

Incidence of Ischemic Hepatitis among Patients in Medical Intensive Care Unit and Variations of Clinical and Biochemical Profiles in Patients With and Without Ischemic Hepatitis

SAMI S.A. GABALI, M.D.

The Department of Internal Medicine, Faculty of Medicine and Health Sciences, Aden University

Abstract

Background: Ischemic hepatitis (IH) is a clinical syndrome encountered in critically ill patients that represents a complication of underlying cardiac, circulatory or respiratory failure.

Aim of Study: Information is scarce about IH in our country. This study intends to explore incidence of IH, its causes, clinical, biochemical profiles and outcomes.

Patients and Methods: This study was conducted over a period of 2 years (from 1st of January 2023 to 31st of December 2024) including 1730 patients admitted in the medical intensive care unit (ICU) in Al-Gamhouria modern Hospital and Burj Al-Atebba Hospital at Aden governorate in Yemen. IH was diagnosed according to the following diagnostic criteria: Clinical setting, such as heart failure, circulatory or respiratory failure; Rapid rise in plasma aminotransferase level (>20 times the upper limit of normal which is 40 units/L); Exclusion of other causes of raised liver enzymes, especially viral hepatitis, drug-induced hepatopathy or autoimmune hepatitis.

Results: IH incidence was 6.5%. Males comprised 61.6% of IH cases, while females 38.4%. Male: female ratio (1.6: 1). Mean age in males: 58.7±12.2 years. Mean age in females: 61.1±12.3 years. The most common underlying cause of IH was shock (54.6%) the most common type within shock associated with IH was cardiogenic shock (80.3%). The most common clinical features of IH were vomiting (54.5%), right upper abdominal pain (52.7%) and hepatomegaly (39.3%). While overt jaundice was less common (8.1%).

Characteristic laboratory Findings in IH was high aspartate to alanine aminotransferase ratio (AST/ALT ratio: 1.7) and low alanine aminotransferase to lactate dehydrogenase ratio (ALT/LDH ratio: 0.9).

Conclusion: IH should be anticipated among critical care patients with circulatory and/or respiratory compromise. It is best managed by early detection according to clinical criteria

and rapid correction of underlying causes in order to prevent end organ damage.

Key Words: Ischemic hepatitis – Shock liver and hypoxic hepatitis.

Introduction

ISCHEMIC hepatitis (IH) (also referred to as shock liver, hypoxic hepatitis) refers to diffuse hepatic injury resulting from acute hypoperfusion and/or systemic hypoxemia [1].

It is characterized by a massive, but transient, increase in serum transaminases levels due to an imbalance between hepatic oxygen supply and demand in the absence of other causes of acute liver damage [2].

Clinical manifestations in IH have little specificity and are largely related to the underlying pathological condition [3].

The first 24-48 hours are characterized by an unexpected massive rise in Aspartate aminotransferase (AST) levels shortly followed by an increase in Alanine aminotransferase (ALT) levels. Diagnostic values are 10 up to 250 times the normal upper limit [4].

Management should focus on correcting hypoperfusion and liver congestion [5].

Patients and Methods

This was an observational prospective study carried out in the medical intensive care unit (ICU) in Al-Gamhouria modern Hospital and Burj Al-Atebba Hospital at Aden governorate/Yemen. From the 1st of January 2023 to 31st of December 2024.

Recruiting all cases admitted to the medical ICU in the above-mentioned hospitals during the study period.

Correspondence to: Dr. Sami S.A. Gabali,
[E-Mail: ssagabali@gmail.com](mailto:ssagabali@gmail.com)

IH was diagnosed according to the following diagnostic criteria [6,7].

- Clinical setting, such as heart failure, circulatory or respiratory failure.
- Rapid raise in plasma aminotransferase level (>20 times the upper limit of normal ULN which is 40 units/L).
- Exclusion of other causes of elevated liver enzymes, especially viral hepatitis, drug-induced hepatopathy or autoimmune hepatitis.

These criteria have been used and validated in recent large series and it is agreed that liver biopsy is neither required nor advisable when they are present [6].

Exclusion criteria: Confirmed cases of viral hepatitis. Cases known to take drugs with hepatotoxic potential (paracetamol >6g per day, antituberculosis medication, halothane anesthetic). Known cases of autoimmune hepatitis. Known cases of liver cirrhosis. Recent history of hepatobiliary surgery. Recent history of liver trauma. Qat and Alcohol intake.

Vital signs and laboratory data were taken, hepatic enzymes include serum alanine aminotransferase ALT, aspartate aminotransferase AST, while biliary enzymes included alkaline phosphatase (ALP) and γ -glutamyltransferase (γ -GT). Total and direct bilirubin, prothrombin time (PT), international normalized ratio (INR) and lactate dehydrogenase (LDH) [8].

Data were collected by the researcher. Data processed into computer using the Statistical Package for Social Sciences software, SPSS version 28.

Results presented as Mean $\pm$ Standard Deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using Chi-Square test or Fisher's exact test as appropriate. Quantitative variables were compared using *t*-test or One-way analysis of variance (ANOVA) test. Statistical significance was determined as a $p < 0.05$.

The ethical review committee of Aden University reviewed the research proposal and granted the ethical clearance for the researcher to undertake the study.

Results

In this study, a total of 1730 patients were admitted in the ICU during the study period.

Table (1) shows number of patients who developed IH was 112 patients comprising an incidence of 6.5%.

Table (1): Distribution of ICU patients according to diagnosis of IH.

ICU patients	No.	%
IH	112	6.5
Non IH	1618	93.5
Total	1730	100.0

Table (2) shows that, within IH patients, 69 patients were males (61.6%) versus 43 patients were females (38.4%) with male: female ratio = (1.6:1) the relation was not significant (p -value=0.06).

Mean age in males: 58.7 ± 12.2 years, while mean age in females: 61.1 ± 12.3 years.

Table (2): Distribution of IH patients regarding sex and age.

Age Group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
<45 years	5	7.2	1	2.3	6	5.4
45-54 years	13	18.8	6	13.9	19	16.9
55-64 years	24	34.8	14	32.6	38	33.9
>65 years	27	39.1	22	51.2	49	43.8
Total	69	100.0	43	100.0	112	100.0

Table (3) shows shock to be the leading underlying cause comprising 54.6% of patients with IH. Followed by congestive cardiac failure (CCF) (34.8%), respiratory failure (8.9%).

Table (3): Distribution of patients according to ischemic hepatitis & underlying causes.

Cause	IH	
	No.	%
Shock	61	54.6
Cardiogenic	49	80.3
Septic	7	11.5
Hypovolemic	3	4.9
Obstructive	2	3.3
CCF	39	34.8
Respiratory failure	12	10.6
Total	112	100.0

Table (4) shows the frequency of different clinical features among patients with IH. In our study. Nausea, vomiting and right abdominal pain was the leading features.

Table (4): Frequency of clinical features among IH patients.

Clinical feature	No.	%
Nausea & vomiting	61	54.5
Right upper abdominal pain	59	52.7
Hepatomegaly	44	39.3
Jaundice	9	8.1

Table (5) shows that in our study, patients with IH have much higher levels of means of AST, ALT and LDH than non-IH patients. The relation was statistically significant. While no significant difference observed regarding values of bilirubin, ALP and INR.

In our study AST: ALT ratio is higher in IH than non-IH (1.7 versus 0.9 respectively) and lower ALT: LDH ratio in IH group (0.9) than in non-IH group (1.6).

Table (5): Distribution of patients according to laboratory values.

Lab. values	IH		Non IH		p-value
	Mean	SD	Mean	SD	
AST	3951	92.7	226	55.8	0.00
ALT	2278	66.8	220	32.8	0.00
LDH	2345	76.3	136	29.7	0.00
D. bilirubin	2.3	1.9	1.7	0.9	0.15
ALP	339	55.1	291	34.9	0.63
INR	1.3	1.2	1.2	0.3	0.98

Table (6) shows that out of 112 patients with IH, 74 patients died, comprising 66.1% mortality in this group versus 19.9% in non-IH. The association was statistically significant (p -value=0.01).

Table (6): Distribution of patients according to outcome.

Item	IH		Non IH		Total	
	No.	%	No.	%	No.	%
Died	74	66.1	323	19.9	397	22.9
Survived	38	33.9	1295	79.1	1333	77.1
Total	112	100.0	1618	100.0	1730	100.0

Discussion

In our study, total number of ICU patients was 1730 patients. Number of patients who developed IH was 112 patients comprising an incidence of 6.5%. A similar result to ours was found in the

study of Run-sun et al., in China who mentioned an incidence of 6.5% of IH in their study [9]. A lower result was reported in the study of Taylor et al., in USA who gave incidence of 4.4% for IH. This could be attributed their study population was only patients with acute liver failure ALF [8].

Within IH patients, our study shows 69 males (61.6%) versus 43 females (38.4%) with male: female ratio (1.6:1).

A close finding to ours was mentioned by Henrion et al in Belgium, describing male: female ratio (2:1) among IH patients [10]. A somewhat lower ratio in the study of Chang et al., in Singapore, who identified the male: female ratio among IH patients to be (1.3:1) [11].

In our study, the percentage of male patients was higher than females up to the age group of 55-64 years, and then at the age of 65 years and more, percentage of female patients became higher than males (51.2% for females against 39.1% for males).

A similar finding was observed in the study of Besech et al., in Poland who reported a higher females percentage than males among IH patients with increasing age (females were 51% versus 49% males) [12].

Regarding the underlying causes of IH, in our study shock was the leading cause comprising 54.6% of patients with IH (among them cardiogenic shock was the most common type of shock 80.3%, followed by septic shock 11.5%, hypovolemic 4.9% and obstructive shock 3.3% in two cases, one with massive pulmonary embolism and the second with cardiac tamponade).

Observations similar to our results were found in the study of Henrion et al., in Belgium, who reported cardiogenic shock in 70% and septic shock 13% of IH cases and stated that passive congestion of the liver due to right heart failure has a crucial role in addition to low hepatic perfusion in occurrence of IH. Which explains why IH is more common in cardiogenic shock than hypovolemic shock [6].

The second underlying cause of IH in our study was congestive cardiac failure CCF without cardiogenic shock (34.8%) of cases.

Seeto et al., in USA, mentioned that in patients with cardiac congestive hepatopathy a mild decrease in hepatic perfusion pressure may be sufficient to cause ischemic hepatitis and in some cases, transient systemic hypotension is sufficient to produce hepatocyte necrosis in patients with pre-existing hepatic congestion [13].

Around 10.6% of IH cases in our study were due to respiratory failure, all of them admitted in the ICU with acute exacerbations of pre-existing chronic obstructive pulmonary disease COPD or

chronic interstitial lung disease, leading to hepatic hypoxemia. Close finding in the study of Waseem et al., who reported 7% of IH cases with respiratory failure [14]. While Birrer et al., in U.S. A reported respiratory failure in 13.9% of cases, concluding that IH can occur in normotensive patients in hypoxic state and not restricted only in patients with shock state [15].

In our study, within 112 patients with IH, nausea and vomiting were in 54.5% of cases, right upper abdominal pain in 52.7%, hepatomegaly in 39.3% and overt jaundice seen in only 8.1%.

Nearly similar to our results in the study of Waseem et al., found nausea, vomiting and right upper abdominal pain in 50% of IH cases [14]. Henrion et al., found hepatomegaly in 50% of cases [10].

In our study, patients with IH have higher levels of means of AST, ALT and LDH than non-IH patients, the relation was statistically significant.

Chavez et al., found mean value of AST 3275 ± 3.00 IU/L in IH versus 394 ± 122 IU/L in non-IH. Mean ALT 1736 ± 137 IU/L in IH versus 227 ± 132 IU/L in non-IH and maximum LDH 4425 ± 3199 IU/L in IH versus 831 ± 310 IU/L in non-IH. All of these values were statistically significant [16].

In our study AST: ALT ratio is higher in IH than non-IH (1.7 versus 0.9 respectively). It is characteristic of IH to be with higher level of plasma AST compared to ALT, as a direct result of higher concentration of AST in hepatic zone 3, the place where ischemic necrosis develops [17].

In our study, the ALT: LDH ratio in IH group was 0.9 while in non-IH group was (1.6).

Waseem et al., pointed that a sharp rise in LDH is a strong indicator of ischemic hepatitis as a cause of the liver injury rather than other mechanism such as viral or hepatotoxic [14]. Fuchs et al. and Cassidy et al., identified ALT: LDH ratio less than 1.5 as a highly characteristic of ischemic rather than any other etiologies of liver injury [18,19].

Regarding mortality, our study showed that from 112 patients with IH, 74 patients died, comprising 66.1% mortality in this group. While in non-IH patients out of 1618 patients, 313 patients died comprising 19.9% mortality in this group. This association was statistically significant.

Close findings to our results could be found in the studies of Raurich et al. and Besech et al., Raurich et al., in Spain found 61.5% mortality [20]. Whereas Besech et al., in Poland noted 66% mortality in IH patients which was statistically significant difference compared to non-IH [12].

References

- 1- LIGHTSEY J. and ROCKEY D.: Current concepts in ischemic hepatitis. *Curr. Opin. Gastroenterol.*, 33: 158, 2017.
- 2- EBERT E.: Hypoxic liver injury. *Mayo Clin. Proc.*, Sep. 81 (9): 1232-6, 2006.
- 3- DENIS C., DE KERGUENNEC C., BERNUAU J., BEAUVOIS F. and COHEN SOLAL A.: Acute hypoxic hepatitis (liver shock): Still a frequently overlooked cardiological diagnosis. *Eur. J. Heart Fail*, 6: 561-5, 2004.
- 4- TAPPER E., SENGUPTA N. and BONDER A.: The Incidence and Outcomes of Ischemic Hepatitis: A Systematic Review with Meta-analysis. *Am. J. Med.*, Dec. 128 (12): 1314-21, 2015.
- 5- FUHRMANN V., JÄGER B., ZUBKOVA A. and DROLY A.: Hypoxic hepatitis-epidemiology, pathophysiology and clinical management. *Wien Klin Wochenschr*, 122: 129-39, 2010.
- 6- HENRION J.: Hypoxic hepatitis. *Liver international*, Aug. 32 (7): 1039-1052, 2012.
- 7- CIOBANU A.: Ischemic Hepatitis – Interrelated Pathology. *Maedica (Buchar)*, Mar. 13 (1): 5-11, 2018.
- 8- TAYLOR R., TUJIOS S., JINJUVADIA K., DAVERN T., SHAIKH O., et al.: Short and Long-Term Outcomes in Patients with Acute Liver Failure Due to Ischemic Hepatitis. *Dig. Dis. Sci.*, Mar. 57 (3): 777-785, 2012.
- 9- RUNSUN S., WANG X. and JIANG H.: Prediction of 30-day mortality in heart failure patients with hypoxic hepatitis. *Front Cardiovasc. Med.*, Oct. 28 (9): 1035675, 2022.
- 10- HENRION J., SCHAPIRA M., LUWAERT R., COLIN L., DELANNOY A. and HELLER F.R.: Hypoxic hepatitis: Clinical and hemodynamic study in 142 consecutive cases. *Medicine*, 82: 392-406, 2003.
- 11- CHANG P., GOH B. and EKSTROM V.: Low serum albumen predicts early mortality in severe hypoxic hepatitis. *World J. Hepatol.*, Aug 8; 9 (22): 959-966, 2017.
- 12- BESECH C., GUILLOT M. and HERBRECHT J.: Hypoxic hepatitis: Predictive factors of mortality. *J. Hepatol.*, April 58 (1): S409, 2013.
- 13- SEETO R., FENN B. and ROCKEY D.: Ischemic hepatitis: clinical presentation and pathogenesis. *Am. J. Med.*, 109: 109-113, 2000.
- 14- WASEEM N. and CHEN P.: Hypoxic Hepatitis: A Review and Clinical Update. *J. Clin. Transl. Hepatol.*, Sep 28; 4(3): 263-268, 2016.
- 15- BIRRER R., TAKUDAN Y. and TAKARA T.: Hypoxic hepatopathy: Pathophysiology and prognosis. *Intern. Med.*, 46: 1063-70, 2007.
- 16- CHÁVEZ-TAPIA N., BALDERAS-GARCÉS B., MEZAMENESES P., HERRERA-GOMA M., et al.: Hypoxic hepatitis in cardiac intensive care unit: A study of cardiovascular risk factors, clinical course, and outcomes. *Ther. Clin. Risk Manag.*, 10: 139-145, 2014.

- 17- ABOELSOU M., JAVAID A., AL-QADI M. and LEWIS J.: Hypoxic hepatitis - its biochemical profile, causes and risk factors of mortality in critically-ill patients: A cohort study of 565 patients. J. Crit Care, Oct. 41: 9-15, 2017.
- 18- FUCHS S., BOGOMOLSKI-YAHALOM V., PALTIEL O. and ACKERMAN Z.: Ischemic hepatitis: Clinical and laboratory observations of 34 patients. J. Clin. Gastroenterol., Apr. 26 (3): 183-6, 1998.
- 19- CASSIDY W. and REYNOLDS T.: Serum lactic dehydrogenase in the differential diagnosis of acute hepatocellular injury. J. Clin. Gastroenterol., 19: 118, 1994.
- 20- RAURICH J., LLOMPART-POU J., FERRERUELA M., et al.: Hypoxic hepatitis in critically ill patients: Incidence, etiology and risk factor for mortality. J. Anesth., 1: 50-56, 2011.

حدوث التهاب الكبد الإقفارى فى مرضى العناية المركزة والاختلافات فى الأنماط السريرية والمخبرية والنتائج فى المرضى المصابين وغير المصابين بالتهاب الإقفارى

التهاب الكبد الإقفارى متلازمة سريرية نواجهها بين مرضى الرعاية الحرجة نتيجة تدهور فى الجهاز الدورى والتنفسى.

الهدف: أجريت هذه الدراسة بهدف وصف الأنماط الاكلينيكية والمخبرية والنتائج لدى مرضى التهاب الكبد الاقفارى.

الأساليب: أجريت هذه الدراسة خلال عامين للمرضى اللذين تم إدخالهم العناية المركزة فى مستشفى الجمهورية الحديث ومستشفى برج الأطباء فى عدن خلال الفترة بين الأول من يناير ٢٠٢٣ إلى الحادى والثلاثين من ديسمبر ٢٠٢٤.

النتائج: عدد حالات التهاب الكبد الاقفارى كان ١١١ حالة بنسبة ٦,٥ ٪. نسبة إصابة الذكور ٦١,٦ ٪ فاقت نسبة إصابة الإناث ٣٨,٤ ٪ بنسبة ذكور إلى إناث ١:١,٦ ولوحظ أن عدد المرضى يزداد بتقدم العمر. متوسط عمر المرضى الذكور كان ١٢,٢±٥٨,٧ سنة. ومتوسط عمر الإناث كان ١٢,٣±٦١,١ سنة.

أكثر الأسباب شيوعاً لالتهاب الكبد الاقفارى كان الصدمة الدورية بنسبة ٥٤,٦ ٪. من بينها الصدمة القلبية بسبب نقصان الوظيفة الانقباضية للبطين الأيسر كانت النوع الأكثر شيوعاً ٨٠,٣ ٪.

الاعراض الأكثر انتشاراً بين المرضى كانت القيء، ألم الجزء الأعلى الأيمن من البطن وتضخم الكبد.

الفحص المخبرى المميز لحالات التهاب الكبد الاقفارى هو ارتفاع نسبة ناقل الأمين اسبارتات الى ناقل الأمين الانين (١,٧). وانخفاض فى نسبة ناقل الأمين الانين الى نازع هيدروجين اللاكتات (٠,٩) بلغ عدد وفيات حالات الكبد الاقفارى ٦٦,١ ٪.

الاستنتاج: التهاب الكبد الإقفارى حالة يجب توقعها فى مرضى الحالات الحرجة ويجب الكشف المبكر لاحتمالية الإصابة بها فى مرضى اختلال الدورة الدموية والتنفسية. وسرعة علاج أسباب المرض لمنع الفشل العضوى المترافق مع التهاب الكبد الاقفارى.