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ORIGINAL ARTICLE

Etiology, clinical features, and outcomes in acute-on-chronic liver failure patients in the intensive care unit of a quaternary care center

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ABSTRACT

Background: Multi-organ failure and a sharp decline in liver function are hallmarks of acute-on-chronic liver failure (ACLF), carrying high mortality.

Objective: To determine the etiology, clinical presentations, and the mortality outcome in patients with acute-on-chronic liver disease.

Methods: In this retrospective study, medical records of 109 patients admitted to the Intensive Care Unit (ICU) of Pakistan Kidney and Liver Institute and Research Center, Lahore, Pakistan, from 1st January 2022 to 31st August 2023 with ACLF were included after ethical approval (PKLI-IRB/AP/149). Data regarding demographics, clinical features, comorbidities, Child-Turcotte-Pugh (CTP) score, Chronic Liver Failure Consortium (CLIF-C score), Model for End-stage Liver Disease-Na (MELD-Na), and ACLF grades were recorded, and their outcome in terms of mortality was noted.

Results: The mean age was 47.4 ± 10.5. The primary cause of cirrhosis was hepatitis C virus (HCV) infection (52.3%), followed by cryptogenic cirrhosis (14.7%). According to the CTP score, 95.4% of the patients had Child-Pugh class C cirrhosis, and 52.3% were classified as grade 3 ACLF. Out of 109 patients, only 31 survived, with a mortality rate of 71.6%. Acute decompensation was mainly secondary to hepatic encephalopathy precipitated by infections and variceal bleeding. The non-survivors had significantly higher INR=3.4 ± 1.8 vs 2.6 ± 1.1 (p=0.002) and ammonia levels =230.1 ± 241.7 µg/dL vs 125.7 ± 65.7 µg/dL (p=0.002) on ICU admission compared to those who survived. The mean MELD-Na score at hospital admission was 32.9 ± 6.5, and in ICU admission was 34.7 ± 6.7 (p<0.001), but was not significant regarding survival (p=0.195). The CLIF-C score increased from 50.4±10.1 (in ward) to 56.1 ±10.2 (ICU transfer) (p<0.001) and was also higher in non-survivors compared to survivors (p<0.001). It is observed that increasing CLIF-C scores is a sign of poor prognosis.

Conclusion: HCV infection was the most common cause of cirrhosis, and hepatic encephalopathy was the common trigger for ACLF. A high INR, hyperammonia, advanced ACLF grade, and an increase in CLIF-C score lead to poor outcomes in terms of survival, while worsening of CLIF-C scores may additionally predict short-term mortality.

Key Words: Acute-on-Chronic Liver Failure, Etiology, Clinical Outcomes

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a condition that is associated with substantial short-term morbidity and mortality. It can manifest as an acute drop in liver function during hospitalization or develop later.[1] According to Asian Pacific Association for the Study of Liver's (APASL) 2021 update, ACLF is most typically defined as the onset of jaundice (serum bilirubin >5 mg/dL) and worsening of coagulation (INR >1.5 or prothrombin activity <40%) within 4 weeks in a patient with or without a diagnosis of chronic liver disease (CLD) exacerbated by encephalopathy and/or ascites, that carries high 28-day mortality rate.[2] ACLF is much more frequent than acute liver failure, with prevalence rates ranging from

20% to 35% worldwide.[3] According to the European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium, the reported global fatality rate ranges from 30% to 50%. It is closely related to the number of organ failures.[3]

Acute hepatic insults like acute viral, alcoholic, or ischemic hepatitis, or non-hepatic events like trauma or surgery, can cause ACLF.[4] Chronic viral hepatitis, alcoholic cirrhosis, and non-alcoholic steatohepatitis (NASH) account for 20–35% of the population deemed high-risk.[1] According to Arshad et al., Hepatitis C virus (HCV)is the leading cause of pre-existing CLD in Pakistan, with a prevalence of 5% and an infection rate of 11.55% in the adult population.[5] HCV and hepatitis B virus (HBV) have been identified as the leading causes of CLD in Pakistan, with corresponding rates of 53.12% and 20.3%.[6] This is supported by another study, which found that HCV-related liver cirrhosis occurred in 78.4% of cases.[7] According to the World Health Organization (WHO), 4 to 5% of the population in Pakistan has hepatitis C, and 2 to 5% of the population in the Indian subcontinent has hepatitis B.[8]

Predicting ACLF in cirrhosis, a study[9] described precipitating factors such as bacterial infections (44%), followed by alcoholic hepatitis (43.6%), severe upper gastrointestinal bleeding (5.9%), and toxic encephalopathy (5.9%), leading to the acute decompensation ACLF and the acute decompensation without ACLF. According to other research, alcoholic hepatitis, acute viral hepatitis, spontaneous bacterial peritonitis (SBP), and drug-induced liver injury are all frequent causes of ACLF.[6,7] There has been a correlation shown between the severity of the grade of ACLF, the severity of prognostic scores like the Chronic Liver Failure Consortium (CLIF-C) organ failure score, the CLIF-C ACLF score, the Model for End-stage Liver Disease (MELD) score, and high 90-day mortality.[9] Jalan et al[4] reported high in-hospital mortality of 53% with a mean length of hospital stay of 14 days[6]. In contrast, according to the CANONIC Study[10], 28-day mortality was 33.9% in patients with ACLF at presentation vs 29.7% who progressed to ACLF while in hospital, compared to 1.9% among patients without ACLF.[10]

This study aimed to identify etiology, clinical presentations, and outcomes in terms of mortality in ACLF patients to gain insights that would refine the management plan, consequently helping to decide care goals in ACLF patients.

METHODS

It was a retrospective study; 109 patients, over 15 years of age, were included. Data of patients, who were admitted with ACLF to the medical Intensive Care Unit (ICU) of Pakistan Kidney and Liver Institute and Research Center (PKLI & RC), Lahore, Pakistan, between 1st January 2022 and 31st August 2023, were retrospectively retrieved from the electronic medical records and patients' files.

Clinical features of CLD and its complications, laboratory testing (including CBC, Urea, Creatinine, Na, Glucose, ammonia, alpha-fetoprotein, lactate, INR, LFT), imaging (ultrasound or CT scan of abdomen), and endoscopic findings were used to diagnose cirrhosis. Patients with hepatocellular carcinoma that exceeded the Milan criteria and hospitalization for causes other than ACLF were excluded.

Among the characteristics that were assessed were age, gender, pertinent investigations, comorbidities, Child-Turcotte-Pugh (CTP) score, CLIF-C score, Model for End-stage Liver Disease-Na (MELD-Na), ACLF grades, and comparing clinical improvement versus death as the primary outcome measure. All these scoring systems are used for assessing the severity of liver disease and predicting mortality among patients with cirrhosis.

ACLF was classified into four grades[3] based on the number of organ failures to evaluate mortality:

1. No ACLF: no nonrenal organ failure or a single nonrenal organ failure without renal dysfunction and cerebral dysfunction
2. ACLF grade 1 (ACLF-1): single renal failure or single nonrenal organ failure that is associated with renal dysfunction with serum creatinine =1.5-1.9 mg/dl) and/or cerebral dysfunction (hepatic encephalopathy grade 1 or 2)
3. ACLF grade 2 (ACLF-2): two organ failures of any combination
4. ACLF grade 3 (ACLF-3): three or more organ failures of any combination.

Ethical Approval

The study was conducted from 15th September to 21st October 2023 after taking ethical approval from the Institutional Review Board of Pakistan Kidney and Liver Institute and Research Center, Lahore, Pakistan (PKLI-IRB/AP/149) on 14-9-2023.

Statistical Analysis

Continuous variables like ammonia, LFTs (i.e., total Bilirubin, ALT, AST), INR, CTP score, CLIF-C score, and MELD-Na score were presented as mean ± SD. In contrast, categorical variables like survival status, Child-Pugh class, ACLF grades, etc., were expressed as frequencies and percentages. The independent sample t-test was applied on continuous variables, and the association between survival status and hepatic encephalopathy, hepatorenal syndrome, hepatic hydrothorax, and portal vein thrombosis, etc., was determined using the Chi-Square test. A $p < 0.05$ was considered statistically significant.

RESULTS

Out of the total 109 patients admitted to the ICU for ACLF during the study time, 78 died, making the mortality rate 71.6%. As shown in Table 1, the overall mean age was 47.4 ±10.5 years, including 80 (73.4%) males and 29 (26.6%) female patients, and there was no statistically significant difference between the mean age of survivors and non-survivors (p=0.313). Gender difference was also not statistically significant between survivors and non-survivor groups (p=0.091). The duration of ventilatory support was prolonged in non-survivors compared to those who survived (p<0.001), reflecting that prolonged ventilatory support indicates a poor outcome. Among the baseline investigations, we only found high INR and hyperammonia to be significant predictors of mortality. Similarly, a high CLIF-C score indicated higher mortality chances (p< 0.001).

The most common underlying cause of cirrhosis in these ACLF patients was HCV (52.3%), followed by cryptogenic cirrhosis (14.7%). HBV was found in 7 patients (6.4%), with an additional three patients having coinfection with HDV. In comparison, another 11 (10.1%) had combinations of HBV and HCV infection. In the remaining 15 patients, four each had alcoholic liver disease and Budd-Chiari Syndrome, two each had primary biliary cirrhosis, NASH, and autoimmune hepatitis, and one patient had Wilson disease. The remaining underlying diseases were not compared due to their small sample size (Figure 1).

Hepatic encephalopathy (grades 3 or 4) was the most common (95 out of 109 patients) trigger for acute decompensation leading to ACLF. Still, it was not statistically significant (p=0.28) between survivors and non-survivors, although most of them (71 out of 95 patients) died. Similarly other triggers leading to ACLF were also not statistically significant among the two groups, survivors vs non-survivors, these include hepatorenal syndrome (p=0.108), hepatic hydrothorax (p=0.824), portal vein thrombosis (p=0.774), esophageal varices (p=0.607), upper gastrointestinal bleeding (p=0.507), SBP (p=1.00), and ascites (p=1.00) (Figure 1)

Among comorbidities, 76 patients (69.7%) had no other medical problems. In contrast, 8 (7.4%) had diabetes mellitus, 7 (6.4%) had hypertension, 14 (12.8%) had combination of diabetes mellitus, hypertension and ischemic heart disease, 4 (3.7%) had other conditions like ischemic heart disease, chronic obstructive pulmonary disease, remote history of transient ischemic attack and remote tuberculosis.

There was only one patient with Child A and 4 in Child B cirrhosis, and they all died. Most patients (104 out of 109) had Child class C cirrhosis, and 73 of them died (Figure 2). However, regarding survival, the Child class was not statistically significant (p=0.180). Similarly, the overall mean CTP score at the time of ICU admission was 12.6±1.7, which was also not statistically significant in terms of survival. There was no significant difference in CTP scores for survivors vs non-survivors (p=0.305).

There were 21 patients in ACLF grade 1, and nine of them died (42.8%), 31 in ACLF grade 2, out of whom 21 (67.7%) died, and 57 were in ACLF grade 3; the majority of them (48; 84.2%) died. This shows that the severity of ACLF was statistically significant in terms of mortality (p<0.001) (Figure 2).

There was a significant rise in mean MELD-Na score when patients were transferred from the ward to the ICU (32.9 ± 6.5 to 34.7 ± 6.7; p<0.001), reflecting the patients' deteriorating condition. But as shown in Table 2, this change was not significant among the survivor group (33.5 ± 5.8) vs the non-survivor group (35.2 ± 6.9) (p=0.195). Similarly, there was a trend of rise in the mean CLIF-C score for patients transferred from the ward to the ICU, which was statistically significant (50.4±10.1 to 56.1±10.2; p<0.001). This trend is also seen in patients who survived in the ICU vs non-survivors (p<0.001). Therefore, rising CLIF-C is found to be a bad prognostic sign in the current study (Table: 2). Out of 109 patients, 67 were potential liver transplant candidates, among whom 45 died from ACLF, while only 3 out of 6 transplanted patients survived.

Table 1: Baseline characteristics of patients with acute on chronic liver failure

Variables	Total (n=109) mean ± SD	Survived (n= 31) mean ± SD	Not Survived (n=78) mean ± SD	p value
Mean age (years)	47.4 ± 10.5	45.9 ± 8.8	47.9 ± 11.11	0.313
Time since CLD diagnosis (weeks)	32.2 ± 64.01	34.03 ± 68.9	27.3 ± 32.1	0.502
Number of days in ICU	4.9 ± 3.5	4.9 ± 3.1	4.9 ±3.6	0.964
Number of days on Ventilator	3.1 ± 3.5	0.9 ± 2.7	4.02 ± 3.5	<0.001*
CTP score on admission	12.6 ± 1.7	12.3 ± 1.4	12.7 ± 1.8	0.305
CLIF-C score on ICU admission	56.1 ± 10.2	50.9 ± 7.5	58.1 ± 10.4	<0.001*
MELD–Na score on ICU admission	34.7 ± 6.7	33.5 ± 5.8	35.2 ± 6.9	0.195
Investigations (on ICU admission)				
Hemoglobin (g/dl)	9.7 ± 2.6	9.4 ± 2.9	9.8 ± 2.4	0.474
WBC (10^9/L)	14.7 ± 8.6	14.4 ± 8.7	14.9 ± 8.6	0.794
Platelets (10^9/L)	121.3 ± 82.04	126.1 ± 105.1	119.4 ± 71.6	0.747
Urea (mg/dl)	109.4 ± 65.8	105.5 ± 63.9	110.9 ± 66.8	0.692
Creatinine (mg/dl)	2.8 ± 1.8	2.7 ± 1.9	2.9 ± 1.9	0.587
Sodium (mEq/L)	129.9 ± 8.3	129.2 ± 7.3	130.2 ± 8.7	0.559
Glucose (mg/dl)	133.5 ± 59.5	71.4 ± 89.7	65.7 ± 74.9	0.757
Lactate, mg/dl	9.8 ± 9.3	7.4 ± 9.2	11.02 ± 9.4	0.370
Total Bilirubin (mg/dl)	14.6 ± 10.1	12.8 ± 8.5	15.4 ± 10.7	0.187
ALT (U/L)	137.8 ± 200.7	145.7 ± 219.8	134.7 ± 194.3	0.808
AST (U/L)	434.7 ± 887.8	419.7 ± 1022.6	440.7 ± 835.5	0.920
INR	3.2 ± 1.7	2.6 ± 1.1	3.4 ± 1.8	0.002*
Ammonia on ICU Admission (µg/dl)	200.4 ± 212.3	125.7 ± 65.7	230.1 ± 241.7	0.002*
AFP (ng/ml)	177.2 ± 926.9	62.1 ± 270.1	146.5 ± 897.5	0.457

*CTP=Child-Turcotte-Pugh; CLIF=Chronic Liver Failure-Consortium; MELD–Na=Model for End-Stage Liver Disease-sodium; ACLF=Acute-on-Chronic Liver Failure; AFP=alpha fetoprotein; independent sample t-test was applied. *p<0.05 was statistically significant.*

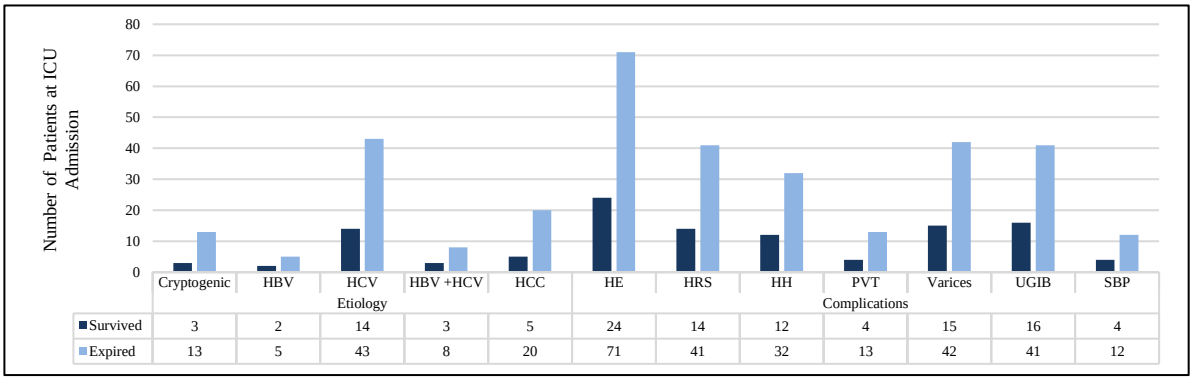

Figure 1: Comparison of etiology and complications according to survival status. HBV=hepatitis B virus; HCV=hepatitis C virus; HCC=hepatocellular carcinoma; HE=hepatic encephalopathy; HRS=hepatorenal syndrome; HH=Hydrothorax; UGIB=upper gastrointestinal bleed; SBP=spontaneous bacterial peritonitis; ICU=intensive care unit

Table 2: Prognostic scores of patients with Acute on chronic liver failure

SCORES	Survived	Not Survived	p value
MELD-Na score on Hospital admission	32.9 ± 4.9	33.04 ± 7.1	0.889
MELD-Na score on ICU admission	33.5 ± 5.8	35.2 ± 6.9	0.195
CLIF- C score on Hospital admission	47.7 ± 8.9	51.4 ± 10.4	0.136
CLIF-C score on ICU admission	50.9 ± 7.5	58.1 ± 10.4	<0.001*

*MELD-Na=model for end-stage liver disease-sodium; CLIF-C=chronic liver failure consortium; independent sample t-test was applied. *p<0.05 was statistically significant.*

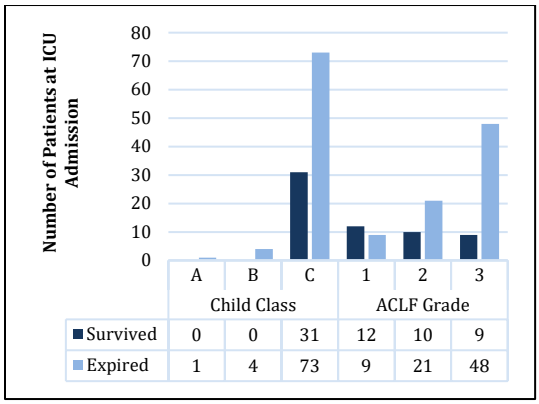

Figure 2: Clinical grading according to survival status. ACLF=acute-on-chronic liver failure

DISCUSSION

This study shows HCV is the most common cause of cirrhosis in our population. Also, there is high in-hospital mortality among ACLF patients, as 71.6% died, including 67.2% who were on the liver transplant list and 50% who had a transplant; this is greater than the previously reported 53% mortality.[4] Since most of our patients had Child-C cirrhosis (95.4%) and grade-3 ACLF (52.3%), the higher mortality rate was ascribed to advanced decompensated cirrhosis.

Liver disease is frequently underdiagnosed, and quite a few present late with decompensated cirrhosis.[11,12] In 2019, there were an estimated 1,472,000 cirrhosis-related deaths worldwide, a 10% rise from 2010.[13] With a global frequency of 20–35% at-risk individuals, ACLF has become a significant medical concern.[1] Additionally, it is among the most common

reasons why patients with CLD are admitted to the ICU and is linked to a high short-term mortality. Loss of the liver's ability to digest, neutralize, or detoxify harmful substances in ACLF

puts patients at risk for hypotension, infections, and multi-organ dysfunction. With an average of 14 days of hospitalization, it carries a high in-hospital mortality of 53%.[4] Since liver transplantation has been reported to increase 1-year survival to 81% in ACLF,[14] it is essential to identify triggering events early and manage them accordingly, particularly sepsis.

Unfortunately, there is not much data available from Pakistan, even though WHO has determined that Pakistan and Egypt share 80% of global hepatitis burden;[15] and in contrast to Western nations, where alcoholic cirrhosis is the leading cause of cirrhosis, hepatitis C is more prevalent among Pakistanis, with a prevalence of 5%.[16] Our study also showed hepatitis C as a leading underlying cause of cirrhosis (52.3%), followed by cryptogenic cirrhosis (14.7%) and hepatitis B (6.4%), while a sizable percentage of patients had co-infections with HBV and HCV (10.1%). According to the Polaris Observatory, in 2020, only 1% of HCV cases worldwide were treated, and less than 10% of treatment-eligible HBV-infected patients received antiviral therapy.[17] Therefore, the emphasis should be on early detection and prevention.

Acute insults such as viral hepatitis, acute alcohol intoxication, drug-induced liver injury, bacterial infections, or an unknown etiology can all cause liver failure.[14] We found that hepatic encephalopathy, hepatorenal syndrome, hepatic hydrothorax, SBP, and portal vein thrombosis are among the triggers for acute decompensation leading to ACLF. Although hepatic encephalopathy was the most common trigger for ACLF in the current study, but was not a statistically significant prognostic factor, in contrast to report from Hafsa et al.[6] However, it was insignificant in other studies that reported acute viral hepatitis, drug-induced hepatitis, alcoholic hepatitis, and SBP as significant prognostic markers [6,7,15]

According to our observation, 28-day mortality in ACLF is not substantially predicted by age, gender, or the underlying cause of the disease. This is the same finding reported in an earlier study.[6] The most common trigger for ACLF was grade IV hepatic encephalopathy in our study, even though it was not found to be a statistically significant prognostic marker. Our study showed high INR, hyperammonia, longer stay on ventilator, and high CLIF-C score as poor prognostic markers, unlike a previous report showing higher serum creatinine, bilirubin, and hepatic encephalopathy as predictors of mortality.[6]

Tasneem et al[15] reported a median survival of 17.1 days and a mortality rate of 39.3%. They found the MELD-Na score, CTP score, and number of organ failures to be predictors of mortality. Another study found that patients with multi-organ failure, ACLF grade greater than 2, MELD-Na score greater than 28, and CTP score greater than 13 lived shorter lives.[18] In contrast to the CTP score (sensitivity: 45.2%) and CLIF-SOFA score (sensitivity: 83.9%), a recent study indicated that the MELD score at the threshold of 21.5 had the highest sensitivity (96.8%) for predicting prognosis;[6] whereas our study showed higher ACLF

grade and CLIF-C score > 58 contribute towards high mortality.

Instead of the MELD score, we used the MELD-Na score as it has recently been shown to be a better prognostic marker.[19] Still, we could not find a statistically significant MELD-Na score between survivors and non-survivors, unlike reported by Kim, RW et al.[20] Similarly, we did not find the CTP score significant in terms of survival, but a high CLIF-C score was a significant predictor of mortality in our study; this is the same finding as reported by Kumar, R et al[21] who also reported CLIF-C score a better prognostic marker for ACLF as compared to CTP and MELD scores. We also found an increase in CLIF-C scores during hospital stay to be a poor prognostic indicator, as not only was there a rise in mean CLIF-C score from ward to ICU, but it was also significantly high in patients who did not survive.

In summary, we found high ACLF grade, high INR, hyperammonia, longer stay on ventilator, and high CLIF-C scores as predictors of mortality. Also, a worsening CLIF-C score during hospitalization may also represent poor prognosis, prompting a decision about continuing aggressive treatment vs a palliative approach.

CONCLUSION

HCV infection was the most common cause of cirrhosis, and hepatic encephalopathy was the common trigger for ACLF. A high INR, hyperammonia, advanced ACLF grade, and an increase in CLIF-C score lead to poor outcomes in terms of survival, while worsening of CLIF-C scores may additionally predict short-term mortality. This study helps to identify patients of ACLF, using diagnostic tools, who will benefit from intensive management. This categorization also makes it possible to locate palliative patients at high risk of mortality in advance, enabling us to decide about goals of care.

Limitations of study and future recommendations

It was a single-center retrospective study with a brief follow-up period (ICU stay till transfer to the ward or death). Also, the lack of a predefined sample size was another limitation, as we assessed the different scores in terms of mortality.

Future studies with a larger patient pool are required to delineate the prognostic markers further.

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AUTHOR'S CONTRIBUTIONS:

- **SS:** Conception of study, data acquisition & analysis, manuscript drafting, critical review
- **FK**: Study design, data acquisition & analysis, manuscript drafting
- **WAR:** Data collection, critical review, manuscript drafting
- **ASC:** Conception of study, study design, interpretation of data, critical review
- **BA:** Data collection, critical review, manuscript drafting
- **UF:** Conception of study, study design, interpretation of data, critical review

All authors approved the final version to be published and agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

CONFLICT OF INTEREST:

None

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