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Research Article

Fulminant Hepatic Failure

Pediatric Fulminant Hepatic Failure: Systematic Review

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Abstract: Fulminant hepatic failure FHF in children is a rare but often fatal condition. Our understanding of this disorder is limited due to the disorder's rarity. The majority of FHF cases in children have no known cause. The mechanisms by which hepatocytes undergo cell death are unknown. The aetiology and degree of CNS involvement influence the outcome. The study aims to summarize current evidence on the prevalence, risk factors and management approaches of irritable bowel syndrome in Saudi Arabia. For article selection, the PubMed database and EBSCO Information Services were used. All relevant articles relevant to our topic and other articles were used in our review. Other articles that were not related to this field were excluded. The data was extracted in a specific format that the group members reviewed**.** Seven studies were included and affirmed that mortality of fulminant hepatic failure is high, and the commonest aetiology is viral infections, particularly HAV. The peak level of total serum bilirubin, the rate of change of the prothrombin time/daily and ammonia level were significant predictors of mortality.

Keywords: Hepatic Failure, Fulminant Hepatic Failure, Hepatic Encephalopathy and Liver Failure

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1. INTRODUCTION

Fulminant hepatic failure is a sickness characterized by significant hepatocyte malfunction. Fulminant hepatic failure is diagnosed when encephalopathy occurs within eight weeks of the development of clinical illness in the absence of clinical evidence of chronic liver disease. FHF (fulminant hepatic failure) denotes the lack of pre-existing liver disease. Hepatic encephalopathy, complex coagulopathy, derangements of intrahepatic metabolic pathways, consequences of renal dysfunction, cerebral oedema, susceptibility to infection, and hemodynamic abnormalities are all symptoms of hepatocyte malfunction. Traditionally, FHF was defined as the development of hepatic encephalopathy within eight weeks of the first signs of illness without a history of underlying liver disease [1]. FHF is further divided into Hyperacute liver failure in cases where encephalopathy occurs within seven days of jaundice onset, Acute liver failure (ALF) for instances with an 8-28-day interval, Subacute liver failure in patients who develop encephalopathy between 5-12 weeks of the beginning of jaundice.[2]

1.1 Follow Up and Management

It was found that patients with the most rapid onset of encephalopathy have the best chance of spontaneous recovery, despite a high incidence of cerebral oedema. This observation has also been seen in children. Children surviving FHF without transplant were admitted to the hospital sooner after the onset of illness than non-survivors and experienced prompt transfer to a transplant centre [3]. A difference is made in neonates less than 30 days old between neonatal liver failure that develops in utero and that which appears to develop throughout the perinatal period [4]. The liver's metabolic functions are disrupted in cases of severe hepatocellular damage. Patients have poor glucose homeostasis, increased lactate production, impaired coagulation factor synthesis, and a diminished ability to remove medications, toxins, and bilirubin. As a result, patients suffer coagulopathy, hypoglycemia, and acidosis, increasing their risk of gastrointestinal bleeding, seizures, and cardiac failure. Bacterial and fungal infections frequently complicate ALF. Bacteria can enter the systemic circulation from the stomach due to reduced hepatic macrophage cell function or the catheter and endotracheal tube insertion[5-8].

1.2 Etiology

There are many causative agents and predisposing factors of FHF. Infections such as Cytomegalovirus, Epstein–Barr virus, echovirus (types 6, 11, 14, 19), Hepatitis B, Herpes simplex virus and Syphilis. Also, Metabolic causes such as Galactosemia, Hereditary fructose intolerance, Hereditary tyrosinemia, Mitochondrial disease, Neonatal hemochromatosis, Niemann–Pick disease type C, Zellweger syndrome, Autoimmune hepatitis and sickle-cell disease. Toxin like Aflatoxin, Amanita, phalloides, copper intoxication and iron [9-14].

1.3 Renal Disturbances

Abnormalities in plasma electrolytes as hypernatraemia occurred from an osmotic diuresis precipitated by hypertonic dextrose or fructose given intravenously, and from the sodium in the fresh frozen plasma used to correct the coagulation disturbance when renal excretion of this ion was inappropriately low.

1.4 Cardiogenic Effects

Cirrhosis-related heart problems include hepatopulmonary syndrome, portopulmonary hypertension, pericardial effusion, cirrhotic cardiomyopathy, and noncirrhotic cardiac abnormalities such as high-output failure induced by intrahepatic arteriovenous fistulae.

1.5 Study Objective

The study aims to summarize current evidence on the prevalence, risk factors and management approaches of Fulminant hepatic failure.

2. METHODS

In this systematic review, we were enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement was used.

2.1 Study Design

A systematic review of the current evidence on Fulminant hepatic failure is considered a robust way of identifying and synthesizing the peer-reviewed articles for evidence in this area to define a cohesive empirical research agenda that builds on prior knowledge. This review included qualitative evidence only to produce an interpretation. Further, a synthesis of qualitative data aims to generate findings that are meaningful, relevant and appropriate to individuals, to inform a research agenda and ultimately to more effectively influence policy and practices on Fulminant hepatic failure. The review used methods of qualitative synthesis to combine, integrate and interpret, where possible, the evidence from the included papers. The review aims to move beyond the aggregation of available data to provide further interpretive insights into Fulminant hepatic failure and define where future research can add to what is known.

2.2 Study Eligibility Criteria

The review included qualitative peer-appraised studies. Qualitative data from mixed methods studies was screened for inclusion and included if the qualitative element was pertinent. All peer-reviewed articles published in English, reporting prevalence and risk factors of Fulminant hepatic failure from the patient, family, healthcare worker perspective and healthcare delivery system were included. Studies published from January 2012 up to August 2021 only were included to ensure the currency of the work while enabling a broad view of the emerging issues to be identified.

2.3 Study Participants

The review included all studies that report on Fulminant hepatic failure from the perspective of all patient categories (adults and children), families and health workers that we came across in the studies on Fulminant hepatic failure.

2.4 Study Inclusion and Exclusion Criteria

The articles were selected based on their prelevance to the project. The English language and geographical restrictions to

Saudi Arabia were considered. All other articles which do not have one of these topics as their primary end or repeated studies and review studies were excluded. The reviewers excluded any studies not available in English, conference abstracts, books or grey literature and editorial comments. Studies reporting only qualitative data were excluded.

2.5 Search Strategy

A systematic search strategy was developed using a combination of Medical Subject Headings (MeSH) and controlled vocabulary to identify peer-reviewed articles on Fulminant hepatic failure. The databases were PubMed/MEDLINE, Scopus/Embase (Elsevier), EbscoHost, and Google Scholar. The search was limited from January 2012 to August 2021.

2.6 Selection of Study

The ENTREQ guidelines for reporting systematic qualitative reviews were used to demonstrate the selection processes and results. All retrieved studies were initially imported into the Endnote library to assist in removing duplicates. After removing the duplicates, the Endnote library was shared between the two reviewers to independently screen the articles by title and abstract, guided by the eligibility criteria. The studies that the two reviewers would have agreed on were subjected to a full-text review. A third reviewer was adjudicating any discrepancies between the two reviewers. The two reviewers independently reviewed the full text of all eligible studies. Regarding differences between the two reviewers, a consensus was sought through discussion on the differences with the third reviewer. Finally, the full texts of all relevant studies found to meet the inclusion criteria were retained for the final framework synthesis.

2.7 Data Extraction

Two reviewers independently extracted data from eligible studies onto a customized data extraction form and populated it with variables about the study population and phenomena of interest. The third review author double-checked and verified extracted articles. Study characteristics that were extracted included the name of the first author and year of publication, data collection period and region in which the study was conducted. Specific details, including the study design, population, sample size, sampling procedures and data collection procedures, will then be captured. In addition, the prevalence and risk factors of Fulminant hepatic failure were systematically identified.

2.8 Data Synthesis and Analysis

No software was utilized to analyze the data. Instead, the reviewers sorted the data by theme and presented the themes in the form of an analysis table (chart). The columns and rows of the table reflected the studies and related themes and enabled us to compare the findings of the studies across different themes and subthemes.

2.9 Mapping and Interpretation

The reviewers used charts to define the identified concepts and map the range and nature of the phenomena. The review explored associations between the themes to help clarify the findings. The review was mapped and interpreted findings in line with the review objectives and emerging themes.

3. RESULTS

Table 1

Author (ref)	Year	Participant	Method of the study	Out Come
15	2020	Forty-seven children (2-16 years old) were registered with FHF.	Cross-sectional	Hepatitis A was the most prevalent cause (15- 32%), with infections complicating 64% of cases. In addition, 12 children (25%) had SR, while 28 (60%) had PO. PO was established by univariate analysis, which revealed an unclear aetiology, hepatic encephalopathy, infection, and acute kidney damage. In multivariate regression analysis, only the PELD score with a threshold of 32 predicted PO.
16	2020	Twenty-four patients less than 17 years old were reviewed retrospectively.	retrospective	the age group of the patients presented with FHF was 4-6 years. Males were affected more than females. Viral hepatitis was the commonest aetiology. The aetiology of FHF in 14 out of 24 of the children was viral hepatitis; HAV was the cause in 50% of them, 12.5% of patients had autoimmune hepatitis, and one patient who got HCV hepatitis at the same time had survived. One patient got coinfection with HAV and CMV. The mortality rate was 75% among patients in this study.
17	2009	Fifteen children with FHF were included retrospectively in this study.	retrospective	Twelve patients had liver biopsies. The patients were divided into three groups depending on the onset of hepatic encephalopathy. Hepatitis A in 4 patients, non-E hepatitis in 4, mushroom poisoning in 3, fulminant Wilson's disease in 2, autoimmune hepatitis in 1, and both hepatitis B and toxic hepatitis (with leflunomide treatment) in 1 patient were detected. Diffuse reduction in hepatic attenuation in 11 patients. Histopathologic evaluation of liver biopsies showed massive hepatic necrosis, inflammatory cell infiltration and ductular proliferation in 8 patients, oedema of gallbladder wall in 5, regenerating nodules and fibrous septa consistent with the cirrhotic

				pattern in 2, and regenerating nodules and necrotic areas in 2 patients.
18	2015	A total of 46 children with FHF were included.	Cross-sectional	22% had Autoimmune FHF, 43% had indeterminate FHF, and 16 had another diagnosis. The mean follow-up time was 4.6 years. AI-FHF and ID-FHF differed for the presence of autoantibodies, immunoglobulin G level, the median age at diagnosis and alanine aminotransferase level. Liver histology did not allow the differentiation between the two conditions. Among the patients with AI-FHF, 4/9 who received steroids recovered; 5/9 required liver transplantation and one died awaiting treatment.
19	2020	There were 28 patients in this retrospective observational study , which included 17 males and 11 females with a mean age of 6- 9 years	retrospective	The most common etiologies were Hepatitis A, 29% in isolation or coinfection with Wilson Disease, and typhoid fever. It was followed by seronegative hepatitis at 29%. The majority, 64%, had acute presentation 7 to 28 days, jaundice 82% being the most common symptom. The severity of encephalopathy was significantly associated with outcome p=0.02. There 21% of patients succumbed to death.
20	2021	25 patients were identified in a cross-sectional study, with 56% females	retrospective	84% of patients had AIH-1, 4% had AIH-2, and 12% had autoimmune sclerosing cholangitis (ASC). An insidious course was found in 84% of cases. Acute hepatitis and fulminant hepatic failure were found to be very rare. 32% had cirrhosis at diagnosis. 80% had complete remission following therapy. The median follow-up period was 45 months. There was no mortality, and only one patient was referred for a transplant. Thus, the transplant-free survival was 96%.
21	2020	11-year-old boy	Cross-sectional	pt presented to the emergency department for fever, icterus, and abdominal pain that had started seven days earlier. No past medical history of chronic liver disease. He spent one month in quarantine owing to the COVID-19 outbreak, ten days before admission. Upon admission to the emergency room, the Glasgow Coma Scale (GCS) was 7–8 and he had active gastrointestinal and nasal bleeding. Thus, immediately after arrival, pt was transferred to (ICU) where he underwent mechanical ventilation. He was then transferred for liver transplantation.

Fulminant hepatic failure is a hepatocyte malfunction that lacks pre-existing liver disease. FHF has many causes, such as cytomegalovirus, Epstein-Barr virus, echovirus, HBV, HSV, and toxins and metabolic errors [9-14]. Autoimmune FHF has the highest prevalence, 84%, among other causative agents [20]. Determinate FHF prevalence 43% [18]. Hepatitis A prevelanceprevalence 15% [15]. Post covid infection 11-year-old boy was admitted with hepatic failure with no history of hepatic manifestation[21]. The mortality rate of fulminant hepatic failure prevalence was recorded at 75% of 24 patient[s16]. Liver biopsies were studied to show the tissue changes during the diseases [17]. Liver transplantation remains the only possible solution in patients with advanced levels of coagulopathy and coma. Delayed referrals to institutions with liver transplantation capabilities are a primary cause of higher mortality in these patients [19]. The severity of hepatic encephalopathy ranges from I to IV. It develops within three weeks after the onset of symptoms In 88% of children. In several ALF series, survival directly correlates with the degree of encephalopathy, with 60% survival with grade I disease declining to 5-25% with grade IV disease Children with FHF proceed rapidly through the phases of encephalopathy.

4. DISCUSSION

A fulminant hepatic failure is a life-threatening event in which coagulopathy frequently precludes a liver biopsy, which is the gold standard for diagnosing AIH. The picture is muddled further by the fact that autoantibodies may be negative at presentation, and anti-nuclear autoantibodies (ANAs) and smooth muscle autoantibodies (SMAs) can be positive even in individuals with diverse aetiologies of liver disease[5]. Fulminant hepatic failure (FHF) aetiology in children may be determined in roughly half of the cases, while the disease remains undetermined in the other half. The autoimmune aetiology, in particular, may be underappreciated. Children may be determined in roughly half of the cases, while the disease remains undetermined in the other half. The autoimmune aetiology, in particular, may be underappreciated. It is also a reversible cause of FHF[7, 8]. Acute viral hepatitis A is the most common cause of fulminant hepatic failure. Coinfection with Hepatitis A and Wilson illness was observed in the patient, as was Hepatitis A coinfection with Typhoid fever. This observation emphasizes the importance of maintaining a low threshold and screening individuals for additional co-existing etiologies in addition to hepatitis A. In Indian adults, Hepatitis E is the most common cause. One patient was diagnosed with CMV hepatitis. Infectious causes account for half of all causes. Patients with seronegative (non-A, non-E) hepatitis were the second most common cause. The patient had Dicarboxylic aciduria and Wilson disease as metabolic reasons. Drugs Valproate toxicity was observed, contrasting Western literature, where acetaminophen toxicity is the most common cause[22]. The clinical spectrum of presentation varies from an asymptomatic elevation of liver enzymes with typical positive immunological markers to severe forms of advanced chronic liver disease, acute hepatitis, and fulminant liver failure. Asymptomatic patients are diagnosed when evaluated for abnormal liver enzymes. [23] Other patients present with either no specific symptoms or only abdominal pain. Jaundice, the most frequently reported presentation, has been observed in more than 50% of Saudi patients. Chronic presentations were

seen in 37.7% of Saudi patients, while cirrhosis with or without decompensation has been reported in 28.8–45.5% of patients. Another uncommon presentation involves cholestatic but not the hepatocellular elevation of liver enzymes, which raises the possibility of other cholestatic liver diseases[19]. The degree of encephalopathy was found to be significantly related to mortality. This pattern has also been seen. Prothrombin time and INR were shown to be unrelated to the outcome. A similar result has been reported in research[23, 24]. Despite specialized therapeutic options for unique orthotopic etiologies, liver transplantation is the only therapy that has been shown to enhance survival in the majority of patients with fulminant hepatic failure. The outcome is influenced by complications such as severe coagulopathy, infection, renal dysfunction, or elevated intracranial pressure. The choice to transplant is based on the likelihood of spontaneous liver recovery, which various parameters can determine. The degree of encephalopathy, the patient's age, and the underlying aetiology of hepatic failure is the most critical criteria for determining the need for transplantation during fulminant hepatic failure. Because of our patient's early fulminant hepatic failure, the only therapy choice was liver transplantation; nevertheless, due to the disease's progressive course and quick advancement to stage 4 with encephalopathy and brain death, he passed. [6, 19, 23]

4.1 Pathophysiology of Intracranial Hypertension in FHF

Normal intracranial pressure (ICP) ranges from 5 to 10 mmHg, whereas intracranial hypertension occurs when ICP surpasses 20 mmHg. A transtentorial herniation is the most common consequence of severe intracranial hypertension in FHF patients. This herniation may cause posterior cerebral artery compression, resulting in infarction of the medial temporal, thalamic, and occipital lobes; cerebral aqueduct and subarachnoid space compression, resulting in obstructive hydrocephalus; and brain stem compression, resulting in brain stem ischemia, haemorrhage, and death. Furthermore, significant intracranial hypertension impairs cerebral perfusion pressure (CPP). CPP is the difference between mean artery pressure (MAP) and cerebral venous pressure (CVP). Because ICP approximates cerebral venous pressure, CPP equals MAP minus ICP. An increase in ICP lowers CPP, resulting in a decrease in cerebral blood flow (CBF). This decrease in CBF may result in cerebral ischemia or infarction, causing neurological impairments in FHF survivors.

4.2 Extracorporeal Liver Support Therapy

Extracorporeal Membrane Oxygenation (ECMO) was created to keep a patient alive during severe cardiopulmonary collapse until native organ function could be restored. The initial concept for an extracorporeal liver support device included this design. Because the remarkable ability of healthy liver tissue to regenerate itself was well recognized, early liver support techniques were geared at providing short-term assistance to allow the organ time to recover. Due to the liver's diverse tasks, which include metabolic regulation, protein synthesis, and detoxification, early methods concentrated on combining synthetic support with detoxification and regulation using a cell-based platform. Exchange transfusion and cross-circulation with both human and ape species were among the early methods. Later, two distinct techniques emerged, one aiming at creating cell-based bioartificial intelligence and the other at developing a cell-based bioartificial support system. The other is devoted to cell-free medical gadgets. The Berlin Extracorporeal Liver Support System, which consisted of a three-dimensional, hollow fibre perfusion device containing primary porcine or human liver cells,18 the Extracorporeal Liver Assist Device, which consisted of a hollow fibre bioreactor filled with human hepatoma cells (C3A),19,20 and the Bioartificial Liver,21 were forerunners in the development of bioartificial liver support systems that made it into systematic clinical tests. All bioartificial, cell-based liver assist devices are currently undergoing pre-marketing clinical trials and are not commercially available to critical care therapists; therefore, this chapter will not focus on them. Concurrently, cell-free methods for renal failure are used in early blood detoxifying research. Hemodialysis and hemofiltration,22,23 hemoperfusion and plasma-perfusion 24, and plasma exchange treatment were all clinically tested milestones in developing cell-free liver support systems. 25 Except plasma exchange, none of the approaches in isolation are now regarded as first-line treatments for liver support. In short, dialysis and filtration were found to be ineffective at removing toxins with a high affinity for albumin, which plays a significant role in the development of secondary complications of liver failure, whereas hemo- and plasma-perfusion therapies were more effective but were also associated with significant complications, such as loss of valuable homeostatic substances, inflammation, and altered coagulation factor levels.

4.3 The spectrum of Liver Damage

HCV infection can develop from a carrier state with no hepatic pathology to fast-advancing chronic active hepatitis and cirrhosis. In the non-dialysis population with HCV, liver biopsy has been acknowledged as the gold standard for predicting disease progression and response to therapy. A low baseline HCV RNA level and mild liver disease in HD patients were reported to be favourable prognostic markers for sustained virological and biochemical responses to interferon. HCV infection and biopsy-proven cirrhosis were discovered to be independent predictors of 10-year survival in renal transplant recipients. [26] The sensitivity of serum aminotransferases in reflecting liver injury in HD patients is still debated. Most investigations found no association between liver biopsy findings and blood aminotransferase levels in HD patients. Aminotransferases were within normal values in most patients with histologically active hepatitis. This observation was explained by the fact that normal aminotransferase ranges were lower in dialysis patients. It was discovered that ALT levels of more than 40 U/L resembled liver histological abnormalities in 68.7% and 50% of patients with high-grade portal and lobular necroinflammatory activity, respectively. When we raised the upper range aminotransferases to 30 U/L, these variations became more pronounced for ALT levels.[27]

5. CONCLUSION

Seven studies were included and affirmed that mortality of fulminant hepatic failure is high, and the commonest aetiology is viral infections, particularly HAV. The peak level of total serum bilirubin, the rate of change of the prothrombin time/daily and ammonia level were significant predictors of mortality. Therefore, liver transplantation is the appropriate treatment for the disease.

6. AUTHOR CONTRIBUTION STATEMENT

Dr. Ahmed Abdelsamie Fadl conceptualized and designed the study. Dr. ALMUTHAYBIRI,MUSAAD MASOUD A and Dr. KABRAH, LAMA KAMAL and Dr. ASSIRI, AMJAD ABDULLAH H searched data bases for literature review. Dr. ALAHMADI, KHALID MOHAMMED M and Dr. Yousra Bala Babkir Abd Alla and Dr. Yassir Mohammed Darwish screened and filtered selected studies. Dr. Mohammed Ali Alaamree and Dr. Ahmed Faroug Ahmed Abdelaal wrote the manuscript. Dr. Norah Sulaiman Aljabarah and Dr. Amaal Abdulrahman Alwayli revised the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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