gastrointestinal disorders

MDPI

Article

Assessment of Glecaprevir/Pibrentasvir Treatment's Influence on Biochemical and Metabolic Markers in Patients with Chronic Hepatitis

Alina Maria Constantinescu [1], Paula Marian [2,*], Harrie Toms John [3,*], Felicia Manole [1,4], Tunde Jurca [1,5] and Nicoleta Negrut [1,6]

[1] Faculty of Medicine and Pharmacy, Doctoral School of Biomedical Sciences, University of Oradea, 410087 Oradea, Romania; alina.constantinescu76@yahoo.com (A.M.C.); manole.felicia@gmail.com (F.M.); jurcatunde@yahoo.com (T.J.); lnm_n10@yahoo.com (N.N.)
[2] Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania
[3] Department of Anaesthesia and Intensive Care, County Emergency Hospital of Bihor, 410169 Oradea, Romania
[4] Department of Surgical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania
[5] Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, 410028 Oradea, Romania
[6] Department of Psycho-Neuroscience and Recovery, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania
* Correspondence: paula.marian85@gmail.com (P.M.); tomsharrie@gmail.com (H.T.J.)

Abstract: Background/Objectives: Liver function tests (LFT) are essential for diagnosing and monitoring liver status in patients with chronic hepatitis. In addition, tracking the systemic implications reflected in the changes in metabolic parameters is essential for correctly managing the cases. This study addresses the critical gap in the literature by evaluating the effects of glecaprevir/pibrentasvir on key liver function markers (AST, ALT, GGT, TB) and metabolic parameters (TC, TG, HbA1c) in patients with chronic hepatitis C (CHC). Moreover, this study will evaluate the impact of glecaprevir/pibrentasvir on A2MG, which provides insights into its effects on liver fibrosis. Awareness of these effects is critical for the optimal management of patients during and following antiviral therapy to ensure that therapeutic success does not come at the expense of overall liver and metabolic health. These parameters should be monitored as they supply clinicians with essential data, informing treatment more accurately and ensuring a holistic approach in CH patients. **Methods:** This study consists of 104 patients with chronic hepatitis C treated with glecaprevir/pibrentasvir and monitored from January to June 2024. Assessments comprised standard liver markers, lipid profiles, glycated hemoglobin, and alpha-2-macroglobulin, as well as specific non-invasive tests of liver injury. **Results:** 95.2% of the patients experienced a sustained virologic response. Biochemical markers and total cholesterol values were significantly decreased with glecaprevir/pibrentasvir therapy. Non-significant elevations in total bilirubin and glycated hemoglobin support the drug's favorable tolerability profile. **Conclusions:** In the treatment of chronic hepatitis C patients, glecaprevir/pibrentasvir therapy leads to normalization in biochemical markers (AST, ALT, and GGT), as well as in total cholesterol.

Keywords: direct-acting antiviral; glecaprevir/pibrentasvir; metabolic markers; biochemical markers; chronic hepatitis C

Citation: Constantinescu, A.M.; Marian, P.; John, H.T.; Manole, F.; Jurca, T.; Negrut, N. Assessment of Glecaprevir/Pibrentasvir Treatment's Influence on Biochemical and Metabolic Markers in Patients with Chronic Hepatitis. *Gastrointest. Disord.* **2024**, *6*, 894–904. https://doi.org/10.3390/gidisord6040063

Academic Editor: Consolato M. Sergi

Received: 2 October 2024
Revised: 9 November 2024
Accepted: 11 November 2024
Published: 13 November 2024

1. Introduction

Chronic hepatitis (CH) caused by hepatitis B and C is regarded as an essential global health problem that affects many people in the world. Worldwide, over 58 million people are known to have hepatitis C virus (HCV), and many of these will progress to chronic

liver disease if untreated [1]. Although the prevalence of HCV is decreasing, HCV infection remains a concern for the World Health Organization due to the significant number of cases among children and adolescents and the high mortality associated with its complications [2]. Long-term inflammation of the liver in CH could result in serious complications such as cirrhosis, liver failure, and the development of hepatocellular carcinoma (HCC) [3]; therefore, all patients require reflex testing for HCV RNA for screening purposes. The advent of direct-acting antiviral drugs has marked a therapeutic revolution due to their high treatment success rate [4]. These diseases are a major cause of morbidity and mortality but also put pressure on healthcare systems. Hence, it is important to know the pathophysiology of various disease processes and how these interventions impact key biomarkers, improving patient outcomes.

Over time, CH fails to eliminate the virus, so liver inflammation and damage persist. Chronic inflammation can also be long-lasting and eventually develop into fibrosis, where the overproduction of extracellular matrix proteins leads to liver scarring. When fibrosis advances, cirrhosis ensues, in which liver architecture and function are largely compromised. The risk of developing HCC in cirrhosis is high, and early detection must be made to improve optimal management [5].

CH is managed through liver function tests (LFTs), crucial for monitoring the liver's health and a treatment plan. This test panel includes aspartate aminotransferase (AST or TGO) and alanine aminotransferase (ALT or TGP), widely used markers for hepatocellular injury. Since both enzymes are excreted into the blood after the injury of hepatocytes, they represent good markers for hepatic inflammation and lesioning [6]. These two biomarkers were elevated in patients with active liver diseases, indicating their potential for disease tracking or monitoring response to treatments [7]. Another important marker is gamma-glutamyl transferase (GGT), especially for alcohol-related liver disease [8]. Total bilirubin (TB) indicates the liver's ability to metabolize the unconjugated part of breakdown products from red blood cells. Elevated values are noted in diseases such as CH and cirrhosis, indicating liver dysfunction where TB contents tend to be high [9].

Liver dysfunction is not the only pathology altered by CH; systemic effects, mediated through metabolic parameters, are involved. Dyslipidemia, an abnormal blood lipid level, is common among patients with chronic liver disease. The biochemical determinations for lipid metabolism, primarily under hepatic control, may present alterations in the levels of total cholesterol (TC) and triglyceride (TG) [10]. In addition, CH could affect glucose metabolism [11], leading to changes in glycated hemoglobin (HbA1c) that reflect long-term blood sugar levels. Properly evaluating these metabolic parameters will help in knowing how one body part affects another and thus move the therapy toward holistic care for a patient.

Another biomarker in CH is alpha-2-macroglobulin (A2MG), which is highly important in identifying liver fibrosis within patients with chronic hepatitis C (CHC) during the early stages [12]. This large protein, in addition to containing a broad-spectrum protease inhibitor (and therefore participating in the control of many inflammatory processes), is associated with the extent of fibrosis in patients with CHC and is important in evaluating liver disease severity [13].

Glecaprevir/pibrentasvir—a fixed-dose combination of glecaprevir (g) and pibrentasvir (p) approved for the treatment of CHC—has been shown to achieve high rates of sustained virologic response (SVR) across diverse genotype subpopulations. This direct-acting antiviral (DAA) targets two essential proteins for viral multiplication: NS3/4A protease and NS5A protein. It stops viral replication, leading to most patients' viral clearance [14]. Clinical trials with glecaprevir/pibrentasvir demonstrated a high SVR rate in various HCV genotypes. Its relatively short treatment duration and favorable safety profile make it an attractive choice in various clinical scenarios [15]. Despite its high efficacy in virus clearance, further research on its effect on liver function markers and metabolic parameters must be conducted.

This study addresses the critical gap in the literature by evaluating the effects of glecaprevir/pibrentasvir on key liver function markers (AST, ALT, GGT, TB) and metabolic parameters TC, TG, HbA1c) in patients with CHC. Moreover, the study will evaluate the impact of glecaprevir/pibrentasvir on A2MG, which provides insights into its effects on liver fibrosis. Awareness of these effects is critical for the optimal management of patients during and following antiviral therapy to ensure that therapeutic success does not come at the expense of overall liver and metabolic health. These parameters should be monitored, as they supply the clinician with essential data, allowing them to inform treatment more accurately and ensure a holistic approach in CH patients.

2. Results

This study included 150 patients, but after applying the exclusion criteria, 104 patients remained. Table 1 presents the characteristics of the study group. SVR was achieved in 99 (95.2%) cases.

Table 1. Characteristics of the study group.

Parameter	Study Group
DD	
Age, years, mean ± SD (min, max)	54.17 ± 10.49 (19, 69)
<25, years, n (%)	2 (1.9)
25–45, years, n (%)	7 (6.7)
46–60 years, n (%)	56 (53.8)
>60 years, n (%)	39 (37.5)
Male gender, n (%)	44 (42.3)
Urban residence, n (%)	61 (58.7)
Clinical data	
FibroSure, n (%)	
F0	29 (27.9)
F1	31 (29.9)
F2	21 (20.2)
F3	23 (22.1)
SteatoTest, n (%)	
S0	32 (30.8)
S1	32 (30.8)
S2	15 (14.4)
S3	25 (24.0)
ActiTest, n (%)	
A0	30 (28.8)
A1	35 (33.7)
A2	22 (21.2)
A3	17 (16.3)
NashTest, n (%)	
N0	51 (49.0)
N1	37 (35.6)
N2	16 (15.4)

Table 1. *Cont.*

Parameter	Study Group
AshTest, n (%)	
H0	104 (100)
Co-morbidities, n (%)	49 (47.1)
hypertension	16 (15.4)
diabetes	17 (16.3)
dyslipidemia	14 (13.4)
obesity	2 (1.9)
Paraclinical investigations, mean ± SD	
ALT, (U/L)	89.55 ± 66.25
AST (U/L)	74.87 ± 16.74
GGT (U/L)	72.12 ± 24.20
TB (mg/dL)	4.14 ± 2.94
TC (mg/dL)	259.49 ± 164.54
HbA1c (mg%)	6.41 ± 1.34
TG (mmol/L)	4.86 ± 1.92
A2MG (g/L)	3.29 ± 0.48

DD—demographic data; HbA1c—glycated hemoglobin; ALT—alanine aminotransferase; AST—aspartate aminotransferase; GGT—gamma-glutamyl transferase; TB—total bilirubin; TC—total cholesterol; HbA1c—Hemoglobin A1c; TG—triglycerides; A2MG—alpha-2-macroglobulin; n—number; M—mean; SD—standard deviation; min—minimum; max—maximum.

No statistically significant association was identified between age group, gender, environment, co-morbidities, and SVR [$\chi^2(3) = 1.351$, $p = 0.717$; $\chi^2(1) = 0.011$, $p = 0.915$; $\chi^2(1) = 0.754$, $p = 0.385$; $\chi^2(1) = 0.107$, $p = 0.744$], as is presented in Figure 1.

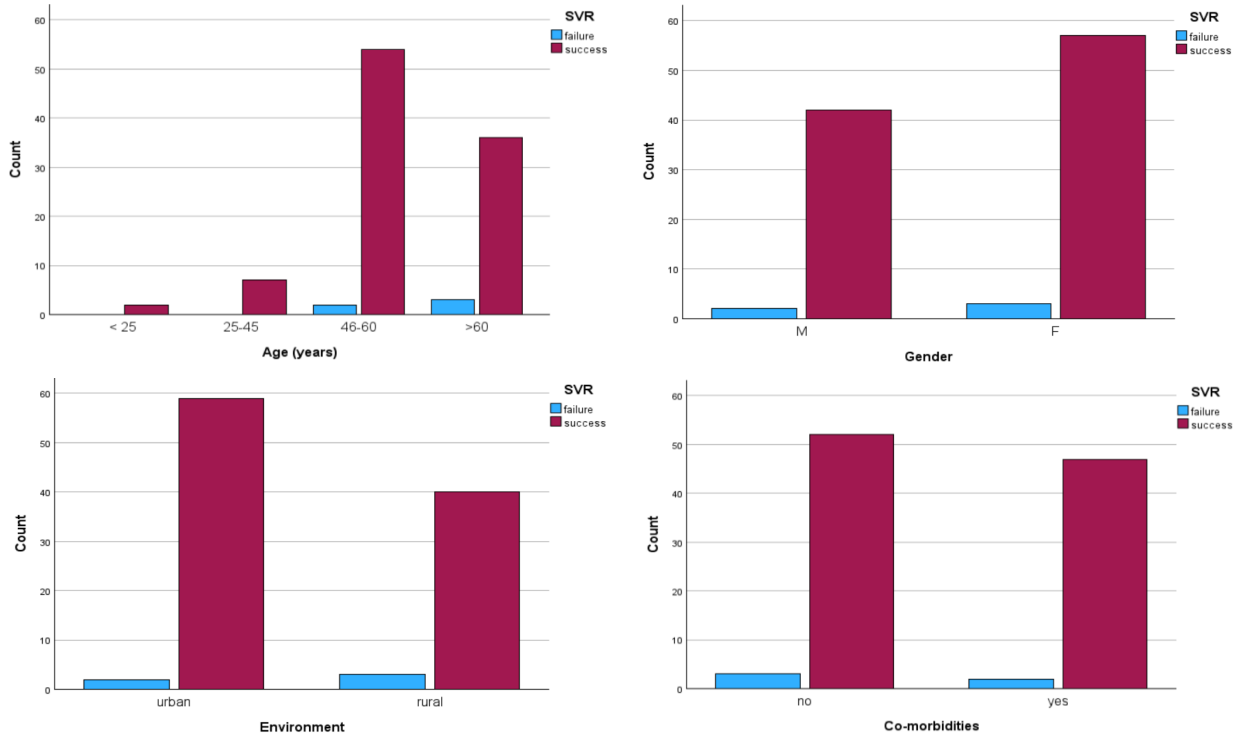

Figure 1. Distribution of the SVR according to age, gender, environment, and co-morbidities. M—male; F—female.

Logistic model analysis showed that FibroSure, SteatoTest, ActiTest, NashTest scores were not significantly associated with SVR ($\chi^2 = 6.803$, df = 3, $p = 0.078$; $\chi^2 = 3.945$, df = 3, $p = 0.267$; $\chi^2 = 3382$, df = 3, $p = 0.336$; $\chi^2 = 4582$, df = 2, $p = 0.101$) (Figure 2). In the case of the AshTest score, all patients in this study had the same score (H0); as a result, an association between this score and SVR could not be determined.

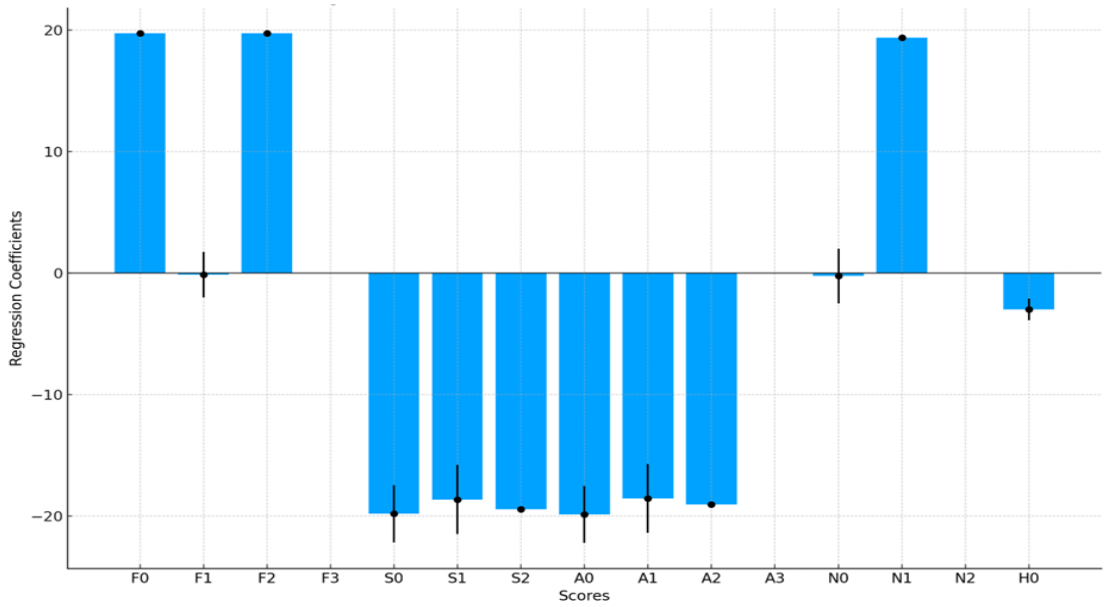

Figure 2. Analysis of the association between clinical scores and SVR. F0–3—scores for FibroSure; S0–2—scores for SteatoTest; A0–3—scores for ActiTest; N0–2—scores for NashTest; H0—scores for AhTest.

Statistically significant differences were indicated between the initial (1) and final (2) values for the following biochemical markers: ALT, AST, GGT, TC, TG, and A2MG. The data are summarized in Table 2.

Table 2. The evolution of laboratory parameters.

Parameter	M ± SD	*p*-Value
ALT_1 (U/L) ALT_2 (U/L)	89.55 ± 66.25 38.65 ± 12.72	<0.001 *
AST_1 (U/L) AST_2 (U/L)	74.87 ± 16.74 33.83 ± 5.67	<0.001 *
GGT_1 (U/L) GGT_2 (U/L)	72.12 ± 24.20 45.79 ± 11.31	<0.001 *
TB_1 (mg/dL) TB_2 (mg/dL)	4.14 ± 2.94 4.62 ± 3.07	0.208
TC_1 (mg/dL) TC_2 (mg/dL)	259.49 ± 164.54 207.77 ± 32.90	0.003 *
HbA1c_1 (mg%) HbA1c_2 (mg%)	6.41 ± 1.34 6.62 ± 1.45	0.300
TG_1 (mmol/L) TG_2 (mmol/L)	2.72 ± 0.73 4.86 ± 1.92	<0.001 *
A2MG_1 (g/L) A2MG_2 (g/L)	3.29 ± 0.48 5.98 ± 2.22	<0.001 *

HbA1c—glycated hemoglobin; ALT—alanine aminotransferase; AST—aspartate aminotransferase; GGT—gamma-glutamyl transferase; TB—total bilirubin; TC—total cholesterol; HbA1c—Hemoglobin A1c; TG—triglycerides; A2MG—alpha-2-macroglobulin; M—mean; SD—standard deviation; *p*-value as determined by *t*-test, *—statistical significance.

3. Materials and Methods

3.1. Study Design

The study was conducted between January 2022 and June 2024, with patients being followed up at the gastroenterology section of the Pitești County Hospital, Romania. The subjects included in the study were treatment-naive patients diagnosed with CHC who were referred to the department for antiviral medication. All patients signed informed consent. This study was approved by the Ethics Commission of Pitesti County Hospital (Approval No. 01/01.03.2019) and complies with the Declaration of Helsinki of the World Medical Association. SVR was considered in patients who had undetectable HCV (ribonucleic acid) RNA 12 weeks after DAA therapy. The inclusion and exclusion criteria were applied to the initial cohort of patients (Figure 3).

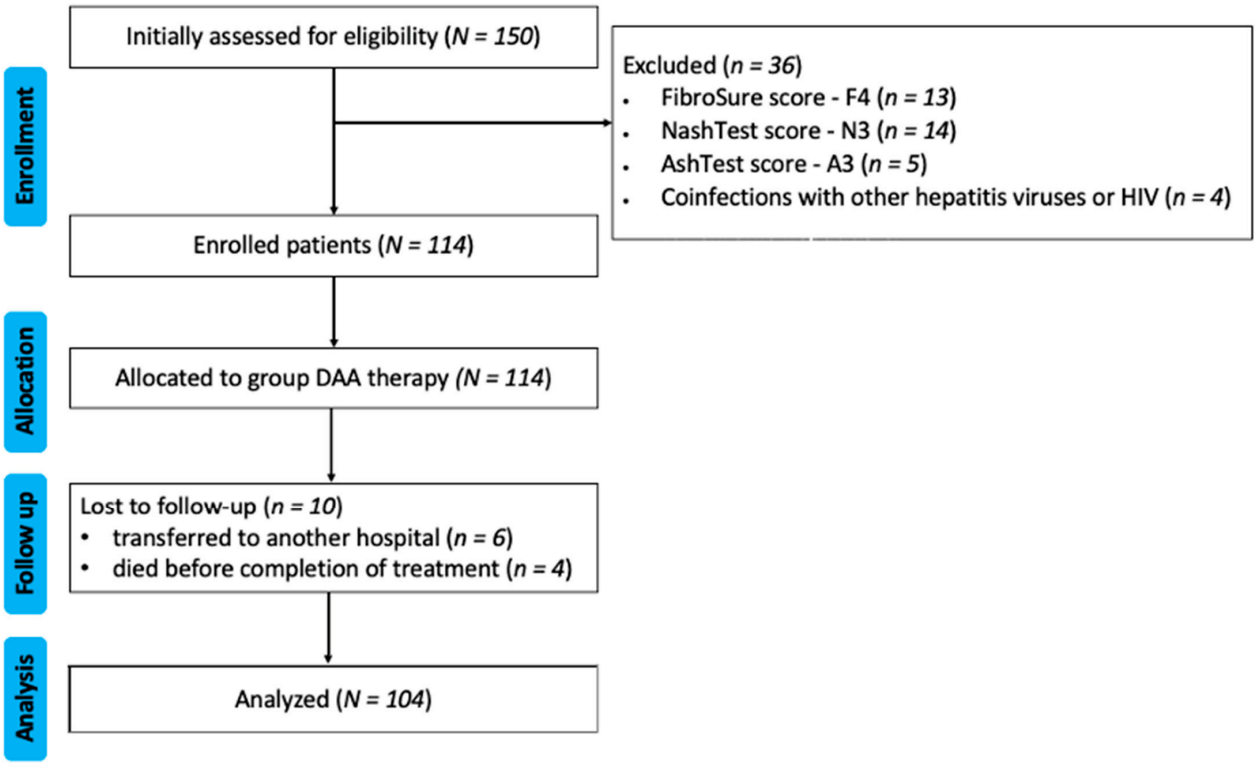

Figure 3. CONSORT flow diagram of the study. N/n—number; HIV—human immunodeficiency virus; DAA—direct-acting antiviral.

Inclusion criteria are as follows:

- Age over 18 years;
- Confirmed diagnosis of CHC;
- Signed informed consent to participate in the study.

Exclusion Criteria are as follows:

- FibroSure score—F4;
- NashTest score—N3;
- AshTest score—A3;
- Coinfections with other hepatitis viruses (B and D) or human immunodeficiency virus (HIV);
- Previous antiviral treatment for CHC;
- Liver/kidney transplant;
- Change in the treatment of associated diseases during the study;
- Transferred to another hospital;
- Death before completion of DAA therapy;
- Cancer.

All patients included in the study were treated with glecaprevir/pibrentasvir (100 mg g/40 mg p). The administered dose was 300 mg g and 120 mg p, taken orally once a day. The duration of treatment was eight weeks, according to the standard protocol for patients with CHC without cirrhosis and previous antiviral treatments. All patients remained on their previous hypolipidemic and diabetic therapy.

3.2. Data Collection

Before initiating antiviral treatment with glecaprevir/pibrentasvir and 24 h after completing the treatment, the following biochemical parameters were evaluated: ALT (normal range 0–55 U/L), AST (normal range 0–34 U/L), GGT (normal range 0–64 U/L), TB (normal range < 1.2 mg/dL), TC (normal range 0–200 mg/dL), TG (normal range 0–1.7 mmol/L), HbA1c (normal range 4.8–5.6%), A2MG (normal range 1.3–3 g/L), and hepatitis C viral load (normal range—undetectable levels).

At the time of inclusion in the study, all patients were tested for hepatitis B virus deoxyribonucleic acid (HBV-DNA), hepatitis D virus RNA (HDV-RNA), and HIV RNA.

To evaluate liver fibrosis, steatosis, necro-inflammatory activity, and other aspects of liver disease, patients underwent the following specific non-invasive tests:

- **FibroSure (FibroTest)** for the evaluation of hepatic fibrosis with the following interpretation scale:
  - F0: no fibrosis;
  - F1: mild fibrosis;
  - F2: moderate fibrosis;
  - F3: severe fibrosis but no cirrhosis;
  - F4: cirrhosis.
- **SteatoTest** for evaluating liver steatosis with the following interpretation scale:
  - S0: no steatosis;
  - S1: mild steatosis (5–33% of hepatocytes affected);
  - S2: moderate steatosis (34–66% of hepatocytes affected);
  - S3: severe steatosis (more than 66% of hepatocytes affected).
- **ActiTest** for evaluation of the hepatic necro-inflammatory activity with the following interpretation scale:
  - A0: no activity;
  - A1: mild activity;
  - A2: moderate activity;
  - A3: severe activity.
- **NashTest** for evaluation of the presence and severity of non-alcoholic steatohepatitis (NASH), with the following interpretation scale:
  - N0: no NASH;
  - N1: mild NASH;
  - N2: moderate NASH;
  - N3: severe NASH.
- **AshTest** for evaluation of the presence and severity of alcoholic steatohepatitis (ASH), with the following interpretation scale:
  - H0: no ASH;
  - H1: mild ASH;
  - H2: moderate ASH;
  - H3: severe ASH.

Blood samples were collected from all patients before starting antiviral treatment and 24 h after completion. The biochemical parameters were measured using standardized laboratory methods. All patients were monitored for treatment side effects, and the data were collected and analyzed to evaluate the changes in biochemical parameters before and after treatment.

3.3. Statistical Analysis

Data were collected and entered into IBM SPSS Statistics Software [version 29.0.2.0 (20)]. A descriptive analysis was performed to present the demographic and clinical characteristics of the patients. The association of different clinical scores with the therapeutic response were classified through ordinal regression. Changes in the mean values of biochemical parameters from baseline to end-point therapy were tested using a paired *t*-test. Statistical significance was considered at a *p*-value less than 0.05.

4. Discussion

The high prevalence of hepatitis C globally, along with its silent progression toward potentially severe late-stage complications, underscores the necessity for early detection and treatment. With an acute phase that is often oligosymptomatic or asymptomatic, approximately 70% of cases progress to chronic infection [16]. The World Health Organization aims to eliminate hepatitis C infections by 2030 [17]. Research on antiviral medication has focused on molecules with direct-acting mechanisms and pan-genotypic effects. The fixed-dose combination of g/p represents a first-line treatment for HCV infections, regardless of genotype (1–6) [18]. However, the literature describes liver injuries associated with this therapy, potentially inducing re-activation of hepatitis B and transient decompensation [18,19].

The demographic data from the post-marketing observation studies (PMOS) cohorts are comparable to the cohort from this study regarding patient age (with a predominance of patients under 65 years, 84% vs. 62%). However, there are differences related to sex (57.6% male vs. 42.3%). The presence of comorbidities differs significantly from that observed in randomized clinical trials (47.1% vs. 74.6%) but is relatively similar to that determined in PMOS (46.9%) [16]. There are differences related to the types of comorbidities; in the study, hypertension, diabetes, dyslipidemia, and obesity were predominant. The average age of the evaluated patients was 54.17 $\pm$ 10.49, similar to the average age in other studies (56 years, 52 years) [20,21].

Regarding the SVR, the results of studies, both randomized (97.5%) and real-world (97.6%), including the present study (95.2%), support a very high rate, with no association identified with age, sex, background, or the presence of comorbidities [16].

A meta-analysis conducted by H-Y Hung et al. in 2022 identified nine studies regarding drug-induced liver injuries. The SVR (for 7650 participants) was 95%, as were the results of our study (95.2%) [22]. Similarly, a study published by S. Yaras et al. in 2023 on 686 patients with CHC and diabetes mellitus) showed an SVR of 91.4% after 12 weeks of treatment [20].

In large, randomized trials, rapid decreases in serum aminotransferases were observed in CHC patients treated with glecaprevir/pibrentasvir, similar to our study (89.55 $\pm$ 66.25 vs. 38.65 $\pm$ 12.72). Transient increases in aminotransferase levels, as mentioned in the literature, occurred in only about 1% of patients; the mechanism is less well understood, likely involving the synthesis of a toxic/immunogenic metabolite or drug interactions [18]. The ALT, AST, and TB levels determined at the initiation of treatment were lower than those observed in the present study. In both studies (the one published by S. Yaras et al. [20] and the present study), the mean values of liver markers tended to normalize post-treatment, supporting the safety of therapy administration even in concurrent diabetes mellitus. This meta-analysis also reports minimal changes in TB, AST, and Hb. Hyperbilirubinemia was more frequently observed in patients with cirrhosis. The present study indicates approximately double initial levels of hepatic markers (AST, ALT, GGT), with a tendency towards normalization upon re-evaluation (24 h after therapy completion). Hyperbilirubinemia can occur during glecaprevir/pibrentasvir treatment and is considered an adverse reaction [23]. Data analysis suggests that total bilirubin levels showed insignificant increases compared to the initial measurement (p = 0.208). A study published by H. Okubo et al. in 2018 (n = 33 patients) indicated an increase in TB in 15% of evaluated patients (grade $\geq$ 2) [23]. In a study on 236 patients, published by H. Tamai and J. Okamura in 2023, liver injuries

were highlighted in approximately 62% of the evaluated patients. There was no severe increase (grade ≥ 3) in liver markers (AST, ALT, ALP) in any patient. TB and GGT showed severe increases in less than 4% and less than 0.5%, respectively [19]. In the present study, data analysis suggests a decrease in hepatic markers (AST, ALT, GGT), with a tendency toward normalization.

The mechanism of action of glecaprevir/pibrentasvir on the lipid profile is unclear; the liver plays a crucial role in lipid metabolism, so improved liver function may lead to better cholesterol and triglyceride levels. A 2021 prospective observational study on 101 patients aimed to monitor lipid profile changes [24]. In this study, lipid values improved similarly to the present; TC decreased toward normal levels. In N. Akutsu et al.'s study, the TG levels were within normal limits at the beginning and at 8 and 12 weeks of treatment, compared to the present study, where values were elevated both initially and post-treatment. Published studies indicate that the lipid profile changes depending on the administered medication [25,26]. T.T. Tran et al., in a phase 3 study (2018), suggest a TG decrease of 28.6 mg/dL and a glucose reduction of 11.2 mg/dL [27], which could be explained by improved liver function and reduced insulin resistance.

The prevalence of type 2 diabetes mellitus associated with CHC in this study cohort was 16.3%, approximately half of the general prevalence identified. The mechanisms underlying increased hepatic insulin resistance and stimulation of lipolysis are complex, involving inflammatory cytokines, increased phosphorylation of insulin receptor substrate-1, and tumor necrosis factor-α [28].

S. Estefan et al. underline the reduction in blood glucose levels, HbA1c, and insulin after DAA therapy. In our study, the HbA1c level increased insignificantly 24 h after completing the treatment [29]. This explanation could be attributed to the fact that approximately 50% of patients who achieved SVR had controlled blood glucose levels. Increasingly, cases have been reported where, following DAA therapy, glycemic profiles improved, and the need for insulin and oral antidiabetic medications was reduced [28,30].

Regarding the liver fibrosis marker, the initial mean value of A2MG (an extracellular macromolecule with a broad-spectrum protease inhibitor role) was close to normal; upon re-evaluation, the mean value doubled [31]. No data are available in the medical literature regarding the evolution of this parameter under glecaprevirpibrentasvir treatment.

Logistic model analysis in the present study showed that FibroSure, SteatoTest, ActiTest, and NashTest scores were not significantly associated with SVR. Logistic regression applied in the study by L.W. Madsen et al. in 2022 indicates that low initial viral load and genotype 3 are predictors of therapeutic response [32]. Multivariate regression analysis, used in another study, identified age and TB as independent risk factors [19].

Medical literature supports a holistic approach to patients with CH in addition to standard treatment. Introducing antioxidants into patients' diets, such as vitamins C, D, and E, quercetin, Silybum marianum, and polyphenols (found in fruits, vegetables, and green tea), will help reduce characteristic inflammation, decrease insulin resistance, and improve the lipid profile [33,34].

Strengths and Limitations of the Study

This study's strength lies in the significant number of patients and the wide range of evaluated parameters. To our knowledge, this is the first study of its kind in Romania. The limitations of this study include the lack of evaluation of lipid-lowering medication (statins or fibrates) and the replacement of statins with ezetimibe two weeks before the start of g/p treatment, according to guidelines. Cholesterol fractions were not evaluated.

5. Conclusions

The therapeutic combination of glecaprevir and pibrentasvir, used in treating patients with CHC, improves biochemical markers (AST, ALT, GGT) and TC. The increase in HbA1c is insignificant, suggesting a safe profile for therapy administration in patients with diabetes mellitus.

Author Contributions: Conceptualization, A.M.C., P.M., H.T.J., F.M. and N.N.; methodology, A.M.C.; T.J. and N.N.; software, H.T.J. and N.N.; validation, P.M. and N.N.; formal analysis, A.M.C. and P.M.; investigation, A.M.C., P.M., H.T.J. and N.N.; resources, N.N.; data curation, A.M.C., P.M., H.T.J. and N.N.; writing—original draft preparation, all the authors; writing—review and editing, T.J., F.M. and N.N.; visualization, all the authors; supervision, P.M., T.J. and N.N.; project administration, N.N. All authors have read and agreed to the published version of the manuscript.

Funding: The APC was funded by the University of Oradea, Romania.

Institutional Review Board Statement: This study was approved by the Ethics Commission of Pitesti County Hospital (Approval No. 01.03.2019) and complies with the Declaration of Helsinki of the World Medical Association.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Acknowledgments: The authors thank the University of Oradea for providing access to their logistic facilities.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Stasi, C.; Milli, C.; Voller, F.; Silvestri, C. The Epidemiology of Chronic Hepatitis C: Where We Are Now. *Livers* **2024**, *4*, 172–181. [CrossRef]
2. Taha, G.; Ezra, L.; Abu-Freha, N. Hepatitis C Elimination: Opportunities and Challenges in 2023. *Viruses* **2023**, *15*, 1413. [CrossRef] [PubMed]
3. Dash, S.; Aydin, Y.; Widmer, K.E.; Nayak, L. Hepatocellular Carcinoma Mechanisms Associated with Chronic HCV Infection and the Impact of Direct-Acting Antiviral Treatment. *J. Hepatocell. Carcinoma* **2020**, *7*, 45–76. [CrossRef] [PubMed]
4. Abu-Freha, N.; Mathew Jacob, B.; Elhoashla, A.; Afawi, Z.; Abu-Hammad, T.; Elsana, F.; Paz, S.; Etzion, O. Chronic hepatitis C: Diagnosis and treatment made easy. *Eur. J. Gen. Pract.* **2022**, *28*, 102–108. [CrossRef] [PubMed]
5. Basit, H. Hepatitis C. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK430897/ (accessed on 10 August 2024).
6. Lala, V. Liver Function Tests. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK482489/ (accessed on 10 August 2024).
7. Giannini, E.G. Liver Enzyme Alteration: A Guide for Clinicians. *CMAJ* **2005**, *172*, 367–379. [CrossRef]
8. Lee, T.H.; Kim, W.R.; Poterucha, J.J. Evaluation of Elevated Liver Enzymes. *Clin. Liver Dis.* **2012**, *16*, 183–198. [CrossRef]
9. Kalas, M.A.; Chavez, L.; Leon, M.; Taweesedt, P.T.; Surani, S. Abnormal Liver Enzymes: A Review for Clinicians. *World J. Hepatol.* **2021**, *13*, 1688–1698. [CrossRef]
10. Unger, L.W.; Forstner, B.; Schneglberger, S.; Muckenhuber, M.; Eigenbauer, E.; Scheiner, B.; Mandorfer, M.; Trauner, M.; Reiberger, T. Patterns and Prevalence of Dyslipidemia in Patients with Different Etiologies of Chronic Liver Disease. *Wien. Klin. Wochenschr.* **2019**, *131*, 395–403. [CrossRef]
11. Silva, T.E.; Ronsoni, M.F.; Schiavon, L.L. Challenges in Diagnosing and Monitoring Diabetes in Patients with Chronic Liver Diseases. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2018**, *12*, 431–440. [CrossRef]
12. Batxelli-Molina, I.; Calvayrac-Pawlowski, S.; Moulin, V.; Lapalus, M.; Hem, S.; Laune, D.; Asselah, T.; Jardin-Watelet, B. Novel α-2-Macroglobulin Cleaved Fragments as Biomarkers of Early Liver Fibrosis in Patients with Chronic Hepatitis C. *Future Virol.* **2015**, *10*, 5–16. [CrossRef]
13. Atanasova, E.; Krastev, Z.; Mateva, L.; de Mey, C.; Antonov, K.; Jelev, D.; Martinova, F. Alpha-2 Macroglobulin Is the Simplest Serum Biomarker for Liver Fibrosis and Fibrogenesis in Chronic Hepatitis C. *J. Med. Dent. Pract.* **2015**, *2*, 153–164. [CrossRef]
14. Cotter, T.G.; Jensen, D.M. Glecaprevir/Pibrentasvir for the Treatment of Chronic Hepatitis C: Design, Development, and Place in Therapy. *Drug Des. Dev. Ther.* **2019**, *13*, 2565–2577. [CrossRef] [PubMed]
15. Forns, X.; Feld, J.J.; Dylla, D.E.; Pol, S.; Chayama, K.; Hou, J.; Heo, J.; Lampertico, P.; Brown, A.; Bondin, M.; et al. Safety of Patients with Hepatitis C Virus Treated with Glecaprevir/Pibrentasvir from Clinical Trials and Real-World Cohorts. *Adv. Ther.* **2021**, *38*, 3409–3426. [CrossRef] [PubMed]
16. World Health Organization: Hepatitis C [Internet]. [Updated 9 April 2024]. Available online: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c/ (accessed on 10 August 2024).
17. Sbarigia, U.; Wirth, D.; Van Nuys, K.; Huber, C.; Brookmeyer, R.; Stahmeyer, J.; Krauth, C. Economic study of the value of expanding HCV treatment capacity in Germany. *BMJ Open Gastroenterol.* **2017**, *4*, e000130. [CrossRef]
18. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]*; National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2012; Glecaprevir\Pibrentasvir. [Updated 7 February 2022]. Available online: https://www.ncbi.nlm.nih.gov/books/NBK548803/ (accessed on 10 August 2024).

19. Tamai, H.; Okamura, J. Risk Factors of Glecaprevir/Pibrentasvir-Induced Liver Injury and Efficacy of Ursodeoxycholic Acid. *Viruses* **2023**, *15*, 489. [CrossRef]
20. Yaras, S.; Demir, M.; Barutcu, S.; Yildirim, A.E.; Gurel, S.; Ucbilek, E.; Kurtulmus, I.A.; Kayhan, M.A.; Vatansever, S.; Adanir, H.; et al. The Efficacy and Tolerability of Glecaprevir/Pibrentasvir Treatment in a Real-World Chronic Hepatitis C Patients Cohort. *Hepatol. Forum* **2023**, *4*, 92–96. [CrossRef]
21. Zuckerman, E.; Gutierrez, J.A.; Dylla, D.E.; de Ledinghen, V.; Muir, A.J.; Gschwantler, M.; Puoti, M.; Caruntu, F.; Slim, J.; Nevens, F.; et al. Eight Weeks of Treatment with Glecaprevir/Pibrentasvir Is Safe and Efficacious in an Integrated Analysis of Treatment-Naïve Patients with Hepatitis C Virus Infection. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 2544–2553. [CrossRef]
22. Hung, H.Y.; Hung, W.L.; Shih, C.L.; Chen, C.Y. Drug-Induced Liver Injury by Glecaprevir/Pibrentasvir Treatment for Chronic Hepatitis C Infection: A Systematic Review and Meta-Analysis. *Ann. Med.* **2022**, *54*, 108–120. [CrossRef]
23. Okubo, H.; Ando, H.; Sorin, Y.; Nakadera, E.; Fukada, H.; Morishige, J.; Miyazaki, A.; Ikejima, K. Gadoxetic Acid-Enhanced Magnetic Resonance Imaging to Predict Paritaprevir-Induced Hyperbilirubinemia during Treatment of Hepatitis C. *PLoS ONE* **2018**, *13*, e0196747. [CrossRef]
24. Akutsu, N.; Sasaki, S.; Matsui, T.; Akashi, H.; Yonezawa, K.; Ishigami, K.; Tsujisaki, M.; Isshiki, H.; Yawata, A.; Yamaoka, S.; et al. Association of the Low-Density Lipoprotein Cholesterol/High-Density Lipoprotein Cholesterol Ratio with Glecaprevir-Pibrentasvir Treatment. *Intern. Med.* **2021**, *60*, 3369–3376. [CrossRef]
25. Chida, T.; Kawata, K.; Ohta, K.; Matsunaga, E.; Ito, J.; Shimoyama, S.; Yamazaki, S.; Noritake, H.; Suzuki, T.; Suda, T.; et al. Rapid Changes in Serum Lipid Profiles during Combination Therapy with Daclatasvir and Asunaprevir in Patients Infected with Hepatitis C Virus Genotype 1b. *Gut Liver* **2018**, *12*, 201–207. [CrossRef] [PubMed]
26. Younossi, Z.M.; Stepanova, M.; Estep, M.; Negro, F.; Clark, P.J.; Hunt, S.; Song, Q.; Paulson, M.; Stamm, L.M.; Brainard, D.M.; et al. Dysregulation of Distal Cholesterol Biosynthesis in Association with Relapse and Advanced Disease in CHC Genotype 2 and 3 Treated with Sofosbuvir and Ribavirin. *J. Hepatol.* **2016**, *64*, 29–36. [CrossRef] [PubMed]
27. Tran, T.T.; Mehta, D.; Mensa, F.; Park, C.; Bao, Y.; Sanchez Gonzalez, Y. Pan-Genotypic Hepatitis C Treatment with Glecaprevir and Pibrentasvir for 8 Weeks Resulted in Improved Cardiovascular and Metabolic Outcomes and Stable Renal Function: A Post-Hoc Analysis of Phase 3 Clinical Trials. *Infect. Dis. Ther.* **2018**, *7*, 473–484. [CrossRef] [PubMed]
28. Rife, K.; Lyman, A.; LeClerc-Kamieniecki, S.; Falck-Ytter, C.; Pascuzzi, K.; Burant, C.J.; Falck-Ytter, Y. Significant HbA(1c) Lowering in Patients Achieving a Hepatitis C Virus Cure. *Fed. Pract.* **2019**, *36*, S26–S32. [PubMed]
29. Estefan, S.; Brandão-Melo, C.E.; Dos Santos Silva, C.M.; Gomes, D.C.K.; Cardoso, P.; Costa, M.H.S. Metabolic Evaluation in Patients with Hepatitis C Treated with Direct Antiviral Agents. *Front. Med.* **2021**, *8*, 631600. [CrossRef]
30. Hum, J.; Jou, J.H.; Green, P.K.; Berry, K.; Lundblad, J.; Hettinger, B.D.; Chang, M.; Ioannou, G.N. Improvement in Glycemic Control of Type 2 Diabetes After Successful Treatment of Hepatitis C Virus. *Diabetes Care* **2017**, *40*, 1173–1180. [CrossRef]
31. Vandooren, J.; Itoh, Y. Alpha-2-Macroglobulin in Inflammation, Immunity and Infections. *Front. Immunol.* **2021**, *12*, 803244. [CrossRef]
32. Madsen, L.W.; Christensen, P.B.; Hansen, J.F.; Røge, B.T.; Holm, D.K.; Dröse, S.; Øvrehus, A. Four Weeks Treatment with Glecaprevir/Pibrentasvir + Ribavirin—A Randomized Controlled Clinical Trial. *Viruses* **2022**, *14*, 614. [CrossRef]
33. Lozano-Sepúlveda, S.A.; Rincón-Sanchez, A.R.; Rivas-Estilla, A.M. Antioxidants Benefits in Hepatitis C Infection in the New Daas ERA. *Ann. Hepatol.* **2019**, *18*, 410–415. [CrossRef]
34. Behl, T.; Kumar, K.; Singh, S.; Sehgal, A.; Sachdeva, M.; Bhatia, S.; Al-Harrasi, A.; Buhas, C.; Judea-Pusta, C.T.; Negrut, N.; et al. Unveiling the Role of Polyphenols in Diabetic Retinopathy. *J. Funct. Foods* **2021**, *85*, 104608. [CrossRef]