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Disorder of Glucose Metabolism and Therapy: Implications on the Natural History of Advanced Chronic Liver Disease

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Keywords

Hepatogenous diabetes · Glucose intolerance · Chronic liver disease · Biguanides

Abstract

Introduction: Hepatogenous diabetes (HD) is a disorder of glucose metabolism (DGM) that develops as a complication of advanced chronic liver disease (ACLD) with an estimated prevalence of 20–70%. It appears to be associated with a larger number of decompensations, but its impact on the natural history of the disease is unclear. The treatment of DGM is hampered by the fact that some therapeutic agents are associated with a risk of complications in ACLD. The aim of this work was to study DGM in a population of patients with ACLD: prevalence, liver disease decompensation episodes, mortality analysis and study of the impact of antidiabetic therapies in patients with ACLD who developed DGM. ***Materials and Methods:*** A cohort of consecutive patients with ACLD without previous DGM, who attended a Hepatology clinic in the period of January to June 2015 was selected. Follow-up was carried out for 5 years. Data on age, gender, date of diagnosis and etiology of ACLD, Child-Pugh and MELD-Na classifications at enrollment, development of DGM, and antidiabetic therapy were collected. Logistic regression models for hospitalizations due to decompensated ACLD, ascites, hepatic encephalopathy (HE), upper gastrointestinal bleeding (UGB), hepatocellular carcinoma (HCC), portal vein thrombosis (PVT), infectious complications, acute-on-chronic liver failure (ACLF), and death were built. A survival analysis for patients with and without DGM was also performed. Treatment effectiveness for patients with DGM was assessed. ***Results:*** Initially, 221 patients were included, 154 (69.7%) of whom developed DGM after the diagnosis of ACLD. DGM patients presented a significantly higher number of hospitalizations. Odds ratio (OR) for death was not significantly related with DGM. At 5 years of follow-up, 68.9% of patients with DGM were alive, against 81.8% without DGM (p = 0.087). From the 154 patients who were diagnosed with DGM, 42.9% were not receiving pharmacological treatment

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for DGM. Treated patients were prescribed with either biguanides (34.8%), a SGLT2 inhibitor (8.6%), or insulin (7.7%). Only 1 patient was treated with a GLP-1 analogue. A tendency of OR favoring treatment was observed for biguanides and SGLT2 inhibitors in all outcomes except ascites. In the univariable analysis, the use of biguanides was associated with lower risk of death (OR: 0.84 [95% CI: 0.73–0.96]) and HE (OR: 0.85 [95% CI: 0.73–0.98]). ***Conclusion:*** DGM occurs with high prevalence in patients with ACLD and it seems to be related to more hospitalizations, which highlights the importance of its early identification and appropriate therapeutic approach. In the absence of contraindications, biguanides should be considered for treatment of patients with ACLD and DGM as they appear to be associated with a tendency to better outcomes and may present some advantage in terms of survival.

Perturbação do metabolismo da glicose e terapêutica: implicações na história natural da doença hepática crónica avançada

Palavras Chave
Diabetes hepatogénica · Intolerância à glicose · Doença hepática crónica · Biguanidas

Resumo

Introdução: A Diabetes hepatogénica é uma perturbação do metabolismo da glicose (PMG) que se desenvolve como complicação da doença hepática crónica avançada (DHCA) com uma prevalência estimada de 20–70%. Parece estar associada a um maior número de descompensações, mas o seu impacto na história natural da doença não é claro. O tratamento da PMG é dificultado pelo facto de alguns agentes terapêuticos estarem associados a um risco de complicações na DHCA.
O objetivo deste trabalho é estudar a PMG numa população de doentes com DHCA: prevalência, descompensações, análise de mortalidade e estudar o impacto de diferentes terapêuticas antidiabéticas em pacientes com DHCA que desenvolveram PMG. ***Materiais e Métodos:*** Foi selecionada uma *coorte* de doentes consecutivos com DHCA e sem PMG prévia, seguidos em consulta de Hepatologia no período de Janeiro a Junho de 2015. O seguimento foi efetuado durante 5 anos. Foram colhidos dados sobre idade, sexo, data de diagnóstico e etiologia da DHCA, classificações de Child-Pugh e MELD-Na no recrutamento, desenvolvimento de PMG e terapêutica anti-diabética. Foram construídos modelos de regressão logística para as hospitalizações por descompensação de DHCA, ascite, encefalopatia hepática (EH), hemorragia digestiva alta (HDA), carcinoma hepatocelular (CHC), trombose da veia porta (TVP), complicações infeciosas, ACLF e morte. Foi efectuada uma análise de sobrevivência para doentes com e sem PMG. Foi avaliada a eficácia do tratamento de pacientes com PMG. ***Resultados:*** Inicialmente, foram incluídos 221 doentes, 154 (69.7%) dos quais desenvolveram PMG após o diagnóstico de DHCA. A população PMG apresentou um número significativamente maior de hospitalizações. A odds ratio para morte não estava estatisticamente relacionada com a PMG. Aos 5 anos de seguimento, 68.9% dos pacientes com PMG estavam vivos versus 81.8% dos pacientes sem PMG (p = 0.087).
Dos 154 pacientes que foram diagnosticados com PMG, 42.9% dos pacientes não estavam sob tratamento farmacológico para a PMG. Aos pacientes tratados foram prescritas biguanidas (34.8%), um inibidor SGLT2 (8.6%) ou insulina (1.1%). Apenas 1 paciente foi tratado com um análogo GLP-1. Foi observada uma tendência de odds ratio a favorecer o tratamento para todos os resultados para as biguanidas e para os inibidores SGLT2 à excepção da ascite. Na análise univariável, o uso de biguanidas estava associado a menor risco de morte (OR: 0.84 [95% CI: 0.73–0.96]) e de EH (OR 0.85 [95% CI: 0.73–0.98]). ***Conclusão:*** A PMG ocorre com elevada prevalência em pacientes com DHCA e parece estar relacionada com mais internamentos, o que destaca a importância da sua identificação precoce e abordagem terapêutica adequada. Na ausência de contraindicações, as biguanidas devem ser consideradas para tratamento de pacientes com DHCA e PMG, porque parecem estar associadas a uma tendência para melhores resultados e podem apresentar alguma vantagem em termos de sobrevivência.

Introduction

Although the term hepatogenous diabetes (HD) was first coined by Megyesi et al. [1] in 1967, there has not been much research on this topic. HD can be defined as a state of impaired glucose regulation caused by loss of liver function implying that it develops after cirrhosis onset in individuals who usually lack risk factors for type 2 diabetes mellitus (T2DM) such as high body mass index, hyperlipidemia, or previous or family history of diabetes mellitus [1–4].

Despite the existence of enough data to support HD as a separate clinical entity, it is still not recognized by the American Diabetes Association (ADA), nor it was officially proposed separate treatment guidelines for this problem. This might be related to bidirectional relationship between the derangement of glucose metabolism and chronic liver disease. T2DM itself, in the context of metabolic syndrome, may favor the development of metabolic associated fatty liver disease which may end up in cirrhosis [1]. The exact mechanism by which HD occurs is not fully understood, but it seems to occur due to two major pathogenetic mechanisms: insulin resistance and pancreatic beta-cell dysfunction [1, 2, 4, 5]. Specific mechanisms related to the etiology of the underlying liver disease might also be responsible for beta-cell dysfunction. For instance, in patients with chronic hepatitis C, beta-cell dysfunction is mediated by autoimmune mechanisms such as molecular mimicry (between hepatitis C virus proteins and the enzyme glutamic acid decarboxylase) and in patients with alcohol-related liver disease and hemochromatosis, the same is caused by ethanol and excessive iron deposition, respectively. Furthermore, steatosis of the pancreas seems to be associated with NAFLD and lipotoxicity can cause pancreatic dysfunction [6].

In patients with advanced chronic liver disease (ACLD), both fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels may be inappropriately normal due to reduced lifespan of erythrocytes, hypersplenism, hepatic dysfunction, and impaired glucose metabolism. In patients with HD, serum insulin levels and the ratio of postprandial glucose to FPG are significantly higher than in patients with classical T2DM. Oral glucose tolerance test (OGTT), which measures 120-min plasma glucose levels, is often required to diagnose HD. Patients with normal FPG (and HbA1c) and abnormal OGTT are likely to be those with HD, while in most subjects with increased FPG levels, diabetes is usually T2DM [5]. Therefore, OGTT should be part of a routine baseline workup for all patients with cirrhosis at the time of diagnosis and during the follow-up clinic visits to enable early detection of HD [2].

Disorder of glucose metabolism (DGM) includes HD and glucose intolerance. Although it seems to be associated with a greater number of decompensations of ACLD and greater mortality, its impact on the natural history of ACLD is not yet fully understood. On the other hand, the treatment of DGM is challenging as many of the therapeutic agents used are associated with a higher risk of complications in ACLD. The aim of this study was to evaluate DGM in a population of patients with ACLD regarding its prevalence, decompensations, mortality and to analyze the impact of different antidiabetic therapies in patients with ACLD who develop DGM.

Materials and Methods

Study Design and Patients

In this single-center retrospective cohort study, all patients with a known previous diagnosis or with a new diagnosis of ACLD and with no previous diagnosis of DGM attending the hepatology clinic between 1 January of 2015 and 30 June of 2015 were included. They were followed over a period of 5 years between 1 January of 2015 and 31 December of 2020. The diagnosis of ACLD was based on clinical, analytical and imaging criteria, as well as liver elastography values (FibroScan>20 kPa and platelets <150,000, according to Baveno VI), since the investigation was done before Baveno VII. Data on age, gender, and date of diagnosis of ACLD for each patient were collected. The date of diagnosis of ACLD was considered as the first consultation registered at the hepatology clinic. Follow-up before enrollment in months was calculated (as the difference between 1st January of 2015 and the date of first consultation) and added to the variables. Data on ACLD etiology were collected, and Child-Pugh and MELD-Na scores at enrollment were calculated.

Disorder of Glucose Metabolism

In this study, all patients had no prior diagnosis of DGM. A diagnosis of DGM (either diabetes or glucose intolerance) during follow-up was made according to the ADA criteria [7]. This way, a diagnosis of diabetes is made when FPG ≥126 mg/dL (or ≥7.0 mmol/L) or classical symptoms of hyperglycemia + random blood glucose ≥200 mg/dL (or ≥11.1 mmol/L) or blood glucose ≥200 mg/dL (or ≥11.1 mmol/L) after 2 h in OGTT with 75 g of glucose or HbA1c ≥6.5%. Glucose intolerance is defined when FPG is between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L) or blood glucose is between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L) after 2 h in OGTT or HbA1c 5.7–6.4% [7]. As previously mentioned, both diabetes and glucose intolerance were classified as DGM, and this diagnosis was used as a proxy of HD. For patients with DGM, data on prescribed treatment were collected.

Outcomes

The study's outcomes included the presence of complications during the follow-up period, like hospitalizations due to decompensated ACLD, ascites, hepatic encephalopathy (HE), upper gastrointestinal bleeding, hepatocellular carcinoma (HCC), portal vein thrombosis (PVT), infectious complications, acute-on-chronic liver failure (ACLF), and death. All complications were classified as present or absent, whether they were found during follow-up or not, respectively. Additionally, the number of hospitalizations was collected. Classifications of ascites and HE beyond presence/absence were not used as outcomes and were only used to assess Child-Pugh and MELD-Na scores. Infectious complications included any diagnosis of infection made during follow-up. Grading of ACLF was not collected.

Statistical Analysis

Patients' characteristics were described for the whole cohort and compared for both ACLD with and without DGM. Univariable and multivariable logistic regression models were built for each outcome. Overall survival in months for ACLD patients with and without DGM was estimated using Kaplan-Meier estimator. A multivariable Cox regression was applied to the same outcome. Presence or absence of DGM diagnosed during follow-up was inputted in the models as an independent variable, and all outcomes were dependent variables (except for Cox regression, in which only the outcome death was analyzed). In ACLD with DGM patients, an analysis of the effectiveness of the prescribed treatment was performed using univariable and multivariable logistic regression. Multivariable models (both logistic and Cox regression) were adjusted for gender, age, duration of ACLD until enrollment in the study, and Child-Pugh and MELD-Na scores.

All data were analyzed using R version 4.3.3 software [ref]. Statistical significance was set for p values <0.05. For comparison of ACLD patients with and without DGM, independent samples t test and Mann-Whitney U test (continuous variables) or χ^2 test (categorical variables) were used, when applicable. Results of logistic regressions are presented as odds ratio (OR) with 95% confidence interval (95% CI). Log-rank test was performed to assess the overall survival using Kaplan-Meier estimator. Cox regression results are presented as hazard ratios with 95% CI.

Sample Size Considerations

Patients were included based on their attendance at the hepatology clinic. Therefore, no sample size calculation was performed, as we expected to have assessed the eligibility of all the patients followed for ACLD. Post hoc power analysis was performed to compare the diagnosis of DGM with the outcome death, assuming the observed incidence of death in each group of patients and a significance level of 0.05.

Results

Descriptive Analysis

In this study, 221 patients with ACLD without previous DGM were included, most of them male (73.3%) and with a mean age of 64.9 years (standard deviation: 10.2). ACLD with DGM was observed in 154 patients (69.7%). Patients with ACLD and DGM were significantly older than those without DGM (66.1 vs. 62.2 years, p = 0.017). There was no statistically significant difference between these patients, regarding gender, follow-up previous to enrollment, etiology, MELD-Na score, or Child-Pugh score. Table 1 shows characteristics of the patients included, for the whole sample and divided according to the diagnosis of DGM during follow-up.

Impact of DGM on Outcomes

Of the initial population, 69.7% (n = 154) developed DGM during follow-up. Comparison was made between patients with DGM and outcomes. Tables 2 and 3 show the incidence of all outcomes in our study and the results of univariable and multivariable logistic regression models. Univariable models showed a tendency of higher odds in patients with DGM, with statistically significant results for hospitalizations (OR: 1.21 [95% CI: 1.05–1.39]) and PVT (OR: 1.10 [95% CI: 1.01–1.19]). Multivariable models (adjusted for gender, age, duration of ACLD until enrollment in the study and Child-Pugh and MELD-Na scores) presented the same tendency of univariable models. However, hospitalization rates were significantly higher only in DGM patients (OR: 1.14 [95% CI: 1.01–1.29]). OR for death was not statistically related with DGM (multivariable OR: 1.03 [95% CI: 0.94–1.15]). Post hoc power analysis showed a power of 44.4% for assessing the association of death with DGM. Hence, with our sample size and the distribution of the outcome death, there is a probability of 55.6% of a type II error.

Survival Analysis

Figure 1 shows the overall survival in months for ACLD patients with and without DGM. At 5 years of follow-up, 68.9% of patients with DGM were alive,

Table 1. Baseline characteristics of the study population and comparison between patients with advanced chronic liver disease (ACLD) with or without disorder of glucose metabolism (DGM)

	Total patients (N = 221)	ACLD with DGM (n = 154)	ACLD without DGM (n = 67)	p value
Female, n (%)	162 (73.3)	118 (76.6)	44 (65.7)	0.127
Age, mean (SD), years	64.9 (10.2)	66.1 (9.4)	62.2 (11.7)	0.017
ACLD follow-up, median (IQR), months	16 (0–55)	18 (0–53)	13 (0–62)	0.918
Etiology of ACLD, n (%)				
Alcohol	208 (94.1)	148 (96.1)	60 (89.6)	0.111
Hepatitis C	10 (4.5)	6 (3.9)	4 (6.0)	0.742
Hepatitis B	6 (2.7)	3 (1.9)	3 (4.5)	0.540
Primary biliary cholangitis	2 (0.9)	2 (1.3)	0	0.869
Hemochromatosis	2 (0.9)	1 (0.6)	0	1.000
Autoimmune hepatitis	1 (0.5)	1 (0.6)	1 (1.5)	1.000
Cryptogenic	3 (1.4)	2 (1.3)	2 (1.5)	1.000
MELD-Na score, median (IQR)	11 (8–15)	11 (9–15)	10 (8–15)	0.174
Child-Pugh score, n (%)				
Child-Pugh score A	151 (68.3)	101 (65.6)	50 (74.6)	0.308
Child-Pugh score B	43 (19.5)	34 (22.1)	9 (13.4)	
Child-Pugh score C	27 (12.3)	19 (12.3)	8 (11.9)	

ACLD, advanced chronic liver disease; DGM, disorder of glucose metabolism; SD, standard deviation; ACLD follow-up, the follow-up for patients with ACLD previous to enrollment in the study; IQR, interquartile range.

against 81.8% without DGM (p = 0.087). Multivariable Cox regression (adjusted for gender, age, duration of ACLD until enrollment in the study, and Child-Pugh and MELD-Na scores) also shown a nonsignificant higher risk in those with DGM (hazard ratio: 1.24 [95% CI: 0.81–2.48]).

Treatment Effectiveness

An evaluation of treatment effectiveness for patients with DGM was performed. All comparisons were made against the absence of treatment. In this study, 42.9% of patients with ACLD and DGM were not receiving pharmacological treatment for DGM. Patients who were treated had been prescribed either biguanides (34.8%), specifically metformin, a SGLT2 inhibitor (8.6%), or insulin (7.7%). Only 1 patient was treated with a GLP-1 analogue. Therefore, effectiveness analysis excluded this individual. A tendency of OR favoring treatment was observed in all outcomes except ascites for biguanides and SGLT2 inhibitors, both in the univariable and multivariable models. A reverse tendency was observed for treatment with insulin. In the univariable analysis, the use of biguanides was associated with lower risk of death (OR: 0.84 [95% CI: 0.73–0.96]) and HE (OR: 0.85 [95% CI: 0.73–0.98]). Contrarily, the use of insulin was associated with a higher risk of ascites (OR: 1.45 [95% CI: 1.12–1.87]) and ACLF (OR: 1.41 [95% CI: 1.11–1.79]). No significant associations with any of the outcomes were found with SGLT2 inhibitors. None of significant associations observed for the univariable model were present in the multivariable model, which was adjusted for gender, age, duration of ACLD until enrollment in the study, and Child-Pugh and MELD-Na scores.

Discussion

In the literature, the estimated prevalence of HD and the prevalence of glucose intolerance are quite variable (20–70% and 60–80%, respectively) [1, 6]. In our study, DGM prevalence was 69.7%. These wide variations depend on several factors, including the diagnostic criteria and methods of assessment of HD used as well as the state and etiology of liver disease [1]. Furthermore, in our study, since the diagnosis of HD was inferred by a diagnosis of DGM during follow-up, it was not possible to exclude the occurrence of T2DM or of DGM due to other causes, namely, chronic pancreatitis, for which no specific exclusion criteria were made. Additionally, this work was

Table 2. Results of the univariable and multivariable models for comparison of outcomes regarding DGM

	Total patients (N = 221)	ACLD with DGM (n = 154)	ACLD without DGM (n = 67)	ACLD with DGM versus ACLD without DGM	
Outcomes	incidence, n (%)	incidence, n (%)	incidence, n (%)	univariable model, OR (95% CI) [p value]	multivariable model, OR (95% CI) [p value]
Death	54 (24.4)	43 (27.9)	11 (16.4)	1.12 (0.99–1.27) [0.068]	1.03 (0.94–1.15) [0.454]
Hospitalization	102 (46.2)	80 (51.9)	22 (32.8)	1.21 (1.05–1.39) [0.009]	1.14 (1.01–1.29) [0.045]
Ascites	90 (40.7)	68 (44.2)	22 (32.8)	1.12 (0.97–1.29) [0.116]	1.06 (0.93–1.19) [0.384]
Hepatic encephalopathy	57 (25.8)	43 (27.9)	14 (20.9)	1.07 (0.95–1.22) [0.275]	1.02 (0.92–1.15) [0.621]
Upper gastrointestinal bleeding	56 (25.3)	43 (27.9)	13 (19.4)	1.09 (0.96–1.23) [0.182]	1.04 (0.92–1.18) [0.503]
HCC	35 (15.8)	26 (16.9)	9 (13.4)	1.03 (0.93–1.15) [0.521]	0.98 (0.89–1.08) [0.640]
PVT	21 (9.5)	19 (12.3)	2 (3)	1.10 (1.01–1.19) [0.029]	1.07 (0.99–1.16) [0.092]
Infections	112 (50.7)	79 (51.3)	33 (49.3)	1.02 (0.88–1.18) [0.781]	1.00 (0.86–1.15) [0.970]
ACLF	41 (18.6)	32 (20.8)	9 (13.4)	1.08 (0.96–1.20) [0.198]	1.08 (0.98–1.20) [0.137]

Incidence cells represent the frequency of individuals for which each outcome occurred. Model cells represent the odds ratio of outcome between ACLD with DGM and ACLD without DGM (reference). Multivariable model adjusts for gender, age, ACLD follow-up previous to enrollment, MELD-Na score, and Child-Pugh score. ACLD, advanced chronic liver disease; DGM, disorder of glucose metabolism; OR, odds ratio; 95% CI, 95% confidence interval.

carried out before the new steatotic liver disease classification and now some of the patients would probably be classified as MASLD and increased alcohol intake (MetALD). However, the exclusion of diagnosis of DGM prior to enrollment of ACLD patients may have attenuated the effect of other causes of DGM.

The impact of diabetes development on the natural history of chronic liver disease remains incompletely understood. However, studies have demonstrated that cirrhotic patients with diabetes have a higher incidence of liver disease complications, such as ascites, HE, gastrointestinal hemorrhage, bacterial infections, spontaneous bacterial peritonitis, and increased mortality rates, compared to nondiabetic cirrhotic patients. These complications occur independently of MELD and Child-Pugh scores for ascites and independently of MELD score for HE. Additionally, previous studies showed that diabetes is more frequent in patients with decompensated cirrhosis than in those with compensated cirrhosis [1, 6, 8]. Diabetes may be more frequent in patients with decompensated cirrhosis due to its effects on the gastrointestinal system, including gastrointestinal dysmotility, immune suppression, and intestinal bacterial overgrowth. Moreover, hyperinsulinemia, insulin resistance, and hyperglycemia can alter homeostasis in the liver and lead to the development of HCC. A meta-analysis has shown that diabetes almost doubles the risk of HCC, and increased levels of insulin-like growth factor-I and insulin-like growth factor-II may induce mitosis and proliferation of HCC cells [1, 5].

Patients with ACLD and diabetes have a higher incidence of complications, including ascites, HE, upper gastrointestinal bleeding, HCC, PVT, infections, and ACLF, compared to those without diabetes. Additionally, patients with ACLD and diabetes have a higher number of hospital admissions and a higher mortality

Table 3. Prescribed treatments of patients with ACLD and DGM and risk of complications

	Biguanide (n = 77)	SGLT2 inhibitor (n = 19)	Insulin (n = 17)
Death – OR (95% CI) [p value]			
Univariable	0.84 (0.73–0.96) [0.013]	0.83 (0.65–1.04) [0.115]	1.27 (0.98–1.65) [0.073]
Multivariable	0.92 (0.82–1.04) [0.210]	0.91 (0.75–1.11) [0.351]	1.24 (1.00–1.55) [0.053]
Hospitalization – OR (95% CI) [p value]			
Univariable	0.90 (0.76–1.06) [0.209]	0.87 (0.67–1.12) [0.288]	1.23 (0.95–1.59) [0.128]
Multivariable	0.95 (0.81–1.12) [0.559]	0.89 (0.71–1.11) [0.300]	1.12 (0.87–1.45) [0.388]
Ascites – OR (95% CI) [p value]			
Univariable	1.05 (0.89–1.23) [0.568]	1.08 (0.84–1.40) [0.539]	1.45 (1.12–1.87) [0.006]
Multivariable	1.10 (0.94–1.27) [0.230]	1.01 (0.81–1.24) [0.957]	1.21 (0.96–1.53) [0.109]
HE – OR (95% CI) [p value]			
Univariable	0.85 (0.73–0.98) [0.023]	0.87 (0.69–1.11) [0.260]	1.20 (0.92–1.55) [0.882]
Multivariable	0.88 (0.77–1.01) [0.069]	0.85 (0.68–1.05) [0.137]	0.98 (0.77–1.25) [0.879]
Upper gastrointestinal bleeding – OR (95% CI) [p value]			
Univariable	0.99 (0.85–1.14) [0.862]	0.94 (0.75–1.18) [0.591]	1.29 (1.01–1.65) [0.045]
Multivariable	1.03 (0.89–1.20) [0.662]	0.94 (0.76–1.17) [0.584]	1.13 (0.88–1.46) [0.349]
Hepatocellular cancer – OR (95% CI) [p value]			
Univariable	0.96 (0.86–1.08) [0.539]	0.99 (0.82–1.20) [0.929]	1.20 (0.97–1.49) [0.092]
Multivariable	1.00 (0.89–1.12) [0.984]	1.03 (0.87–1.23) [0.703]	1.09 (0.89–1.34) [0.405]
Deep venous thrombosis – OR (95% CI) [p value]			
Univariable	0.93 (0.83–1.03) [0.176]	0.94 (0.78–1.13) [0.518]	1.01 (0.83–1.24) [0.924]
Multivariable	0.98 (0.88–1.09) [0.693]	0.94 (0.78–1.13) [0.499]	0.94 (0.76–1.17) [0.605]
Infections – OR (95% CI) [p value]			
Univariable	0.97 (0.82–1.14) [0.682]	0.91 (0.70–1.18) [0.476]	1.08 (0.82–1.41) [0.596]
Multivariable	0.99 (0.83–1.17) [0.890]	0.88 (0.69–1.14) [0.338]	0.94 (0.71–1.25) [0.681]
ACLF – OR (95% CI) [p value]			
Univariable	0.91 (0.80–1.03) [0.131]	0.87 (0.71–1.07) [0.202]	1.41 (1.11–1.79) [0.006]
Multivariable	0.91 (0.80–1.03) [0.148]	0.83 (0.69–1.01) [0.071]	1.16 (0.92–1.47) [0.217]

Cells represent odds ratio for occurrence of each complication during follow-up in patients with ACLD and DGM with each treatment compared to no treatment (reference; n = 66 [42.9%]). Multivariable model adjusts for gender, age, ACLD follow-up previous to enrollment, MELD-Na score, and Child-Pugh score. ACLD, advanced chronic liver disease; DGM, disorder of glucose metabolism; OR, odds ratio; 95% CI, 95% confidence interval.

rate [9]. In our study, hospitalizations were significantly higher in DGM patients. OR for death was not statistically related with DGM, which may be related to an eventual insufficient statistical power. Survival was also worse in DGM patients but with no significance. On the other hand, the observation that the survival of patients with DGM was worse may have to do with the fact that these patients were significantly older than those without DGM.

Treating diabetes in cirrhotic patients is particularly challenging and potentially harmful due to several reasons. The liver is a major site for drug metabolism, which may be compromised in liver failure. Liver diseases also increase the susceptibility to hypoglycemia and lactic acidosis. Malnutrition, which is a common feature of subjects with end-stage liver disease, may be worsened by nutritional regimens restricting caloric intake. Additionally, the presence of ascites and/or edema often hinders the performance of physical exercise [1, 6, 9].

According to the literature, an ideal oral hypoglycemic agent for patients with cirrhosis should have insignificant hepatic metabolism, low binding to plasma protein, nonhepatic route of elimination, relatively shorter half-life, and no risk of hypoglycemia or hepatotoxicity. Metformin (a biguanide) is an example of such an agent, as it remains unmetabolized in the body, does not bind to plasma proteins, has a short half-life of approximately 5 h, and is eliminated by the kidneys. However, metformin

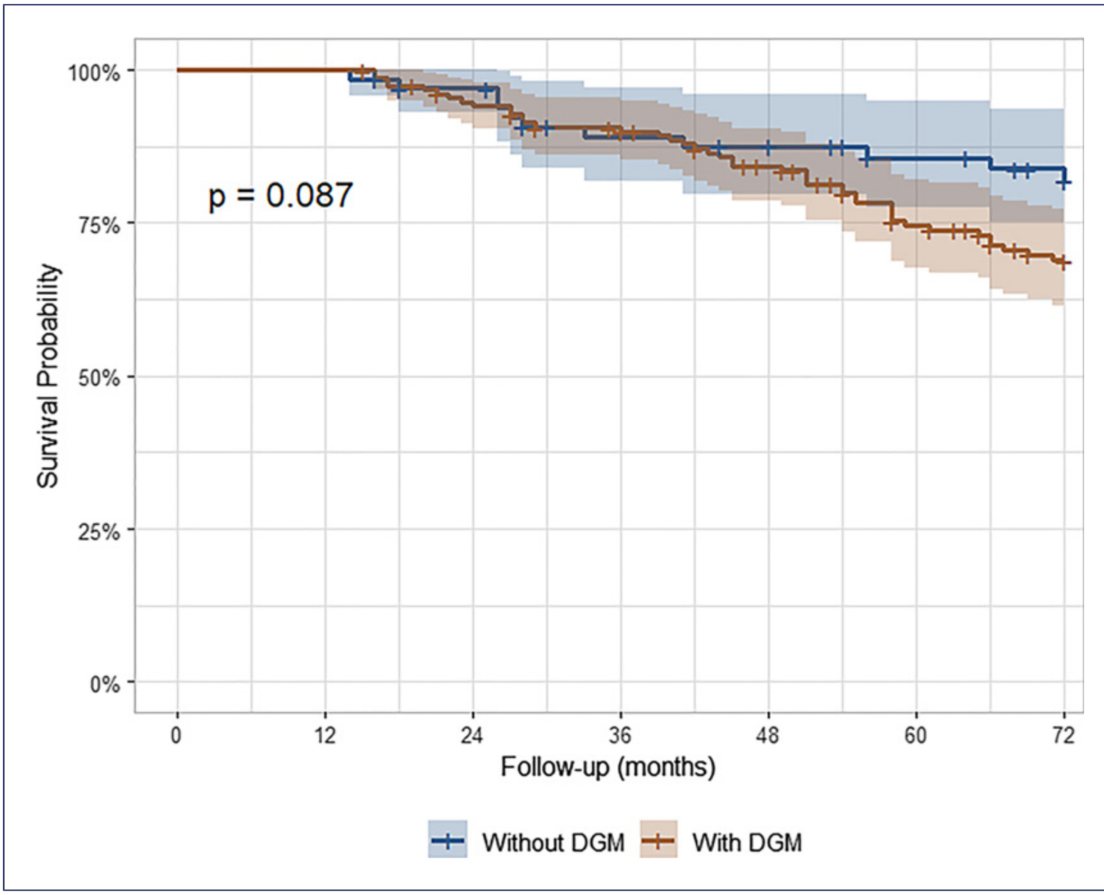

Fig. 1. Overall survival in months for ACLD with and without DGM.

targets insulin resistance, which is a key driving factor for HD pathogenesis. Metformin has also been associated with cardioprotective and anticancer effects and has been shown to decrease the risk of HCC and liver-related death in cirrhotic patients with diabetes [2].

Most physicians are hesitant to recommend metformin in cirrhotic patients due to undue apprehension about an increased risk of lactic acidosis, which is extremely rare unless patients have concomitant renal dysfunction or hypoxemia. The dose of metformin should also be reduced or avoided in patients with moderate liver disease (Child-Pugh B) and should be avoided in severe hepatic dysfunction (Child-Pugh C) [2, 5, 6].

When analyzing the impact of different antidiabetic therapies in patients with ALCD and DGM, we found a nonsignificant tendency for biguanides and SGLT2 inhibitors toward better outcomes and insulin toward worst outcomes, compared to no treatment. This is to reinforce the safe profile of treating with biguanides. Data on glycemic control were only used to assess DGM during follow-up. Therefore, no measures of glycemic control were used to adjust our models or as independent variables.

Our study was conducted at a single center and without a control group, and we believe it is a weakness which may limit the generalizability of the findings. Furthermore, the fact that is a retrospective study means that data were already collected for all patients, and biases are more likely and more difficult to overcome. However, this design allows for the development of new hypotheses regarding the natural history of HD.

The prevalence of DGM in patients with ACLD is very high. More studies are needed to clarify the findings, but the results of our study show that it is crucial to have an early identification and adequate therapeutic approach of DGM due to its high prevalence and influence on the tendency for worse outcomes. In the absence of contraindications and compared to the absence of treatment, biguanides should be considered for treatment of patients with ACLD and DGM given the severity of the underlying disease and since they appear to be associated with a tendency to better outcomes and may present an advantage in terms of survival.

This is a study that included a reasonable number of patients at different stages of their chronic liver disease. Different diagnostic methods of DGM were used, and patients were evaluated over a long follow-up period and for many different outcomes. Furthermore, this is an original article on a topic that has rarely been covered and needs to be highlighted and rediscussed. Future research could consider conducting multicenter studies to increase the sample size and the generalizability of the findings and including a control group to provide a better understanding of the impact of DGM on patient outcomes.

Statement of Ethics

The current study was approved by the Ethic Committee "Comissão de Ética para a Saúde da ULSTMAD" (Doc No. 63/2024), and it followed the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws, as well as the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data, which was enacted on April 27, 2016.

Conflict of Interest Statement

The authors have no conflicts of interest to declare related to this study.

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Author Contributions

Sofia Garcês Soares, Teresa Frazão, Célia Tuna, Margarida Montes, Ana Rocha, and Lígia Rodrigues Santos collected the patient data. Sofia Garcês Soares planned the manuscript, did the literature review, and created the first draft. Luís Nogueira and Manuel Marques-Cruz did the statistical analysis. Paulo Carrola, Sónia Carvalho, Inês Pinho, and José Presa did a critical expert review and revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study should be inquired to the corresponding author.

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