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COVID-19 Induced Hepatitis (CIH), Definition and Diagnostic Criteria of a Poorly Understood New Clinical Syndrome

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ABSTRACT

Background: Covid-19 Induced Hepatitis (CIH), is a novel terminology which is used in this article for the first time in the medical literature. However, SARS-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a coronavirus that out-broke in December 2019 in China.

Objective: To study the pattern of liver impairment in patients with Covid-19 as well as to find acceptable and practical diagnostic criteria of Covid-19 Induced Hepatitis (CIH). This review article gives new insight and guidance about the diagnosis of Covid-19 Induced Hepatitis (CIH), possible causes of liver damage and review of recently published data about the impairment of liver function in Covid-19 patients.

Methodology: Extensive literature review of newly published data and study in PubMed cited journals and other international publisher journals. Research of all studies that reviewed liver derangement in COVID-19 were mainly reviewed. Statistical analysis of submitted data were checked using SPSS. PubMed Chinese language versions were also used.

Results: 60% of patients with SARS can have abnormal liver functions. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) have noticeably been abnormal in around 14-53% of patients with Covid-19 (7/114, 6.14%) (P > .05). Impairment in liver enzymes, mainly ALT/AST, in severe Covid-19 pneumonia was significantly higher than patients with mild disease, with mean average (37.87±32.17 vs 21.22± 12.67;38.87 ± 22.55 vs 24.39 ± 9.79, P < .001). Patients with Community Acquired Pneumonia (CAP) had significantly less impaired liver synthetic function (32/114, 28.07%) compared to Covid-19 pneumonia (60/115, 52.17%), which has been demonstrated with high INR (P<0.01). Mild sinusoidal dilatation with lymphocyte infiltration, minimal, has been displayed in the liver tissue of 114 deceased with Covid-19 and liver impairment, which was obtained in one hour after their death. Fatality among Covid-19 and CLD with Child T-P score A was 23.9%, and Child T-P score B 43.3% with 63.0% fatality among patients with Child T-P score C, Moon AL. Acute liver failure in Covid-19 has been reported only in 2 occasions, one adult, and infant who had recent liver transplant.

Conclusion: Covid-19 Induced Hepatitis (CIH) is a new clinical syndrome, which can be defined as a "benign new transient hepatitis in a SARS-CoV-2 patients which is characterized by the following; **G**radual onset, elevated **A**ST and **A**LT, **D**ilated sinusoidal with lymphocytic infiltration of liver parenchyma, non-**O**bstructive jaundice, stable **U**nderlying liver disease and no **R**adiological new hepatobiliary changes." Using ***GADOUR*** criteria may support the diagnosis, however, sensitivity and specificity are yet to be established. Meticulous statistical studies need to be done before establishing overly sensitive scoring system can be reach.

KEYWORDS

Covid-19 Induced Hepatitis, GADOUR criteria

INTRODUCTION

Covid-19 Induced Hepatitis (CIH), is a new terminology which is used in this article for the first time- to our knowledge- in the medical literature. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a novel coronavirus that out-broke in December 2019 in China. Needless to mention, it has become an international threat to health and wellbeing of human beings directly or indirectly. Although most of the clinically proven infected people would not have severe spectrum of symptoms, [1,2] yet the fatality in mainland china is around 1.4%-3% [4].

COVID-19 shares around 50% genome sequence of Middle East Respiratory Syndrome (MERS-CoV), whereas it shares up to 82% genome sequence of SARS-CoV [5]. There is uncertainty of the liver damage in some cases of Covid-19, but, autopsy of around 27 patients showed that the virus was detectable in Liver, kidneys and other organs [6].

In order to set up and establish the definition of Covid-19 Induced Hepatitis (CIH), we will need to study the pattern of liver enzymes' changes, synthetic functionality of the liver during different phases of COVID-19 illness, the liver metabolism, as well as liver histopathology simultaneously.

In this article, we are going to conduct a focused literature review of the pattern of liver damage or injury (hepatitis) in Covid-19 patients and shed a light on CIH and try to define this syndrome clinically.

LITERATURE REVIEW

Around 60 % of patients with SARS had some liver impairment with 14%-53% had underlying liver disease [5], therefore it is crucial to understand the pathophysiology of this new phenomenon Covid-19 Induced Hepatitis (CIH) and how to manage such challenge in view of limited data and clinical trials.

Any liver injury that leads to hepatocytes' inflammation and/or damage is known as Hepatitis, most commonly caused by viral infections. Interestingly, most of hepatitis viruses, damage the hepatocytes although they do not destroy them as they (viruses) replicate in the liver cells, but they can cause liver damage with time if not treated.

Theoretically, advanced liver disease (Liver Cirrhosis) patients,are known to have an increased risk of developing Acute on Chronic Liver Failure (ACLF), due to Cirrhosis-Associated Immune Dysfunction (CAID), that may lead to death [7]. Nevertheless, so far, no fatality due to Acute Liver Failure secondary to Coivd-19 has been reported.

Hepatocytes and Cholangiocytes; metabolic response and functionality in Hospitalized Covid-19 patients

According to the data published by *The Fifth Medical Centre of PLS General Hospital in China*, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) have noticeably been abnormal in around 14-53% of patients with Covid-19 [8]. Although, arguably theseenzymes are not always secreted by the liver [9], yet the consensus of the clinicians was that the elevation of ALT and AST was sufficient enough to point towards liver damage alongside other hepatocytes' injury indicators. However, total Bilirubin (TBIL) was rarely been observed high or elevated in patients with COVID-19 associated pneumonia who had elevated ALT and AST according to ZhangY and his colleagues (7/114, 6.14%) (P >.05) [9].

Around 63% of Intensive Care Unit (ICU) patients with Covid-19, had an elevated AST compared with 25% of Covid-19 patient with elevated AST who did not require admission to the Intensive Care Unit (ICU) [10]. Gamma-Glutamyl Transpeptidase (GGT) was not significantly elevated in Coivd-19 patients as well as Lactate Dehydrogenase (LDH). Elevated Alkaline phosphatase (ALP), which indicates cholangiocyts injury, was observed in only1.8% ofpatients with Coid-19 [9].

Guan et Al, reported 1099 cases of confirmed Covid-19 infection, 2.3% of them had pre-existing liver disease. AST was elevated in 18.2% (112 patient) of 615 patients without severe diseaseand in 39.4% (56 patient) of the 142 who had severe disease. However, there was no clinically significant difference between ALT elevation and AST [11].

The synthetic function of the liver is usually assessed by monitoring the International Normalization Ratio (INR) or Prothrombin Time (PT) in addition to serum albumin level (ALB), hence, this has been studied as part of the liver impairment monitoring in Covid-19 patients with or without pneumonia. Patients with Community Acquired Pneumonia (CAP) had significantly less impaired liver synthetic function (32/114, 28.07%) in comparison with Covid-19 pneumonia (60/115, 52.17%), which has been demonstrated with high INR (P< .01) [9]. Reduced Albumin (ALB) level has been noticed in 54.78% of patients with Covid-19 pneumonia, whereas, patients with CAP have significantly higher proportion of reduced serum albumin level (83.33% -P< .001) [9].

Neutrophils Lymphocytes Ratio (NLR), which was found to have correlation with alcoholic hepatitismortality and steroids treatment [12], has also been monitored in patients in Coivd-19 patient with impaired liver functions. Interestingly, NLR correlates negatively to CRP and ALB (P< .001) in patients with severe Coivd-19, whereas there was no correlation between NLR and Globulin among the same patients (P> .05) [9].

The histological feature of Covid-19 Induced Hepatitis (CIH)

Moderate acute hepatitis with crumbling hepatocytes' apoptotic activities (Figure 2), has been reported in one case of post-liver transplant patient who has developed Covid-19 [13]. Mild sinusoidal dilatation with minimal lymphocyte infiltration, has been displayed in the liver tissue of 114 deceases with Covid-19 and liver, impairment which was obtained within one hour after their death (Figure 1) [9].

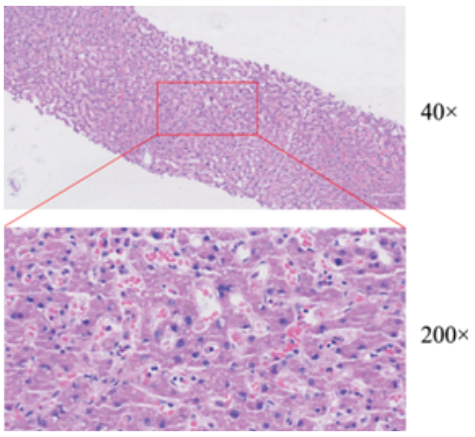

Figure 1: Sinusoidal dilatation with lymphocytes infiltration (Curtesy of Zhangy) [9]

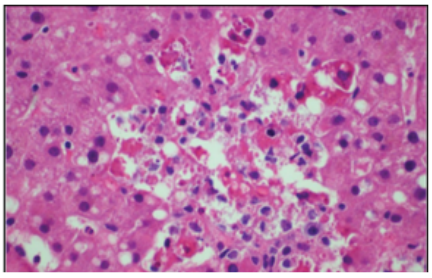

Figure 2: Clusters of apoptotic hepatocytes (Curtesy of Chang JF) [13]

Although, data are very limited with regard to the histopathological manifestation of CIH, sinusoidal and central venous lymph-histiocytic inflammation may suggest Covid-19 Induced Hepatitis (CIH) [13].

Covid-19 Induced Hepatitis (CIH) and pre-existing liver disease

Immune dysregulation is well known association with Chronic Liver Disease (CLD) and liver cirrhosis. That puts all patients with CLD or liver cirrhosis at significant risk of contracting SARS-CoV-2 and developing some complications [14,15]. However, the relation between Covid-19 fatality in patients with CLD is yet to be defined.

In a multicentric, recently publish study, the distribution of 152 cases of confirmed Covid-19 with CLD was as follows; Non-Alcoholic Fatty liver Disease (NAFLD) patients were around 22.4% followed by Alcoholic Liver Disease (ALD) patients of 19.7% and Hepatitis B patients were 11.8% with 10.5% had Hepatitis C whereas rest (35.6%) had other liver conditions. The median length of hospital stay or death for patients with Covid-19 and CLD was 10 days (IGQ 5-14 days), 23.3% were admitted to ICU among them 17.5% required invasive ventilators whereas 18.6% were put on non-invasive respiratory support machines, 4.9% needed dialysis. The mortality among those patients in ICU was 39.8% [16].

Most of the patients with CLD who contracted Covid-19 did not require ICU admission as they did not have severe disease (59.5%) [16]. Although the cause of death in most of them was Covid-19 pneumonia (78.7%), yet 12.2% died because of decompensated CLD.

The use of internationally approved and known liver scoring systems such as Child Tucotte-Pugh (CTP) and Model for End stage Liver Disease (MELD) have beautifully demonstrated the association between severity of underlying liver disease, liver cirrhosis, and the mortality rate in Covid-19 patients [16]. Fatality among patients with CTP A, B, and C was 23.9%, 43.3% and 63.0% respectively. *Moon AL* (Figure 3) [16].

Viral Hepatitis (A, B, C, and E) and Covid-19 Induced Hepatitis (CIH)

Currently, there is no confirmed information connecting viral hepatitis and SARS-CoV-2 during the course of infection. However, there are several possible mechanisms of liver injury in patients with COVID-19 infection, including; drug toxicity, progression of underlying liver disease,psychological stress and systemic inflammatory response and severe steatohepatitis [17]. However, direct effect of the virus on liver cells has to be considered.

Mild hepatic inflammation with moderate microvascular steatosis in COVID-19 patients lead to an increased risk ofdeveloping drug-induced liver injury [18]. In China for example, high burden of CLD mainly viral Hepatitis B, Fatty liver disease and liver cirrhosis have been detected and they might be considered as the most common predisposing factor for liver damage among Chinese patients with COVID-19 [17-19]. Another recent study found that chronic HBV virus infection, has not been negatively impact on [18,19]. According to *Sean and Timothy*, (2020) people with hepatitis C (HCV), other types of hepatitis diseases or human immunodeficiency viruses (HIV) are likely to develop a greater risk of becoming seriously ill with COVID-19 disease [20]. Also, elderly people and people of all ages who are immunocompromised can develop serious medical conditions, especiallypeople with liver injury, who will be most susceptible to getting severely ill from COVID-19. Therefore, patients with chronic liver diseases, including HBV and HCV, may be more vulnerable with *higher risk* of serious complications [21].

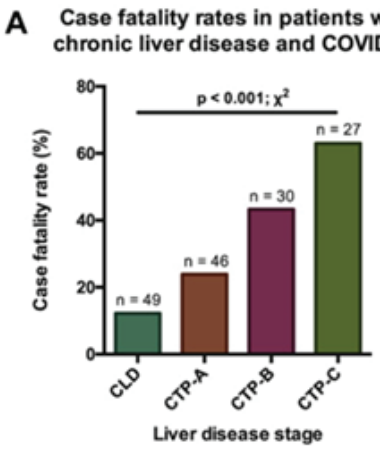

Figure 3(A): Associated between Mortality of Covid-19 patients and Child T-Pugh score

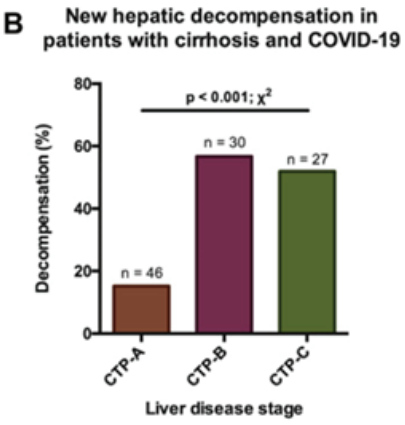

Figure 3(B): Liver decompensation by the stage of Cirrhosis. (Curtesy of Moon AL) [16]

Most of COIVD-19 related studies, have yet to exposethe exact relation and interaction betweenCLD and SARS-CoV-2. Hence, urgent researches are required to decode the mystery.

Mechanism of hepatic injury in patients with Covid-19

SARS CoV-2 RNA has been detected in the stool of 2-10% of patients who presented with diarrhoea and had Covid-19 infection [22], therefor, direct liver exposure is possible theoretically. In fact, both types of Corona virus, SARS-CoV and SARS CoV-2, bind into the target cell through binding to Angiotensin-Converting Enzyme 2 receptors (ACE 2). After the virus being replicated in the target cell, subsequently, it infects other cells and tissues including liver and lung tissues [22].

Interestingly, in confirmed SARS patients, pathologic studies have noticed the presence of SARS in liver tissue, however, viral inclusions were not observed in the liver tissue and viral load was relatively low [23]. Expression of ACE2 receptor is enriched in the cholangiocytes, suggested by *Albeit* in a preliminary study, which suggests that liver tissue may be dysregulated when ACE2-positive cholangiocytes are directly connected with Covid19 [24].

Neutrophil Induced Liver Injury (NILI), is known to cause a life-threatening Liver failure due to sepsis. Dying liver tissues, dead hepatocytes, release potent neutrophil extravasation promoters into the liver parenchyma, which are IL-1, IL-8, platelet activating factor, TNF-α and cytokines which in turn lead to neutrophils activation [30,31].

Fortunately, no data to date have suggested or reported any fatality due to Acute liver failure in Covid-19 patient.

There are multiple clinical pathways, which could lead to acute

liver damage in patients with COIVD-19. However, the pattern of liver damage varies from patient to patient and fluctuates depending on many factors like background liver disease and the severity of the COVID-19 infection. Some of these factors are discussed below.

Acute liver failure in Covid-19 has been reported only intwo occasions, one adult [25], andone infant who had recent liver transplant [26].

Severity of Covid-19 infection

The severity of Covid-19 infection has reportedly been related to the presentation of CIH [1].Severe Covid-19 associated pneumonia was defined as; COVID19 pneumonia with either respiratory rate >30 breaths per minutes, SpO_2<93% on room air, or PaO_2/FiO_2 ≤ 300 mmHg. Amongst 115 patients with Covid-19 pneumonia and deranged liver function test, 31 had severe pneumonia (31/115, 26.96%) [9].

ZhangY and colleagues, reported that impairment in liver enzymes, mainly ALT/AST, in severe Covid-19 pneumonia was significantly higher than patients with mild disease, P< .001) (Table 1) [9].

In 1099 patients with severe Coivd-19, acute hepatitis proved by deranged Liver function test, mainly ALT in 552 hospitals in China [1], (Curtesy of ZhangyY [9]).

Drug Induced Liver Injury in Covid-19 patients

Zhang et al, recently highlighted the fact that Covid-19 liver impairment could be secondary to Drug Induced Liver Injury (DILI) [9]. Furthermore, large population of Covid-19 patients have been reported to be suffering from hypertension and diabetes, hence, they have been using antihypertensive agent such as ACE inhibitors and ACE2 receptor blockers, which in turn may lead to overexpression of ACE2. Therefore, upregulation of ACE2 could increase the susceptibility of developing Covid-19, *fang et al*, hence CIH [27].

Microvesicular hepatic steatosis has been reported during post-mortem histological examination of liver tissues in Covid-19 patients, although it is not yet clear whether this finding is among the diagnostic criteria or not, it does indicate a possibility of underlying NAFLD. Thus, patients with metabolic syndrome, would have more sensitive hepatocytes for hepatotoxicans drugs like acetaminophen, which are widely used as anti-pyretic drugs, *Massart et al*. [28].

Table 1: Association Between Severity of Covid-19 and Derangement if Liver Function, Zhangy [9]

Variable	Mild Covid-19 (n=84)	Severe Covid-19 (n=31)	*t*-value	*P*-value
ALT (9-50 U/L)	21.22 ± 12.67	37.87 ± 32.17	3.996	<.001
≤50 U/L	81	23		
50-150 U/L	3	7		
>150 U/L	0	1		
AST (15-40 U/L)	24.39 ± 9.79	38.87 ± 22.55	4.807	<.001
≤40 U/L	79	19		
40-120 U/L	5	12		
>120 U/L	0	0		
ALP (30-120 U/L)	71.58 ± 24.09	79.51 ± 24.57	1.559	.122
≤120	82	27		
120-300	2	2		
>300	0	3		
GGT (8-57 U/L)	28.47 ± 24.93	56.90 ± 73.28		<.001
≤57	74	26		
57-142.5	10	2		
>142.5	0	3		
CRP (0-10.0 mg/L)	18.27 ± 29.87	80.75 ± 69.18	33.930	<.001
≤10	46	3		
10-100	36	17		
>100	2	11		
NLR	2.28 ± 1.29	7.58 ± 7.04	6.661	<.001
TBIL (5-21 µmol/L)	10.27 ± 4.26	14.12 ± 6.37	3.734	<.001
≤21	81	26		
21-31.5	3	4		
>31.5	0	1		
INR ≤ 1.15	1.15 ± 0.09	1.21 ± 0.13	2.521	.013
≤1.15	42	13		
1.15-1.38	40	16		
>1.38	2	2		
ALB (40-55 G/L)	40.41 ± 3.24	34.40 ± 4.11	8.177	<.001
≥40	49	3		
30-40	35	23		
<30	0	5		
GLB (20-30 G/L)	28.39 ± 3.46	31.28 ± 4.60	3.625	<.001
≤30	59	14		
>30	25	17		

HIV and HCV infected patients are more prone to develop DILI, mainly when they receive Highly Active Anti-Retroviral Therapy (HAART), *Naidoo et al*. [29].

Despite the fact that Covid-19 could have direct effect on normal liver tissue and some drugs, which are being used to treat Covid-19 as well as other underlying medical conditions, could also cause liver damage, more robust studies need to be done on a larger cohort to establish the relation between Covid-19 and DILI, if it exists.

Less common causes of Covid-19 Induced Hepatitis (CIH)

Hypoxic liver injury is well associated with severe hypoxaemia. Although ischaemic hepatitis and ischaemic cholangitis might directly result form hypoxaemia in patients with pneumonia, it has not been reported yet any case of ischaemic hepatitis in a Covid-19 patients.

Secondary sclerosing cholangitis is a rare cholestatic liver disease, which is usually chronic and associated with complex multiple causes. It is characterised by fibrosis, biliary obstruction, inflammation and biliary cirrhosis, *Alberto Quaglia*. Even though, it is thought to be one of potential causes of impairment in Covid-19 patients, however, no histological nor radiological features have supported this.

DEFINITION OF COVID-19 INDUCED HEPATITIS (CIH)

Fortunately, no data to date have suggested or reported any fatality due to Acute liver failure in Covid-19 patient. According to current information and after excluding other causes of hepatitis, we can define acute CIH as a benign new onset transient hepatitis in a SARS-CoV-2 patients, which is characterized bythe following; **G**radualonset of elevated **A**ST and **A**LT, **D**ilated sinusoidal with lymphocytic infiltration of liver parenchyma , non-**O**bstructive jaundice, no**U**nderlying liver disease and no new**R**adiological hepatobiliary changes **(*GADOUR criteria*)**.

Thus, applicability of ***GADOUR*** criteria would require a thorough and intensive investigation, such as viral hepatitis, full autoimmune liver profile, doppler hepatology study and eventually liver biopsy.

DISCUSSION

WHO has emphasized that; the novel coronavirus, SARS-CoV-2 is more contagious and fatal than the previously known SARS-CoV. Although, SARS-CoV-2 shares 80%, roughly, genetic sequence of SARS-CoV [32,33]. Furthermore, ACE2 receptors, are the same entry cells for both, SARS-CoV and SARS-CoV-2 [32]. Despite the fact that; SARS-CoV-2 has a significantly higher rate of infectivity, yet SARS-CoV had more severe signs and symptoms. Abnormalities of the liver enzymes are common in both SARS, however, not a prominent feature [34,35]. The consensus of most of the published data suggests that the liver was not the target organ of SARS infection. The exact link between hepatitis and Covid-19 is yet to be found. It has been not been possible to make a diagnosis of liver injury in Covid-19 patient by using international Serious Adverse Event Consortium (iSAEC) [36]. Hence, developing a robust diagnostic criteria and scoring for Covid-19 Induced Hepatitis (CIH) thought to be crucial.

Expression of ACE2 in the hepatocytes has previously been reported as weak [36,37], therefore, direct hepatic damage by SARS-CoV-2 is non-significant. Although, at times, ACE2 expression takes place in the intrahepatic bile duct (IHBD), yet there was no significant difference in ALP between patients with mild or severe Covid-19 pneumonia [36]. Injury of ductal epithelium of hepatobiliary systems is thought to be very week in Covid-19 patients as the level of ALP overall has been reported to be lower in comparison to patients with Community Acquired Pneumonia (CAP). Raised ALP is well associated with obstructive jaundice, so far, no case have been reported to show any evidence of obstructive biliopathy, hence, Covid-19 Induced Hepatitis (CIH) would not present with obstructive picture of impaired liver enzymes nor radiological features of biliary obstruction.

Needless to mention that ACE2 expression also takes place in the cardiovascular system, mainly cardiac vessels, hence, elevated LDH can be explained by cardiac vessels involvement in SARS-CoV-2. However, as ALP, there was no significant elevation in Covid-19 patients vs Community Acquired Pneumonia (CAP) patients [38].

Low serum albumin level, Hypoalbuminemia, has been associated with multiple cases of Covid-19, however, it was not directly linked with the disease nor the severity as poor nutritional status thought to be major contributory factor for developing hypoalbuminemia [39]. Therefor, detailed nutrition assessment is highly recommended. NLR has Widley been used to assess the severity of bacterial infection [40]. According to *Liu et al*, NLR can predict the severity of Covid-19 at early stage of illness [41].

Nevertheless, there is currently no data reported decompensation of underlying liver disease to support that; Covid-19 could lead to direct deterioration nor worsening of underlying primary liver condition, hence, we suggest that patients with pre-existing liver condition and suspected Covid-19 Induced hepatitis (CIH) is to be closely monitored and treating underlying CLD should not be interrupted during Covid-19 unless clinically necessary.

Alongside, supportive liver treatment and treating the underlying illness, such as pulmonary embolism PE or DIC, empirical antibiotics has been recommended in Covid-19 patients, which in turn would expedite healing of the transient liver damage, *Tian et al*. [42].

CONCLUSION

CIH is a new phenomenon which is yet to be fully understood. Diagnosing the syndrome is proven challenging due to limitations of available data and resources. Obtaining detailed and thorough hepatology assessment, including history, clinical examination and investigations would help in establishing the diagnosis and guiding the treatment.

Even though, management of the condition is yet to be fully developed, most of data suggest treating underlying condition is important, however, apart from the known supportive liver treatment, no specific liver treatment is required. Meticulous statistical studies need to be done before establishing an overly sensitive scoring system can be reach.

Although ***GADOUR*** criteria might give a hint to the diagnosis of the disease, more data and studies interpretation would be required in order to adopt a clinically acceptable pathway to explore the diagnostic criteria and treatment.

Conflict of Interest

There is no conflict of interest mentioned author

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