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Review Article

Acute Liver Failure with Determinate rather than Indeterminate Etiology Facilitates Therapy and May Avoid Liver Transplantation: A Critical Analysis

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Abstract

Acute liver failure (ALF) is a disorder with various etiologies. Although the causes leading to this disruptive condition are well documented in published ALF cohorts, there is significant concern among patients who experience ALF with indeterminate causes, an issue requiring thorough analysis. This review aimed to analyze cohort studies on ALF with a focus on unknown causes leading to classification as indeterminate ALF. The analysis revealed that, among 67 worldwide adult and pediatric ALF cohorts, indeterminate causes of ALF ranged from 2% to 100%, with an average of 30%. Among the 13 pediatric ALF cohorts, the corresponding range was 22% to 100%, with an average of 47%, while among the 55 adult ALF cohorts, the range was 2% to 78%, with an average of 26%. The percentage values were higher in pediatric cohorts due to the higher incidence of rare genetic causes compared to adult patients. Notably, higher rates of indeterminate causes were found in cohorts studied before the availability of diagnostic serologic screening parameters and polymerase chain reaction techniques for various hepatitis virus infections. Patients with indeterminate ALF may not have received a specific treatment that, if effective, could have helped prevent liver transplantation. It is concluded that, in future cases, all efforts must be undertaken to clearly establish the cause of severe liver injury, enabling effective therapy when available and helping reduce the risk of progression to ALF and the need for liver transplantation.

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Introduction

Acute liver failure (ALF) is a serious end-stage of a group of acute liver diseases with multifaceted clinical features that include variability of etiology.[1] Among these are acute infections caused by hepatitis A virus, hepatitis B virus alone or combined with hepatitis D virus, hepatitis C virus, hepatitis E virus infections, herpes simplex virus types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus type 6, parvovirus B19, adenovirus, hemorrhagic fever viruses, and Coxsackie B virus. Additional causes include conventional and illegal drugs, herbs, mushrooms of the Amanita group, carbon tetrachloride, trichloroethylene, and white phosphorus. ALF has also been found in ischemic hepatitis, shock liver, heart failure, acute Budd-Chiari syndrome, autoimmune and metabolic diseases, Wilson disease and other genetic disorders, acute fatty liver of pregnancy, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), hyperthermia, heat stroke, massive tumor infiltration, and Reye syndrome. Similar causes were presented in other reports.[2,3] If medical treatment of ALF is not effective, liver transplantation may be indicated to prevent a fatal outcome.[1–3]

Analyses of ALF studies reported from the US, Germany, Spain, the UK, Japan, Sudan, India, and Bangladesh provided a quantitative overview of the causative factors implicated in ALF cases. However, in five out of eight (63%) of the country-specific reports, the rate of indeterminate (i.e., unknown) causes was above 25% in the study cohorts comprising patients with ALF.[1] For these patients, a specific therapy with good therapeutic potential was possibly withheld, turning their disease into a risk for an unnecessary liver transplantation.

In this review, published ALF cohort reports were analyzed for determinate versus indeterminate causes. Published studies on ALF cases with determinate culprits showed insufficient diagnostic approaches to verify the true diagnosis. In three dozen of the worldwide published ALF reports, the indeterminate rate of ALF cases was variable and reached up to 62%. In other words, patients experiencing ALF may be at risk if the underlying cause is not verified and may have been excluded from effective specific treatment that could help prevent liver transplantation.

Literature search strategy and search terms

The literature search strategy involved the PubMed database and Google Science, using the following terms: acute liver

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failure, ALF, fulminant liver failure, FLF, causes, etiology, and combinations thereof. The search was completed on 25 April 2025. Papers in the English language were preferred. Selected were papers that focused on ALF cohorts with listed determinate and indeterminate causes.

Definitions

ALF

No universally accepted nomenclature has been adopted,[1–3] but among the most favored definitions was that of the European Association for the Study of the Liver, as comprehensively outlined in its clinical practice guidelines on the management of acute (fulminant) liver failure.[3] In line with these proposals, the term ALF refers to a highly specific and rare syndrome, characterized by an acute abnormality of serum liver function tests in an individual without underlying chronic liver disease. This is associated with the development of a coagulopathy of hepatic origin and a clinically apparent altered level of consciousness because of hepatic encephalopathy. The term ALF is often incorrectly used to describe acute deterioration of liver function in patients with chronic liver disease such as cirrhosis, a condition that should better be termed acute-on-chronic liver failure. Among many important details, special attention was focused on determinate and indeterminate causes of ALF.

ALF with determinate causes

ALF cases with published determinate causes are those for which a definite diagnosis was provided. Among these ALF cohort studies, however, uncertainty often remains as to what specific diagnostic tools were applied, whether a special therapy was used, and whether patients of this cohort underwent treatment using artificial and bioartificial liver devices such as the Molecular Absorbent and Recirculating System, attempting to bridge to recovery of liver function or a liver transplantation, and finally, whether there was a fatal outcome.

ALF with indeterminate causes

ALF cohort cases with published indeterminate causes lack a specific diagnosis and cannot be used for characterization of the overall ALF cohort, a major shortcoming in clinical ALF cases. Indeterminate or unknown causes of ALF are to be differentiated from ALF cases due to seronegativity, non-A-E virus infections, or parts thereof, which would ignore many other potential liver causes.

ALF with undetermined causes

Finally, ALF cases were described in the context of undetermined causes. This vague term refers to causes not yet resolved, undecided, not known, or not discovered. For reasons of clarity, this undetermined group should be incorporated into the ALF group with indeterminate causes.

ALF cases with assumed determinate causes

In reports on ALF, diagnoses reflecting the causes are commonly provided with case numbers or as percentages of the overall cases comprising the cohort under consideration.[1–3] However, to classify these causes as determinate culprits may be premature if diagnostic approaches with specific parameters, such as in suspected viral infections, were often not communicated. Even worse, the diagnosis of assumed drug-induced liver injury (DILI) among ALF cohorts was reported in 36 ALF cohorts with 21,709 cases, but in none of the cases was the diagnosis of DILI verified[4] using a validated diagnostic algorithm like the worldwide applied Roussel Uclaf Causality Assessment Method (RUCAM).[5–7] Alternative non-drug causes often confound the diagnosis of suspected DILI, turning them into non-DILI cases.[8,9] In addition, none of the 21,709 cases was categorized as one of the four major idiosyncratic immune DILI types, such as drug-induced autoimmune hepatitis (DIAIH), which benefits from steroid therapy as opposed to non-immune DILI, for which steroids may be used on a case-by-case basis.[10,11] As it currently stands, the published cases of DILI confined to ALF cohorts are seemingly inhomogeneous, with a mix of possible and unverified DILI cases, not allowing for a clear feature description.[4] Whether artificial intelligence innovations can help distinguish true from incorrect culprits in the ALF and liver transplantation context remains to be established.[12]

ALF study cohorts with indeterminate causes

The issue of indeterminate causes among ALF cohorts is of major clinical concern because the lack of a firm diagnosis prevents the initiation of a specific treatment. This diagnostic gap has been known since 1989 and persists to this day. Selected countries with 67 reports on ALF with indeterminate causes are listed (Table 1).[13–79]

The percentage data consider both adult and pediatric ALF study cohorts with indeterminate causes, including 13 pediatric cohorts.[28,38,42,43,55,57,61,71–74,76,77] As expected, reports on indeterminate causes did not provide any additional details on these insufficiently evaluated cases, viewed as a major clinical problem, because virtually all authors presented their indeterminate cases with only negative data, without offering further details or discussing why that had happened.

Issues of ALF with indeterminate causes

High rates

ALF with indeterminate causes varies geographically,[1–3,80–82] with reported rates of up to 35%[1] and 50% of cases,[80] or ranging from 5% to 70%,[2] from 17% to 44%,[3] or from 2% to 70%.[81] However, in a large US population study with 6,142 candidates waiting for a liver transplantation, indeterminate causes were not specifically mentioned apart from many other determinate culprits.[83] Among pediatric ALF, up to 50% of cases remain indeterminate.[80,82] Currently analyzed, indeterminate causes of ALF among 67 worldwide ALF adult and pediatric cohorts ranged from 2% to 100%, with an average of 30%: among the 13 pediatric ALF cohorts, the corresponding range was from 22% to 100% with an average of 47%, and among the 55 adult ALF cohorts, the range was from 2% to 78% with an average of 26% (Table 1). Percentage values were commonly higher in cohorts consisting of pediatric patients due to high rates of rare genetic causes as compared with those comprising adult patients. It is also understandable that higher rates of indeterminate causes were found in cohorts studied before the availability of sophisticated diagnostic serologic screening parameters and polymerase chain reaction techniques for various hepatitis virus infections.

Management quality of indeterminate cases

Opinions about the reasons why ALF cohorts were classified as indeterminate causes were not commonly provided,[1–3,13–79] and only a few reports addressed this issue through retrospective evaluation via systematic re-analyses.[80–82] Classifying an ALF case as being of an indeterminate cause may

Table 1. Selected countries providing reports of ALF with indeterminate causes

Reporting country	Year	ALF cases of indeterminate etiology (n/%)	First author
UK	1989	36/9%	O'Grady[13]
US	1995	141/48%	Daas[14]
US	1999	44/15%	Schiødt[15]
US	2000	50/28%	Shakil[16]
Japan	2001	50/62%	Kato[17]
Nordic countries	2002	135/43%	Brandsæter[18]
US	2002	52/19%	Ostapowicz[19]
Canada	2002	22/27%	Tessier[20]
India	2003	13/7%	Khuroo[21]
US	2003	36/20%	Lee[22]
Chile	2003	12/48%	Uribe[23]
Australia	2004	27/34%	Gow[24]
Japan	2004	209/66%	Sato[25]
UK	2005	110/57%	Wigg[26]
Pakistan	2006	18/4%	Sarwar[27]
US	2006	171/49%	Squires[28]
Spain	2007	86/32%	Escorsell[29]
Sudan	2007	14/38%	Mudawi[30]
Sweden	2007	31/11%	Wei[31]
India	2008	389/40%	Bhatia[32]
Lithuania	2008	5/18%	Dukauskiene[33]
Germany	2008	21/21%	Hadem[34]
US	2008	160/14%	Lee[35]
Sweden	2008	33/47%	Wei[36]
UK	2009	24/2%	Marudanayagam[37]
US	2009	320/47%	Narkewicz[38]
Germany	2011	21/21%	Canbay[39]
US	2011	110/14%	Khandelwal[40]
Japan	2011	78/42%	Oketani[41]
US	2011	34/39%	Sundaram[42]
Türkiye	2012	16/22%	Bariş[43]
UK	2012	2,098/43%	Germani[44]
Germany	2012	26/24%	Hadem[45]
US	2012	219/13%	Lee[46]
Japan	2012	27/28%	Sugawara[47]
Spain	2013	4/24%	Fábrega[48]
US	2013	245/12%	Lee[49]
Germany	2014	32/21%	Canbay[50]
US	2014	164/45%	Karkhanis[51]
Argentina	2014	40/26%	Mendizabal[52]
China	2014	15/47%	Zhao[53]
UK	2015	245/12%	Bernal[54]

(continued)

Table 1. *(continued)*

Reporting country	Year	ALF cases of indeterminate etiology (n/%)	First author
Germany	2015	16/43%	Kathemann[55]
China	2016	437/44%	Li[56]
US	2017	300/30%	Alonso[57]
UK	2017	17/3%	Donnelly[58]
Iran	2017	16/36%	Moini[59]
US	2017	187/92%	Somasekar[60]
US	2018	247/48%	Narkewicz[61]
Australia	2019	21/12%	Hey[62]
Inda	2019	19/27%	Mallick[63]
India	2019	25/31%	Nabi[64]
US	2019	150/6%	Rakela[65]
India	2019	4/7%	Singh[66]
US	2019	304/12%	Stravitz[67]
Thailand	2019	14,289/69%	Thanapirom[68]
Germany	2020	2,588/56%	Weiler[69]
Italy	2020	36/17%	Amoroso[70]
Argentina	2020	70/52%	Mendizabal[71]
India	2022	29/23%	Amatya[72]
Singapore	2022	14/41%	Chiou[73]
Netherlands	2022	5/100%	Lexmond[74]
US	2022	1.329/78%	Wong[75]
Saudi Arabia	2023	21/46%	Alhadab[76]
Italy	2023	37/41%	Di Giorgio[77]
US	2024	2.673/17%	Amaris[78]
Japan	2025	326/24%	Nakayama[79]

ALF, acute liver failure.

include a patient in whom testing was not complete, making the case indeterminable; several diagnoses may co-exist that confound the principal investigator; missing laboratory data may be contributory; inability to extract an accurate medical history due to impaired mention by the patient; lacking final case evaluation by a senior hepatologist; as well as data entry errors or omissions.[80] In suspected pediatric ALF of indeterminate cause, genetic evaluations by whole-exome sequencing and phenotypic analysis associated with biochemical markers were often not done.[82]

Attempts at re-classification

Using the post-hoc assessment approach, three studies attempted a re-evaluation of ALF cases that were primarily classified as of indeterminate causes.[80–82] Improving the identification process should reduce the number of truly indeterminate causes.[80] This approach is highly appreciated to avoid similar pitfalls in future ALF studies and prevent inhomogeneity of ALF cohorts that may cause clouded or even wrong data interpretation.

US ALF study

The data of the US Acute Liver Failure Study Group (ALFSG) registry were first reassessed in 2018.[80] This registry listed overall 303 patients with ALF of indeterminate causes, which were now re-evaluated by a US expert committee to establish causality. There were 11 patients who did not meet the criteria of ALF, 142 patients received new specific alternative diagnoses, while cases of 90 patients remained as of true indeterminate causes, and 60 ALF patients were classified as undeterminable.[80] Thus, in half of the indeterminate ALF cohort, the experts were unable to provide an identifiable etiology by rectifying the diagnosis. It seems that the 31 US academic liver transplant centers that enrolled their cases in the ALFSG registry did not follow a unique diagnostic approach, as evidenced by the note of the expert committee that prior to the re-evaluation, special definitions for each etiology in the sense of etiology-specific algorithms had to be developed by a special causality adjudication committee.[80] ALF cases were given a new definite/highly likely diagnosis if the information was judged more than 75% likely, and probable if the likelihood was less certain (51–75%).[80] If disagreement among the assessing group could not be resolved and continued, adjudication was finalized by majority vote. This attempt at re-classification is open for discussion, as it is based on opinion, i.e., global introspection, which is a non-validated diagnostic approach by definition. Percentage

causality gradings are arbitrary, as opinions are often contradictory and rarely reflect conditions of the real world.

The special causality adjudication committee focused the re-adjudication of ALF etiology on new analysis of intrinsic DILI due to acetaminophen (N-acetyl-para-aminophenol (APAP)), i.e., paracetamol, idiosyncratic DILI (iDILI), autoimmune hepatitis (AIH), shock/ischemia, viral hepatitis, and other viruses.[80] Testing for APAP as parent compound and adduct formation revealed newly assigned APAP cases, a perfect diagnostic approach. The new AIH diagnosis was based on positivity of serum autoimmune markers, high serum globulins, compatible liver histology, and the absence of ingested known hepatotoxic substances like drugs or alternative medicines.[80] In this report, the simplified AIH score of Hennes *et al*. was mentioned as reference 17 without providing the corresponding score to establish the AIH diagnosis. Another shortcoming was the omitted search for cases of DIAIH as a special subtype of autoimmune iDILI,[10] a diagnosis that requires the use of the validated and worldwide applied updated RUCAM[7] and the validated and universally applied simplified AIH diagnostic algorithm.[10] Disappointing was also the causality search for iDILI, because the active committee members used the US Drug-Induced Liver Injury Network tool,[80] which never received an internal or external validation, as it is based on opinion (global introspection) and provides only arbitrary percentage ranges of causality gradings.[84] This tool uses no validated scoring system applicable to important elements of iDILI, making it obsolete. Even worse, the committee members used DILI data from the LiverTox website, which paradoxically includes DILI cases without applying a robust validated causality assessment such as the RUCAM, thereby providing disputable results outside of scientific credibility.[85]

The re-adjudication of ALF cases with indeterminate causes was marked by both light and shadow.[80–82] For the first time, it was attempted to solve the worldwide troubling issue of indeterminacy, initially recognized in the UK in 1989[13] and perpetuated in Japan in 2025[79] (Table 1), and again for the first time, it was clear that the management of severe acute liver injury and ALF at US liver transplant centers is poorly organized regarding universally accepted causality assessment and ALF definition, leading to indeterminate cases that are hardly re-assessable by adjudication committees using non-validated diagnostic approaches.[80] Patients with ALF of indeterminate causes are at risk because a possible therapy is withheld that could help make a liver transplantation unnecessary.

True determinate ALF causes

The re-evaluation of published cases with previously indeterminate etiology provided ALF cases with assumed true determinate causatives.[80–82] Among the new ALF causes in adults were: APAP;[80,81] iDILI, but with limited certainty due to issues of causality assessment;[80,81] AIH, but without considering DIAIH cases due to lack of use of specific causality assessment methods;[80,81] shock/ischemia;[80] hepatitis A and B;[80,81] herpes simplex virus, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and parvovirus B19;[80] and in pediatrics, various genetic liver diseases.[82] If these newly detected causatives had been recognized in time, this could have allowed for an appropriate therapy for some adult patients with acute liver injury or ALF, for which an effective therapy is available.

Outcome of patients with indeterminate ALF

Agreement exists that the prognosis of patients with indeterminate ALF is poor.[80–82,73] More specifically, the analysis of the outcome for adult indeterminate ALF cases showed an overall survival at 21 days of 59%, which was attributed to a transplant rate of 40%, with only 20% transplant-free survival, exemplifying the known clinical severity of indeterminate ALF.[80] The poor prognosis of adult patients with true-indeterminate and indeterminable ALF was confirmed by a similar death rate of 30% vs. 27%, respectively, with almost half of the patients requiring a liver transplant, while only 23% survived without a transplant.[81] Among pediatric patients with ALF of indeterminate causes, 27% died without liver transplantation, and an additional 3% did not survive despite a liver transplantation, while 18% survived with a liver transplantation and 52% did so without a liver transplantation.[82] In another pediatric cohort of ALF with indeterminate cause, 71% died or received a liver transplant, while 29% recovered spontaneously.[73] In a prospective US study with 45% indeterminate ALF cases, corticosteroid use did not improve survival in the treated patients.[51] In the context of this report, the high rate of ALF cases with indeterminate causes is remarkable, suggesting a low quality of the prospective study design. As an end result, several prognostic models of ALF have not found etiology itself to be an independent determinant of outcome, but specific treatments used long before the transplantation were not evaluated in detail.

Analysis of the current situation

It is obvious that many patients with indeterminate ALF have been confronted with a missed diagnosis (Table 1).[13–79] For some of these affected patients, the diagnostic shortcoming may have been deleterious if a treatable disease like Wilson disease, DIAIH, or AIH[7,86] remained unrecognized and untreated during the pre-hospital phase or after admission to the first hospital. Accordingly, for these patients with potentially treatable diseases, a therapy to effectively withhold the transition from an initially severe liver injury to an ALF was missed, as was the chance to thereby circumvent a liver transplantation. In other words, the pre-transplantation diagnostic modalities are under clinical fire, rather than the transplantation centers, as the end of the process conceptually engages primarily with the preparation for liver transplantation.

Prospective considerations

It is frightening to see the high number of adult and pediatric patients with acute liver injury and ALF of indeterminate causes published in the past.[1–3,13–82] Future diagnostic approaches should have a prospective design with a clear concept of how best to recognize treatable severe acute liver injury diseases, such as those caused by some hepatotropic virus infections, intoxicating paracetamol or *Amanita phalloides,* or autoimmune and genetically triggered disorders like Wilson disease, DIAIH, or AIH, with diagnostic proposals as published earlier.[7,10] The detailed etiological evaluation must include specific biomarkers, virus serology with antibodies, polymerase chain reaction, autoimmune parameters, and the validated updated RUCAM.[7,10,86]

Conclusions

ALF is a serious life-threatening end-stage disorder with verified causatives in some cases, but poor clinical diagnostic management has classified a large portion thereof as indeterminate ALF, not allowing for an early initiation of effective pre-transplant therapy. This must be viewed as an avoidable

pitfall in clinical hepatology in the care of affected patients. Due to this diagnostic gap during their pre-transplant hospital stay, some patients have been cut off from the chance to receive effective treatment to prevent progression of their disease to ALF with the need for liver transplantation. Considering these aspects, patients with severe liver injury should receive an early evaluation regarding causatives. Among the well-treatable diseases are infections by a few hepatotropic viruses, intoxications by paracetamol, Wilson disease, DIAIH, and AIH. Of academic value were retrospective attempts by the US ALFSG registry to re-adjudicate the indeterminate ALF cases to determinate ALF cases, an approach that does not help the already transplanted patients. More specifically, however, by applying better diagnostic approaches in their re-analysis, assessors were able to convert some indeterminate ALF cases to determinate ones due to the detection of new diagnoses such as AIH, infections by hepatitis A and B, herpes simplex virus, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and parvovirus B19, and various genetic liver diseases in pediatrics. In general, if these newly detected causatives had been recognized in time, this could have allowed for an appropriate therapy for some patients with acute liver injury or ALF for which an effective therapy is available.

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Conflict of interest

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Author contributions

Providing the outline, drafting of the manuscript (RT), table conceptualization, literature collection, and editing of the manuscript (AE). Both authors agreed on the final version to be submitted for publication.

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