



Role of Hepatitis C Infection in Acute Liver Injury/Acute Liver Failure in North America

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Abstract

Background While hepatitis A and B are well-known causes of acute liver failure (ALF), few well-documented cases of hepatitis C virus (HCV) infection (absent preexisting liver disease or other liver insults) have been described that result in ALF. We reviewed the Acute Liver Failure Study Group registry for evidence of HCV as a primary or contributing cause to ALF.

Methods From January 1998 to January 2017, 2,332 patients with ALF (INR ≥ 1.5 , any degree of hepatic encephalopathy) and 667 with acute liver injury (ALI; INR ≥ 2.0 , no hepatic encephalopathy) were enrolled. Anti-HCV testing was done routinely, with confirmatory RT-PCR testing for HCV RNA where necessary.

Results A total of 136 patients were anti-HCV-antibody positive, as follows: 56 HCV RNA negative, 65 HCV RNA positive, and 8 with no result nor sera available for testing. Only three subjects with ALI/ALF were determined to represent acute HCV infection. Case 1: 47-year-old female with morbid obesity (BMI 52.4) developed ALF and recovered, experiencing anti-HCV seroconversion. Case 2: 37-year-old female using cocaine presented with ALI and fully recovered. Case 3: 54-year-old female developed ALF requiring transplantation and was anti-HCV negative but viremic prior to transplant experiencing anti-HCV seroconversion thereafter. Among 1636 APAP overdose patients, the 52 with concomitant chronic HCV had higher 3-week mortality than the 1584 without HCV (31% vs 17%, $p=0.01$).

Conclusions ALI/ALF solely related to acute hepatitis C infection is very rare. Chronic HCV infection, found in at least 65 (2.2%) of ALI/ALF patients studied, contributed to more severe outcomes in APAP ALI/ALF; ClinicalTrials.gov number, NCT000518440.

Trial Registration ClinicalTrials.gov number NCT000518440.

Keywords Viral hepatitis · Fulminant hepatic failure · Liver transplantation

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Abbreviations

ALI	Acute liver injury
ALF	Acute liver failure
ALFSG	Acute liver failure study group
APAP	Acetaminophen
BMI	Body mass index
DILI	Drug-induced liver injury
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
HCV	Hepatitis C virus
INR	International normalized ratio
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis

RT-PCR Reverse transcriptase polymerase chain reaction
 NAPQI *N*-acetyl-*p* benzoquinoneimine

Introduction

Acute liver failure (ALF) is most commonly defined as the development of coagulopathy (international normalized ratio (INR) ≥ 1.5) and encephalopathy in a patient with an acute hepatic illness of ≤ 26 weeks' duration, without underlying chronic liver disease [1]. With approximately 2000 cases diagnosed each year in the USA, ALF is a relatively rare clinical entity [2]. The most common causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease, and shock or hypoperfusion, though a small proportion of cases are ultimately considered as indeterminate [3, 4]. Etiologies also vary worldwide, with drug-induced etiologies (i.e., acetaminophen and idiosyncratic DILI) more common in Western countries while viral hepatitis (i.e., hepatitis A, B, and E) predominates in emerging countries [3–6]. All etiologies of ALF are characterized by varying severity of encephalopathy, coagulopathy, metabolic abnormalities, features of systemic inflammatory response syndrome, circulatory dysfunction, and multi-organ failure. Despite these clinical features, the etiology of ALF is important to delineate, as it determines specific treatments and provides one of the best indicators of prognosis [4, 7, 8]. While hepatitis A, B, and E are well-known causes, there have been few well-documented cases of acute hepatitis C virus (HCV) infection causing ALF absent preexisting liver disease or concomitant liver insults with prior literature limited to individual case reports [9–14]. Our aim was to review the Acute Liver Failure Study Group registry for any evidence of HCV as a primary or contributing cause of ALF and ALI.

Patients and Methods

The Acute Liver Failure Study Group (ALFSG) is a multi-center consortium of 23 sites, funded by the National Institute of Diabetes and Digestive and Kidney Diseases with an aim of elucidating the causes, clinical features, and outcomes of adult patients with ALF and Acute Liver injury (ALI). Between January 1998 and January 2017, 2332 adult patients meeting entry criteria for ALF and 667 adult patients meeting entry criteria for ALI were enrolled [4]. ALF was defined as coagulopathy (INR ≥ 1.5), any degree of hepatic encephalopathy, and an illness of ≤ 26 weeks' duration in patients without known chronic liver disease [4]. ALI was defined as an INR ≥ 2 , absence of hepatic

encephalopathy, and an illness of ≤ 26 weeks' duration in patients without known chronic liver disease [15]. Comprehensive demographic, clinical, and laboratory values were recorded prospectively at enrollment and serially for 7 days. Outcomes at 21 days post-enrollment were classified as transplant-free survival, liver transplantation, or death. A written informed consent was obtained from enrolled subjects if not encephalopathic or from legally authorized representative if impaired mentation was present. Each center's Institutional Review Board approved the study, centers abided by the Health Insurance Portability and Accountability Act (HIPAA), and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

The primary etiology of ALF or ALI was determined initially by the site investigator. Different from hepatitis A and B where IgM antibodies are available, there is no readily available marker that defines acute hepatitis C [16]. Accordingly, a diagnosis of acute HCV infection required the presence of HCV RNA with absence of anti-HCV antibody (presumed diagnosis during the seronegative window period) or the presence of both HCV RNA and anti-HCV antibody with a recent prior negative HCV-antibody test (diagnosis based on anti-HCV seroconversion) [17–20]. Anti-HCV-antibody and reverse transcriptase polymerase chain reaction (RT-PCR) testing for HCV RNA was done at local sites. If RT-PCR had not been performed locally, available banked sera were tested at a central laboratory. Competing causes of ALF or ALI that were evaluated based on detailed history, extensive laboratory and serologic testing, hepatobiliary imaging, and liver biopsy (if indicated) included acute hepatitis A, B, or E and herpes family or occult/novel viruses, idiosyncratic drug-induced liver injury (DILI), acetaminophen-induced liver toxicity (APAP), shock/ischemic injury, autoimmune hepatitis, Wilson's disease, pregnancy, Budd-Chiari syndrome, and infiltrating malignancy [4].

All cases were subsequently examined by a causality adjudication committee of 9 experienced hepatologists, with each case validated or revised after rigorous elimination of other etiologies. Additional laboratory testing (including, but not limited to, APAP-CYS protein adducts [21], HEV testing, viral sequences via microarray analysis, and metagenomics next-generation sequencing) were performed on sera when available and as indicated. Local sites were also asked to provide diagnostic biopsy and/or explant pathology results, which may not have been available for site investigators at enrollment.

Between-group differences of categorical variables were tested using the chi-square test and all statistical analyses were performed using IBM SPSS Statistics (version 26; SPSS Inc. Chicago, IL). A *p* value < 0.05 was considered statistically significant.

Results

Of the 2332 ALF and 667 ALI patients, 110 (4.72%) and 25 (3.75%), respectively, tested positive for anti-HCV antibody (Fig. 1). Five cases were subsequently determined to not meet criteria for ALF or ALI by adjudication; 56 of the 130 remaining patients (43.1%) tested negative for HCV RNA indicating either false positive or resolved HCV infection. Among the 56 patients with undetectable HCV RNA, an alternative etiology for ALF or ALI was determined in all; six underwent liver transplantation (10.7%)

and 9 died (16.1%), yielding a transplant-free survival of 69.6% (39 of 56) (Table 1). Among 8 ALF patients who tested positive for HCV antibody where RT-PCR for HCV RNA could not be performed, alternate diagnoses were also identified: five were due to APAP overdose, one due to autoimmune hepatitis, one due to DILI, and one due to shock/ischemia.

There were 66 remaining patients with both detectable anti-HCV antibody and HCV RNA; 65 were determined to represent chronic HCV infection with an alternative etiology for ALF or ALI in each case (Table 1). Of note, based on adjudication with compatible medication and ingestion

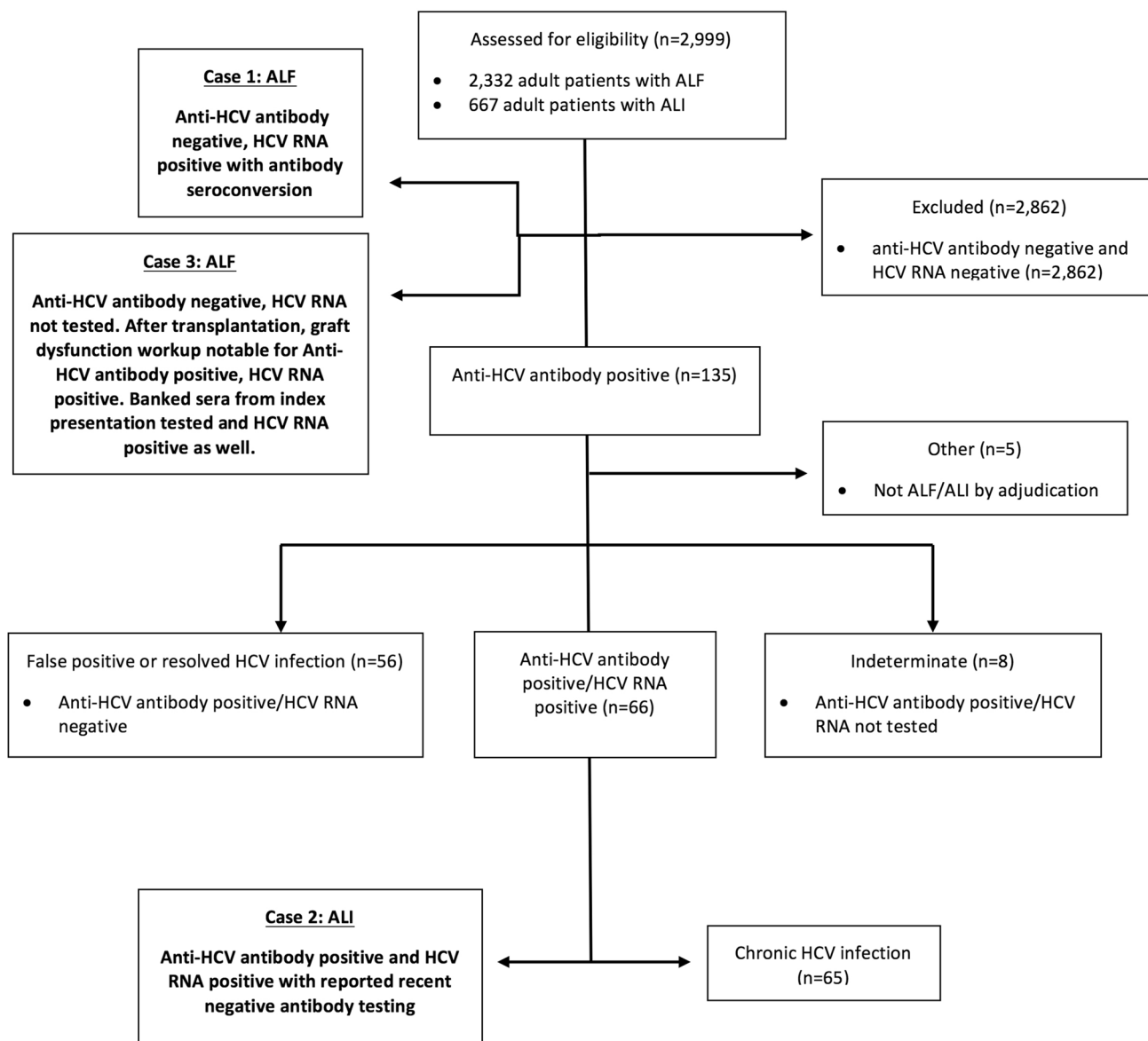


Fig. 1 ALF and ALI cases stratified by HCV status; 56 patients were anti-HCV-antibody positive and HCV RNA negative consistent with prior resolved infection or false-positive test result; 66 patients were

anti-HCV-antibody positive and HCV RNA positive, consistent with current HCV infection; 8 patients were anti-HCV-antibody positive, but HCV RNA testing could not be obtained

Table 1 (Top, left) Adjudicated etiologies of 56 ALF or ALI in patients with HCV-antibody-positive, HCV RNA-negative sera indicating false positive or prior, resolved HCV infection. (Bottom, left) Associated 3-week outcomes. (Top, right) Adjudicated etiologies of ALF or ALI in patients with HCV-antibody-positive, HCV RNA-

positive sera indicating chronic HCV infection ($n=65$). Not included is the proposed case of acute HCV infection with HCV-antibody-positive, HCV RNA-positive sera. (Bottom, right) Associated 3-week outcomes

Etiology of ALF or ALI in HCV-antibody-positive, HCV RNA-negative cases	Cases (n)	Etiology of ALF or ALI in HCV-antibody-positive, HCV RNA-positive cases	Cases (n)
Acetaminophen (APAP)	34	Acetaminophen (APAP)	52
Hepatitis B Virus	5	Shock/Ischemia	5
Shock/Ischemia	4	Idiosyncratic Drug-Induced Liver Injury	3
Idiosyncratic Drug-Induced Liver Injury	4	Hepatitis B Virus	2
Autoimmune Hepatitis	5	Indeterminate	2
Wilson’s Disease	1	Malignancy	1
Hepatitis A Virus	1		
Indeterminate	2		
Outcome	Cases (n, %)	Outcome	Cases (n, %)
Transplant-Free Survival	39 (69.7%)	Transplant-Free Survival	40 (61.5%)
Liver Transplantation	6 (10.7%)	Liver Transplantation	1 (1.5%)
Death	9 (16%)	Death	21 (32.4%)
Unknown	2 (3.6%)	Unknown	3 (4.6%)

histories and serum APAP levels and/or APAP-CYS adduct testing, 52 of the 65 (80%) were deemed secondary to APAP overdose. Of these, 29/31 had toxic adduct levels and 31/40 tested has toxic APAP levels. Only three had not been tested for either marker of toxicity but had strong histories only. The remaining etiologies included shock/ischemia (5), idiosyncratic drug-induced liver injury (3), de novo acute hepatitis B virus (2), indeterminate (2), and malignancy (1). Acute hepatitis B virus cases were diagnosed based on the detection of hepatitis B surface antigen (HBsAg) and presence of immunoglobulin M antibody to hepatitis B core antigen. Two cases, one presenting 5 years post-transplantation for chronic HCV and the other with a known history of chronic HCV, remained indeterminate after undergoing extensive serologic testing. Liver biopsy in one was consistent with chronic hepatitis C plus possible DILI but no agent could be implicated. Among these 65 chronic anti-HCV-positive patients, one underwent liver transplantation (1.5%) and 21 died (32.4%), yielding a transplant-free survival of 61.5% (40 out of 65).

Case Histories

Three remaining cases were attributed to acute hepatitis C, two of whom were anti-HCV negative and one antibody positive at initial testing. Details of each case are outlined below (Table 2).

Case 1: A 47-year-old African-American female with a history of morbid obesity (BMI 52.4 kg/m²) and diabetes

mellitus presented with abdominal pain and was found to have elevated aminotransferases, coagulopathy, and Grade 2 encephalopathy consistent with ALF. Serologic and imaging workup ruled out other etiologies. Initially, anti-HCV antibodies were not detected, but re-testing during the hospital course revealed a positive HCV antibody and a HCV RNA viral load of 595,000 IU/mL, genotype not determined. A diagnosis of acute HCV infection, presumably acquired via sexual transmission with a known HCV-positive partner, was made. Though histological findings of confluent necrosis confirmed acute hepatitis, liver biopsy also revealed a background of nonalcoholic steatohepatitis (NASH). The patient recovered fully without requiring transplantation.

Case 2: A 37-year-old Caucasian female with a history of intravenous drug use presented with abdominal pain and jaundice. She demonstrated elevated aminotransferases and coagulopathy, but no encephalopathy. The patient was HCV-antibody and HCV RNA positive (with a recently reported negative antibody negative test); viral load 1,720,000 IU/mL, genotype not determined. She endorsed recent cocaine and opioid use prior to admission, with urine toxicology screens positive for both. The patient recovered without a transplant.

Case 3: A 54-year-old African-American female with a history of obesity (BMI 36 kg/m²) and prior gastric bypass surgery with flank pain and elevated aminotransferases and coagulopathy developed hepatic encephalopathy consistent with ALF. Serologic and imaging workup did not identify an etiology; HCV antibody was negative and HCV RNA testing was not obtained at the time. Initially presumed to

Table 2 Clinical and Laboratory characteristics of acute HCV cases. Case 1 (left). 47-year-old African-American female with a history of morbid obesity and metabolic syndrome diagnosed with acute HCV infection developed a brief period with ALF, with spontaneous recovery. Histological analysis also revealed background features consistent with nonalcoholic steatohepatitis. Case 2 (middle). 37-year-old Caucasian female with a history of chronic intravenous drug use and

drug screen positive for cocaine and heroin diagnosed with acute HCV infection developed ALI, with spontaneous recovery. History and recent drug use make it difficult to exclude coexisting liver injury from toxic cocaine metabolites. Case 3 (right). 54-year-old African-American female with a history of obesity and gastric bypass surgery diagnosed with acute HCV infection developed ALF, with recovery after orthotopic liver transplantation

	Case One	Case Two	Case Three
Age (years)	47	37	54
Gender	Female	Female	Female
Ethnicity	African-American	Caucasian	African-American
Peak AST (IU/L)	7660	4032	2286
Peak ALT (IU/L)	3919	3292	1281
Peak total Bilirubin (mg/dL)	7.5	12	8
INR	2	2	3.51
Hepatic Encephalopathy Grade	Grade II	None	Grade III
HCV-Antibody status	initially negative, then positive	Positive	negative
HCV RNA Viral Load (IU/mL)	595,000	1,720,000	6,200,000
Confounding Factor	morbid obesity with Type II Diabetes Mellitus)	History of intravenous drug use with recent use (Urine tox positive for cocaine and opioids)	obesity and history of gastric bypass surgery
Liver Injury	Acute Liver Failure	Acute Liver Injury	Acute Liver Failure
Outcome (at 21 days)	Transplant-free survival	Transplant-free survival	Transplanted, with subsequent survival

have indeterminate ALF, she received an orthotopic liver transplant and recovered. Explant histology showed panlobular hepatitis with regeneration and massive necrosis; no evidence of cirrhosis or fatty liver (Fig. 2). At approximately 10 months post-transplant, new aminotransferase elevations prompted hepatitis C antibody and RNA testing with

positive results for both. Given these findings, stored serum obtained *prior to transplantation* was retrieved, demonstrating an HCV RNA viral load of 6,200,000 IU/mL (genotype 1a), confirming a highly likely diagnosis of acute hepatitis C. She had presumably acquired her infection via sexual transmission with a new partner known to be HCV positive.

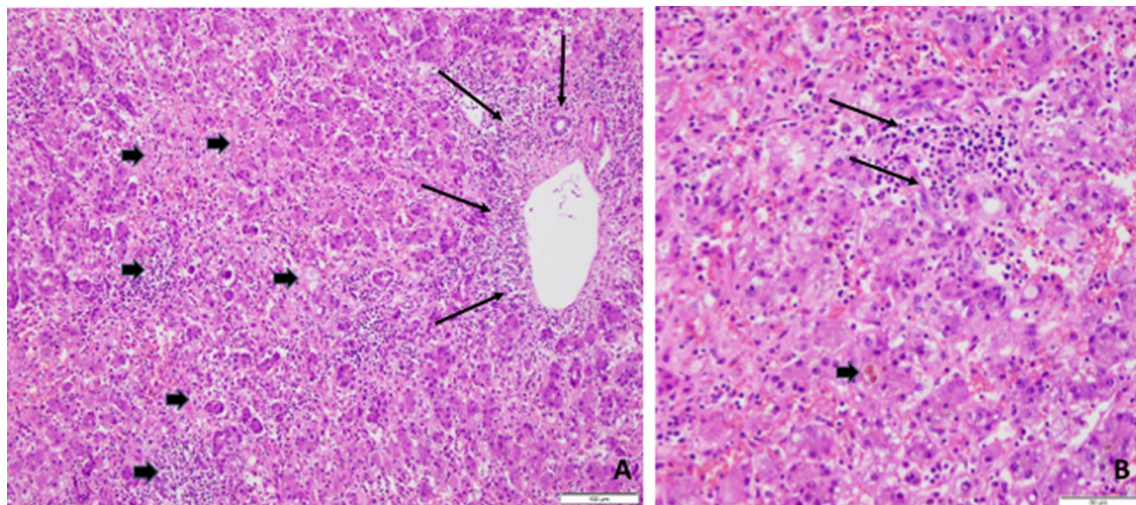


Fig. 2 Explanted Liver from Case 3 (H&E stain). A (low power) Lobules (short arrows) show a significant panlobular inflammatory infiltrate with lobular architectural disarray and prominent hepatocyte drop-out. A portal tract on the right (long arrows) reveals an inflam-

matory infiltrate with interface activity. No bile duct injury is seen. There is no evidence of cirrhosis. B (high power) The lobular inflammatory infiltrate (long arrows) consists predominantly of lymphocytes with plasma cells. Cholestasis (short arrow) is also noted

She was subsequently treated and achieved a sustained virologic response.

Comparison of Acetaminophen Overdose Cases With and Without Detectable HCV RNA

To determine whether hepatitis C coinfection might impact outcomes, we compared the 65 subjects found to have active chronic hepatitis C (anti-HCV, HCV RNA positive) with the anti-HCV-negative, HCV RNA-negative group. Since acetaminophen-induced ALI/ALF comprised 80% of the RNA-positive group, we only made the comparisons within this etiology. Those who were RNA positive demonstrated increased overall mortality when compared to the RNA-negative group, although rates of transplant-free survival and transplantation were not significantly different (Table 3).

Discussion

The present study demonstrates that while the finding of a positive HCV antibody and/or chronic hepatitis C is prevalent in patients with ALI/ALF with an overall incidence of 4.5%, acute hepatitis C is rarely if ever the sole cause of ALF or ALI. Only three of 2,999 consecutive cases of ALF or ALI were deemed related to acute HCV infection. All patients had at least one comorbid condition and only one required transplantation.

Case 1 experienced HCV-antibody seroconversion. Additionally, her high BMI and confirmed NAFLD on liver biopsy certainly contributed to her clinical course and outcome [22–24]. Case 2, who met criteria for ALI but not ALF, presented with possible acute HCV infection given her high aminotransferases, significant HCV viral load, and positive HCV-antibody test. Though she alleged that she had negative antibody testing months prior, no earlier HCV records were available. Her history of chronic intravenous drug use, recent cocaine use, and positive urine drug screens makes it difficult to exclude concomitant liver injury secondary to cocaine and/or chronic hepatitis C. Finally, Case 3 appeared to represent the best example of acute hepatitis C leading to ALF. She was diagnosed

retrospectively having had a negative HCV antibody but positive HCV RNA on presentation with ALF. Despite a high likelihood for preexisting NAFLD, she did not have other features of metabolic syndrome and her explant did not show any features of NASH or cirrhosis; only massive lobular necrosis [25].

Previously described instances of acute HCV infection as a primary driver of ALF are limited to case reports. In one case, a patient with presumed transfusion-acquired acute HCV infection presented with high levels of viremia and jaundice, coagulopathy, and encephalopathy, consistent with HCV-precipitated ALF; however non-viral etiologies were not excluded [9]. A more recent report details an instance of acute HCV-mediated ALF requiring liver transplant, complicated by immediate recurrent biopsy-proven HCV-mediated hepatitis and subsequently managed with sofosbuvir and ribavirin [12]. While most cases of acute HCV infection are asymptomatic, it has been proposed that there might be specific virulent strains, such as the JFH-1 variant isolated from a patient with HCV-mediated ALF in Japan, that could result in fulminant hepatic failure [26]. However, subsequent *in vivo* analysis of the same strain showed only mild infection with low-level viremia and absence of laboratory or histological hepatitis.

The limited published literature combined with the dearth of cases in the ALFSG registry suggests that HCV rarely causes acute hepatic synthetic dysfunction and encephalopathy severe enough to meet criteria for ALF. Only 10–15% of acute HCV infections demonstrate symptomatic hepatitis, accompanied by moderate aminotransferase elevations and mild hyperbilirubinemia without synthetic dysfunction [19, 28–30]. Both hepatitis A and B evoke vigorous immune responses in those who are not immunosuppressed, with the majority of patients demonstrating clinical acute hepatitis and clearing the virus readily [30, 31]. By contrast, HCV eludes host mediated immune clearance via neutralizing antibodies, modulating complement expression, and suppressing key mediators of interferon signaling [31–34]. The same mechanisms responsible for viral persistence of HCV may explain why it rarely causes ALF [35]. Thus, acute hepatitis C likely has a different mechanism of liver injury that makes ALF a rare event, in our series, a one in a thousand occurrence.

Table 3 Effect of chronic HCV status on outcomes in acetaminophen-induced ALI/ALF. Chronic HCV infection was associated with increased overall mortality, though rates of transplantation and spontaneous survival did not differ

Outcome	Acetaminophen-induced ALI/ALF without Chronic HCV (n, %)	Acetaminophen-induced ALI/ALF with Chronic HCV (n, %)	p value
Transplant-Free Survival	1072 (67.7%)	32 (61.5%)	0.22
Liver Transplantation	95 (6%)	1 (1.9%)	0.18
Death	272 (17.2%)	16 (30.8%)	0.01
Unknown	155 (9.8%)	3 (5.8%)	0.24
Total	1584 (100%)	52 (100%)	

In reviewing ALF and ALI patients with preexisting chronic HCV, the most common primary etiology was APAP in 80% of the cases. Though acetaminophen is the most common cause in ALF and ALI in the USA (i.e., ~50% of cases likely related to APAP), its association with chronic HCV patients appears much higher than with other etiologies of ALF and ALI. Both chronic hepatitis C and APAP toxicity have been associated with high-risk behaviors [36, 37]. Future studies are needed to validate the increased representation of acetaminophen cases in our HCV-infected ALF population and delineate the role that impulsivity may play in developing each.

The presence of HCV infection in the APAP group was significantly associated with increased 3-week mortality compared to APAP patients without HCV or who were anti-HCV positive but RNA negative. We were unable to analyze the effects of chronic HCV on other etiologies of ALI/ALF due to small case numbers. Chronic HCV infection in APAP overdose hospitalizations has been associated in the past with risk of progression from ALI to ALF, as well as increased length of stay and overall mortality [38]. Patients with chronic HCV demonstrate higher oxidative stress, evidence by increased levels of superoxide dismutase and lipid peroxidation metabolites, ultimately leading to reduced glutathione stores [39–41]. Depleted glutathione stores may subsequently exacerbate the effects of APAP overdose by reducing the capacity to detoxify N-acetyl-p benzoquinoneimine (NAPQI) into non-toxic metabolites. Further prospective and mechanistic studies are needed to clarify if chronic HCV potentiates the hepatotoxicity in APAP overdose, as well as in other forms of ALI and ALF.

Our study is not without limitations. It is possible but unlikely that very early cases of acute HCV infection went undiagnosed, as data suggest HCV RNA becomes reliably detectable by 10–14 days after viral exposure and confirmatory HCV RNA testing was not done in every patient [20, 42]. Another limitation is the lack of a clinically available specific diagnostic test, for example IgM HCV antibodies, which might more definitively identify acute infection in difficult to adjudicate cases, such as case 2. Additionally, in 8 patients, HCV status was unable to be determined due to lack of available sera. However, each of the 65 cases deemed chronic HCV infection and 8 cases deemed indeterminate presented with definite alternative etiologies of ALI/ALF. Our study population limited to North American sites would not accurately capture cases that might have greater severity in other areas of the world. Further studies with robust evaluation to exclude competing causes in geographically distinct populations are needed to estimate the true worldwide incidence of HCV-mediated acute liver failure. Nonetheless, the large study population of the ALFSG over more than 20 years has afforded a robust survey vehicle, to help determine if hepatitis C can cause ALF. Finally, resources to

perform viral quasispecies analysis and evolution over time were not available to test our 3 cases of presumed HCV-related ALI/ALF.

In summary, among 2999 patients enrolled in 23 North American sites over a 20-year period, at most only three acute hepatitis C ALF or ALI cases were identified. Our data also demonstrate that chronic HCV infection may lead to more severe outcomes when combined with other etiologies of ALI or ALF, primarily APAP hepatotoxicity. However, acute HCV as the sole etiology of ALF, in the absence of antecedent liver disease or coexisting liver insults, is rare, despite the resurgence of acute HCV infections in the USA.

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Declarations

Conflict of interest WML serves as a consultant for Affibody, Genentech, Forma, Karuna, SeaGen, Cortexyme, Pfizer, and Alnylam. He receives research funding to conduct clinical trials from Merck, BMS, Intercept, Novo Nordisk, Eiger, and Alexion. RJF receives research support from AbbVie, Gilead, and Bristol Myers Squibb and has consulted for Sanofi. RTS receives funding from IL and Exalenz. AR, JR, GC, BMM, and GL have no financial disclosures to report. All authors certify that they have no non-financial interests (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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