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COMPLICATIONS ASSOCIATED WITH HEPATOCELLULAR FAILURE: AN INTEGRATIVE LITERATURE REVIEW

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Abstract: INTRODUCTION: Hepatocellular insufficiency syndrome corresponds to the chronic and decompensated form of liver disease. The affected patient has clinical signs of hepatic and systemic dysfunction related to a terminal cirrhotic stage. Knowing the clinical complications related to Hepatocellular Insufficiency Syndrome is an important point for the therapeutic management of this condition, as it guarantees the provision of more assertive medical care capable of increasing patient survival. METHODOLOGY: This research project proposes to carry out an integrative review of the literature on complications related to Liver Failure Syndrome. This present study begins by asking: What are the main complications of Chronic Liver Failure? The articles gathered that could answer the generating question were consulted through online databases with references from 2017 to 2023, from PUBMED, Virtual Health Library (VHL) and, finally, the Scientific Electronic Library Online (Scielo). As a guiding mechanism for this search, the following descriptors were used: liver, liver failure and morbidity. RESULTS: The importance of studies that provide guidance on the clinical complications of hepatocellular failure is remarkable because early recognition of these conditions offers the patient a chance of a therapeutic approach before terminal stages of liver failure are reached.
Keywords: Liver, Liver failure, Morbidity.

INTRODUCTION

The physiological functioning of the human body requires the multifunctionality of the liver (SILVERTHORN, 2017). Liver function has been narrated since the beginnings of humanity and medicine, when Greek theater mentioned the liver's ability to regenerate as a punishment for Prometheus, who after revealing the secret of fire to mortals, was punished by Zeus: chained on

Mount Caucasus, every day a vulture fed on part of Prometheus' liver, but the organ promptly regenerated, making Prometheus' torment eternal. For the Babylonians and Assyrians, the history of medicine points out that the liver was considered the Seat of Life and therefore would be the organ through which the gods and demons exercised their interference in the social conduct and health of individuals (DE CASTRO; JÚNIOR; DA SILVEIRA, 2013).

As science advanced, studies on liver functionality gained strength. It is currently known that the liver is the second largest organ in the human body, being responsible for the biosynthesis and metabolism of several compounds essential to human homeostasis. In addition to its exocrine function, participating in digestion through the secretion of bile salts, the liver regulates, stores and processes various substances (SILVERTHORN,2017). This broad function is explained by the characteristic vascularization of the organ: the liver receives arterial blood, like all other organs and tissues, but it also receives all blood from the intestines through the portal vein. With this, the liver becomes capable of eliminating toxins and coordinating intermediary metabolism.

Furthermore, due to the specific microarchitecture of the liver, hepatocytes are also capable of producing plasma proteins, metabolize bilirubin and form bile (MCPHEE; GANONG, 2018).

Knowing the importance of hepatic metabolism, it is clear to say that organ dysfunction is an important health condition. Liver dysfunction encompasses a set of pathologies, such as liver cirrhosis, hepatocellular carcinoma, non-alcoholic fatty disease, viral hepatitis, among others (PAREDES, 2019). Liver diseases account for a mortality rate that varies between 2 and 3 million people per year. Globally, patients with liver disease experience acute complications related to liver cirrhosis, the virulence of hepatitis and complications of hepatocellular carcinoma. Furthermore, alcohol abuse increases the risk of developing alcoholic liver disease. It is worth noting that other metabolic diseases are also important causes of liver dysfunction, as obesity and diabetes are major causes of non-alcoholic liver disease (GOLDMAN; SCHAFER, 2018).

Liver diseases are distributed heterogeneously worldwide. Factors such as gender, ethnicity, race, geographic region and social level directly affect the way in which the causes of liver dysfunction affect the population (PAREDES, 2019). It is worth noting that progressive liver damage that lasts for a period of more than 6 months, with changes in the synthesis of clotting factors and other proteins, added to the release of toxins and harmful products derived from the metabolism and excretion of bilirubin (in particular, ammonia), define chronic liver disease (IILDA, 2005).

Chronic liver disease, also called Liver Failure Syndrome (SIH), is an important cause of morbidity and mortality. SIH is characterized by its insidious evolution. Microscopically, it is a progressive loss of liver architecture, with successive cycles of loss and regeneration of the parenchyma (MCPHEE; GANONG, 2011). As a result of this process, there is the formation of fibrotic plaques in the liver parenchyma, in addition to the beginning of an angiogenesis process and sustained deposition of the extracellular matrix, followed by the formation of regeneration nodules. These changes are pathognomonic hallmarks of chronic liver dysfunction (GOLDMAN; SCHAFER, 2018).

In general, Liver Failure Syndrome has a difficult early diagnosis. The first symptoms appear when the patient is already with an advanced level - and difficult to treat - of liver fibrosis. It is common for complications of

SIH to appear as the main causes of demand for health services, highlighting in this context hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome and hepatic heart disease (MAIO.; DICHI.; BURINI, 2000). This study, therefore, aims to analyze the main complications associated with hepatocellular failure in scientific publications.

METHODOLOGY

The present work was developed through an integrative literature review. This type of approach consists of a form of research capable of synthesizing information about existing studies that deal with the topic proposed by the study. Within health practices, literature review is an important instrument for gathering scientific evidence that can guide care practices (SOUZA; SILVA; CARVALHO, 2010).

The criteria used to construct this integrative review was the selection of articles published between 2018 and 2023, written in Portuguese and English. Research that did not evaluate complications of Hepatocellular Insufficiency, other integrative or systematic literature reviews, incomplete, repeated or non-scientific articles were not included in this Integrative Review.

The study began by asking: What are the main complications related to Chronic Liver Failure? The articles gathered that answered this generating question were consulted through online databases with references from 2018 to 2023, through PUBMED, Virtual Health Library (VHL - LILACS) and, finally, the Scientific Electronic Library virtual library Online (Scielo). As a guiding mechanism for this search, the following descriptors were used: liver, liver failure and morbidity, using the Boolean operator "AND". In this context, 08 articles were selected, with the aim of elucidating the best evidence about SIH. Data analysis resulted in the construction of tables 1, 2 and 3 - which present the inclusion and exclusion criteria, in addition to the year of publication, methodology and results achieved by the selected studies.

STEPS	DESCRIPTORS	SCIELO	LILACS	PUBMED
1	LIVER and HEPATIC FAILURE	50	83	3
2	LIVER and MORBIDITY	61	132	0
3	LIVER FAILURE and MORBIDITY	12	19	0
4	LIVER and LIVER FAILURE and MORBIDITY	7	10	0
	TOTAL	130	244	3

TABLE 1: Articles found in the databases selected by crossing the proposed descriptors. Jaboatão dos Guararapes, 2023

Source: ALBUQUERQUE; LEFOSSE (2023)

JUSTIFICATION	SCIELO	LILACS	PUBMED	TOTAL
Articles that did not evaluate complications associated with hepatocellular failure	50	172	2	224
Incomplete	6	0	0	6
Not scientific in nature	2	7	0	9
Systematic and integrative reviews	0	0	0	0
Texts that are not written in English or Portuguese	22	37	0	59
Publication period prior to the last 5 years	39	15	0	54
Repeated	7	10	0	17
TOTAL EXCLUDED	126	241	2	369
TOTAL INCLUDED	4	3	1	8

TABLE 2: Justifications for excluding articles based on the proposed criteria. Jaboatão dos Guararapes, 2023.

Source: ALBUQUERQUE; LEFOSSE (2023)

Authors, place and year of publication	Objective	Kind of study	Result
FLAMM, SL **United States, 2018.**	To analyze theprevalence inHepatic Encephalopathy in patients from theprimary care withdiagnosis in Chronic Liver Failure.	Retrospective Cohort	70% of patients participating in the study, with a previous diagnosis of cirrhosis, developed a clinical picture compatible with hepatic encephalopathy.
HASAN, Irtiza; RASHID, Tasnuva; CHIRILA, Razvan M. **Romania, 2021.**	Clarify new indications regarding to themanagement clinicalin patients hospitalized with diagnosis inHepatorenal Syndrome.	Retrospective Cohort	Hepatorenal Syndrome is a serious course of liver failure that presents a mortality rate of more than 50% in hospitalized patients with a previous diagnosis of cirrhosis and AKI.
JACQUES, RDOC; MASSIGNAN, LDS; WINKLER, MS; BALBINOT, LOL; BALBINOT, SS; SOLDERA, J. **Brazil, 2021.**	To analyze if thedefinition in chronic liver failure is able in predict mortality in cirrhotic patients withPeritonitis	Retrospective Cohort	The prevalence of Chronic Liver Failure was 58% in study patients diagnosed with SBP. The absence of Chronic Liver Failure and low CLIF-SOFA and MELD scores were independently associated with longer survival at intervals of 28 and 90 days.
	Spontaneous. Bacterial.		
MOCELIM, CD; ROCHA, MR; PACHECO, MP; BISSOLI, F. **Brazil, 2019.**	To assess if the routine performance from the arterial blood gas analysis in all cirrhotic patients it can be replaced by pulse oximetry alone to screen for Hepatopulmonary Syndrome.	Observational Study	HPS is a complication of liver failure that places the patient as a candidate for liver transplantation. Early diagnosis, through HPS screening, advances the process.
OLIVEIRA, JCD; CODES, L.; LUCCA, MMFBD; SOARES, MAP; LYRIO, L.; BITTENCOURT, PL **Brazil, 2022.**	To assess The frequency It is gravity ofliver involvement in hospitalized pregnant women in unit in intensive therapy with pre-eclampsia/eclampsia It isto assess the influence in maternal outcomes, It is adverse fetal outcomes.	Retrospective Cohort	Abnormalities in liver enzymes were observed in 49% of subjects, generally less than five times the upper limit of normal. There was no correlation between mean liver enzyme levels and maternal and fetal outcomes.
NARASIMMA, M.; HERNAEZ, R.; CERDA, V.; LEE, M.; SOOD, A.; YEKKALURI, S.; SINGAL, AG **United States, 2023.**	Measuring psychological harm to patients with cirrhosis It is Hepatocellular carcinoma in surveillance stage.	Prospective Cohort	Patients reported apprehension, anxiety and emotional distress related to Hepatocellular Carcinoma surveillance.
PEREIRA, R.; BAGULHO, L.; CARDOSO, FS **Brazil, 2020.**	Characterize a cohort inpatients withacute chronic liver failure in unit in intensive care and analyze risk factors from the global mortalityl.	Retrospective Cohort	Regarding the number of organ failures in patients participating in the study, 4.2% had organ failure; 42.3%, two bodies; 32.4%, three bodies; 16.9%, four bodies; and 4.2% five bodies. Liver transplantation was performed in 15.5% of patients. The mortality rate for 28 days was 56.3%, and the mortality rate in the therapy unit intensive was 49.3%.
REZENDE, IFB; CONCEÇAO-M ACHADO, MEP; SOUZA, VS; SANTOS, EMD; SILVA, L.R. **Brazil, 2020.**	Investigate The occurrence in sarcopenia inchildren It is adolescents with chronic liver diseases.	Case series	Sarcopenia was identified in 40% of patients, 54.1% had a deficit in muscle strength and 50.6% a deficit in muscle mass in pediatric patients at a public reference institution for chronic liver disease.

TABLE 3: Main results found in the selected articles about complications related to Hepatocellular Insufficiency. Jaboatão dos Guararapes, 2023.

Source: ALBUQUERQUE; LEFOSSE (2023)

RESULTS

After screening the articles capable of answering the research question, TABLE 3 was formulated with a summary of the selected studies in order to visualize the arrangement of the following variables of each study: authors, location, year of the study, objective of the study. study, type of study and main results collected. The results obtained through this analysis resulted in the construction of this present integrative review article to be presented for scientific publication.

DISCUSSION

The liver is the largest organ in the human body, corresponding to approximately 1.5 to 2.55 kg of lean body mass. Regarding hepatic architecture, the presence of hepatic polygons formed by small lobes that contain the centrilobular vein, more centralized, and portal spaces, located at the polygonal vertices, is recorded. In turn, each portal space corresponds to the portal triad (a venule - branch of the portal vein, an arteriole - branch of the hepatic artery and a bile ductule) (TORTORA.; DERRICKSON, 2016). This system is covered by endothelial and phagocytic cells that make up the hepatic sinusoids, where metabolic exchanges in the liver occur (IILDA, 2005).

Patients with chronic liver disease are characterized by the progressive loss of this structural and metabolic functionality of the liver parenchyma (PAREDES, 2019). Regarding the progression of the disease, many affected patients initially develop a clinical form that is not very symptomatic and permeated by non-specific symptoms, such as nausea, vomiting and pain in the right hypochondrium (MCPHEE; GANONG, 2018).

With the passage of time and continued exposure to environmental factors responsible for the onset of liver failure, the affected patient reaches a "cirrhotic" state, that is, a chronic and irreversible level of liver failure (MARTINELLI et al., 2003). The first phase of this condition is called "compensated" because the body responds to aggressive stimuli, ensuring that there is no portal hypertension and liver failure. It is known that 5.5 to 7% of compensated cirrhotic patients progress to the "decompensated" phase, where the complications associated with liver failure syndrome begin to appear. At this stage, the average patient survival is 1.6 years (GOLDMAN; SCHAFER, 2018).

Hepatocellular insufficiency syndrome corresponds to the chronic and decompensated form of liver disease. At this stage, the affected patient has clinical signs of hepatic and systemic dysfunction related to a terminal cirrhotic stage (SANTOS, 2001). Knowing these symptoms is an important point for the therapeutic management of liver failure syndrome because it guarantees the provision of more assertive medical care that can increase the patient's survival (SILVA, 2010).

An important systemic alteration found in chronic liver disease is hepatic encephalopathy (HE). This condition is characterized by neurological impairment secondary to the process of liver failure (SANTOS; COSAC, 2020). The clinical picture of HE is a consequence of the accumulation of toxins, most commonly ammonia, which reaches the general circulation without being purified by hepatic metabolism (OLIVEIRA, 2017). Under physiological conditions, the liver is capable of metabolizing ammonia into urea and glutamine so that it can be eliminated through feces and urine, which does not occur in chronic liver dysfunction. The result of this liver metabolism failure is the accumulation of arterial ammonia, resulting in neurological symptoms (FERREIRA et al., 2012).

Studies by Flamm (2018) indicate that 70% of cirrhotic patients followed up in a primary

health care unit, in a retrospective cohort, were diagnosed with hepatic encephalopathy. The clinical signs of this condition are non-specific and variable, ranging from states of mental confusion to serious developments, such as comatose stupor. It is known that gastrointestinal hemorrhages are the most common precipitating factors, which may be related to their higher prevalence in the group of cirrhotic patients due to the pathophysiology of the underlying disease. Flamm (2018) further explains that early diagnosis is capable of reducing the number of brain damage in affected patients.

Regarding renal repercussions, it is worth highlighting hepatorenal syndrome as a consequence of an advanced cirrhotic process. This context is justified by the fact that patients with chronic liver disease accumulate dilating agents in the systemic circulation. This occurs as a result of the release of pro-inflammatory cytokines (TNF-ALFA and IL-6) that act on mesenteric lymph nodes and endothelial tissues, stimulating them to secrete endogenous nitric oxide and cannabinoids (MCPHEE; GANONG, 2018). This phenomenon is responsible for the decrease in effective circulating volume and a state of arterial hypotension.

In response, the organism promotes vasodilation of the splenic bed, capable of generating a condition of relative hypovolemia and, consequently, resulting in poor perfusion and acute pre-renal insufficiency (GOLDMAN; SCHAFER, 2018), which can be classified as: a) type I, renamed SHR-AKI, which is more prevalent; and b) type 2, SHR-CKD, which occurs in 25% of cases. In accordance with the evidence from Hasan et al. (2018), hepatorenal syndrome is a serious complication of hepatocellular failure as it is related to mortality rates above 50% when analyzing hospitalized patients with a previous diagnosis of cirrhosis and Acute Renal Failure.

The exacerbation of endothelial vasodilatory mechanisms also promotes pulmonary repercussions. In general, pulmonary capillaries are small in diameter so that there is maximum proximity between the alveoli and the red blood cells, ensuring an effective exchange surface (GARCIA et al., 2007). Patients with chronic liver failure have dilated pulmonary capillaries, making hematosis difficult within a process that simulates a right-to-left shunt. As a consequence, we have hepatopulmonary syndrome (HPS), characterized by a decrease in the effective volume of circulating air, compensatory hyperflow, platypnea and orthodeoxia (NACIF et al., 2014).

Patients diagnosed with HPS are candidates for liver transplantation. Early diagnosis of this condition benefits the patient as it speeds up the donation-transplant process. Thus, in line with the data Mocellin et al. (2019), arterial blood gas analysis is essential in the screening of cirrhotic patients to avoid late diagnoses of HPS, regardless of the patient's functional class. Studies by the same author indicate that screening must be carried out through geometric studies and cannot be replaced by the use of pulse oximetry.

Another important systemic complication associated with insufficiency hepatocellular is cirrhotic cardiomyopathy. Data show that up to 50% of cirrhotic patients develop some degree of heart failure due to characteristic vasodilation. It is also known that these patients have a hyperdynamic state associated with reduced perfusion of peripheral tissues, which marks the existence of high-output heart failure characteristic of cirrhotic cardiomyopathy (FERREIRA et al., 2012).

Furthermore, hepatocellular carcinoma stands out as a final complication of the chronic process of liver failure. It is a primary liver tumor resulting from cellular mutations that cause hepatocytes to multiply in a disorderly manner (PIMENTA; MASSABK,

2010). These mutations may derive from external agents that initiated the liver injury process.

Hepatocellular carcinoma is characterized by its aggressiveness and high mortality rates after the onset of symptoms, with non-fluctuating jaundice and ascites being the main complications (CHEDID et al., 2017). Clinical signs are insidious and, in general, preceded by the previously mentioned renal and neurological changes. When diagnosed early, there is a good chance of survival. However, late diagnosis, already in the symptomatic phase, gives the patient a life expectancy of less than one month, as the treatments available in this context are not very effective (GOMES et al., 2013). A striking consequence that is little addressed by available studies are the psychological complications linked to HCC diagnoses. In a prospective cohort study, Narasimman (2023) presents results that highlight apprehension, anxiety and emotional distress as symptoms related to the Hepatocellular Carcinoma surveillance process.

In the pediatric field, evidence points to sarcopenia as an important complication of Hepatocellular Insufficiency. In line with this, Rezende et al. (2020) identified sarcopenia in 40% of the patients participating in their study, 54.1% developed a deficit in muscle strength and 50.6% presented a deficit in muscle mass. These conditions are related to the deficiency of protein synthesis common to the process of liver failure.

In relation to obstetric complications, the research by Oliveira et al. (2022) sought to understand the relationship between liver failure and development of pre-eclampsia/eclampsia. The cohort study in question shows that liver enzyme abnormalities were observed in 49% of individuals, generally less than five times the upper limit of normal. There was no correlation between mean liver enzyme levels and maternal and fetal outcomes. The development of pregnancy hypertensive syndromes is multifactorial, with no independent relationship with liver damage (Oliveira et al., 2022).

Regarding other complications resulting from Hepatocellular Insufficiency, Jacques et al. (2021) showed that 58% of patients hospitalized with a diagnosis of Spontaneous Bacterial Peritonitis also had Hepatocellular Insufficiency. The study data showed that the absence of Chronic Liver Failure is associated with greater survival at intervals of 28 and 90 days. Another study analyzing patients hospitalized with Chronic Liver Failure points out that the mortality rate at 28 days was 56.3%, and the mortality rate in the intensive care unit was 49.3%. Still, 42.3% of patients developed two-organ failure and liver transplantation was performed in 15.5% of patients (PEREIRA; BAGULHO; CARDOSO; 2020).

CONCLUSION

The importance of studies that provide guidance on the clinical complications of hepatocellular failure is remarkable because early recognition of these conditions offers the patient a chance of a therapeutic approach before terminal stages of liver failure are reached. The preparation of this course conclusion work hopes to serve the scientific medical community as a way of clarifying the complications of liver failure syndrome, being able to guide and direct medical assistance in taking assertive and effective actions. It is also stated that there is an understanding of the need to develop more research in order to improve the range of evidence available on this topic.

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