies	2 studies +ass. [72], (in POD subgroup) [80]			cut-off ≥0.1 µg/kg/min [72], [80]
	Peritoneal dialysis	no ass. [126]			
	Phosphorus administration	–ass. on bivariate a. (in patients with serum phosphorus <2.5mg/dL and 2.5-5mg/dL at 1 week) [94] no ass. on bivariate a. (in patients with serum phosphorus >5mg/dL at 1 week) [94]			
	Pig liver perfusion	no ass. [126]			
	Plasma exchange 3 studies	3 studies no ass. [42], [73], [74]			
	Plasmapheresis	no ass. [29]			
	Pressors 2 studies	+ass. (adm and at 3 weeks) [21] no ass. [58]			
	Protease inhibitor 2 studies	2 studies no ass. [73], [74]			
	Steroids / corticosteroids 4 studies	4 studies no ass. [42], [73], [74], [126]			
	Ventilation / intubation 6 studies	6 studies +ass. (adm and at 3 weeks) [21], [27], [50], (adm and during ICU stay)[51], (on week3) [58], [126]			

If not otherwise reported: admission value of indicator reported and indicator considered as continuous variable.
+ass. = lower/less in survivors, higher/more in non-survivors = significant positive association with mortality;
–ass. = higher/more in survivors, lower/less in non-survivors = significant reverse association with mortality;
no ass. = no significant association with mortality;
NR = significant association with mortality not reported;
cut-off = cut-off point used for categorical variable; cont. = continuous variable; cat. = categorical variable; peak / nadir = peak / nadir value of the indicator; survl = patients who survived; death = patients who died; survl vs death = comparison between survivors and death; LT = liver transplantation; LTU = liver transplantation unit; death+LT = patients who died or underwent liver transplantation; survl vs death+LT = comparison between survivors and death + transplanted

ALS = artificial liver support; APAP = acetaminophen, paracetamol; HE = hepatic encephalopathy; POD subgroup = patients with etiology of paracetamol overdose; nPOD subgroup = patients with etiology other than paracetamol overdose
ALF = Acute Liver Failure; ATT = Antituberculosis therapy; BMI = Body mass index; (C)HDF = (continuous) hemodiafiltration; ELV/SLV = Estimated liver volume/ Standard liver volume; HAV, HBV, HEV, HDV = Hepatitis A, B, D, E virus; HDL = High density lipoprotein; KCC = King's College Criteria; LDL = Low density lipoprotein; LECT2 = leukocyte cell-derived chemotaxin2; M65 = epitope of cytokeratin 18 released from destroyed cells; MBL = Mannose-binding lectin; MELD = Model for End-Stage Liver

*Disease; NANB = non-A non-B hepatitis; SAPS-III = Simplified Acute Physiology Score; sE-selectin = endothelial selectin, sICAM-1 = soluble intercellular adhesion molecule-1, sICAM-3 = soluble intercellular adhesion molecule-3, sP-selectin = soluble platelet selectin, sPECAM-1 = soluble platelet endothelial cell adhesion molecule, sVCAM-1 = soluble vascular cell adhesion molecule-1, SOFA = Sequential Organ Failure Assessment score; PE = Plasma exchange; TB = Total bilirubin; TNF = Tumor necrosis factor; *ICP + CBF changes defined as different phases of disease = changes in intracranial pressure and cerebral blood flow. Phases'definition: phase1: ICP≤25,mmHg aCBF<30 mL/100g/min;*

phase2: ICP≤25, aCBF≥30; phase3: ICP>25, aCBF≥30; phase 4: ICP>25, aCBF 10-29;

phase 5: ICD>25, aCBF<10.

**SIRS = Systemic inflammatory response syndrome considered as present if two or more conditions were met: temperature >38℃ or <36℃, heart rate >90 bpm, respiratory rate >20 breaths/min or arterial carbon dioxide tension <32 mm Hg, WBC >12×109/l or <4×109/l.*

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