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THE IMPACT OF REMOTE SURVEILLANCE IN DELTA VIRAL LIVER CIRRHOSIS

321.01 – INTERNAL DISEASES (GASTROENTEROLOGY AND HEPATOLOGY)

Summary of the doctoral thesis in medical sciences

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The thesis was developed within the Department of Internal Medicine, Gastroenterology Discipline of the "Nicolae Testemitanu" State University of Medicine and Pharmacy

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CONTENT

INTRODUCTION

Current status and importance of the addressed problem. Liver cirrhosis ranks 15th among the leading causes of disability-adjusted life years (DALYs) worldwide [1]. Despite a modest decline in chronic viral liver diseases of hepatitis B and C etiology, hepatitis delta virus (HDV)–related liver cirrhosis remains a major public health concern in the Republic of Moldova. HDV-related liver cirrhosis is a highly morbid condition, associated with frequent hospitalizations and elevated mortality rates. More than one quarter of all deaths among patients with HDV-induced liver disease are directly attributable to hepatic complications. Therefore, sequential screening for decompensation represents a critical component in the management of patients with compensated liver cirrhosis, aiming to predict and prevent disease progression [2,3]. Surveillance in HDV-related liver cirrhosis encompasses the entire continuum of care, ranging from prevention through primary healthcare services to tertiary medical care. Multiple factors may reduce the intensity and effectiveness of surveillance and monitoring in liver cirrhosis, including patient-related factors such as limited health literacy, financial constraints, and restricted access to specialized healthcare facilities; provider-related factors such as inadequate awareness and adherence to clinical guidelines and protocols; limited effectiveness of specialized medical interventions; gaps in knowledge regarding long-term disease risks; and failure to identify patients at high risk for decompensation [4,5]. Inadequate monitoring and surveillance of patients with liver cirrhosis contribute to increased rates of hospital readmissions. Early readmission of patients with decompensated cirrhosis is costly and associated with poorer clinical outcomes [7]. Ninety-day mortality rates have been shown to be significantly higher among patients readmitted within 30 days compared with those who were not rehospitalized [8–10].

Surveillance acts as a proactive measure for monitoring liver function in individuals with cirrhosis, offering the best opportunity for early detection of hepatic decompensation and hepatocellular carcinoma, reduction of hospital readmissions, and optimization of treatment outcomes. The impact of hepatic decompensation on the effectiveness of cirrhosis surveillance may be mitigated through the availability of continuous surveillance strategies; however, these approaches remain insufficiently evaluated and implemented in HDV-induced liver disease [11,12].The implementation of patient-centered care strategies, including the integration of patient-reported outcomes, represents a proactive surveillance measure in liver cirrhosis management [13]. The increasing burden and costs of liver cirrhosis on patients and healthcare systems underscore the need for alternative approaches to healthcare delivery for this population. Mobile devices, such as smartphones and tablets, have become integral to daily life, and their use is now widespread. Recent studies have demonstrated overall positive outcomes from tailored applications for patients with HDV-related liver cirrhosis, with e-health interventions enabling continuous monitoring, personalized guidance, and improved access to medical services [14]. Nevertheless, robust evidence supporting self-management e-health interventions specifically designed for patients with HDV-related liver cirrhosis remains limited [15–17].

The research hypothesis. This research enables the identification of criteria for measuring the effectiveness of high-quality surveillance in patients with HDV-related liver cirrhosis in the Republic of Moldova by evaluating patients' quality of life under surveillance, the incidence of hepatic decompensation, and the rate of hospital readmissions among monitored patients. For the first time, factors contributing to inadequate surveillance and monitoring in patients with HDV-related liver cirrhosis will be analyzed, alongside the identification and emphasis of measures aimed at improving surveillance. This research is warranted given the severity of the disease and the limited availability of effective therapeutic options.

Aim of scientific research. To evaluate the impact of remote surveillance in patients with HDV-related liver cirrhosis in order to develop an integrated monitoring and personalized management algorithm aimed at reducing hepatic decompensation and improving patients' quality of life.

Objectives of the Research

1. To quantify the burden of liver disease by analyzing years of life lost (YLL) and disability- adjusted life years (DALYs).
2. To determine the sociodemographic and clinical–evolutionary profile of patients with hepatitis delta virus (HDV)–related liver cirrhosis in the Republic of Moldova.
3. To identify predictive factors associated with insufficient surveillance and the risk of decompensation in patients with HDV-related liver cirrhosis. To define and integrate a Decompensation Risk Index in patients with HDV-related liver cirrhosis.
4. To evaluate the effectiveness of remote surveillance (telemonitoring) on quality of life and reduction of hospital readmissions, using the Chronic Liver Disease Questionnaire (CLDQ).
5. To develop a practical surveillance and monitoring algorithm for patients with HDV-related liver cirrhosis, integrating clinical and biological data and telemonitoring parameters.

Synthesis of the general methodology applied in the scientific research. The study included patients with hepatitis delta virus–related liver cirrhosis selected from the Hepatology Department of the Public Medical-Sanitary Institution (PMSI) "Timofei Moșneaga" Republican Clinical Hospital and the Therapy Department of the Medical Service of the Ministry of Internal Affairs of the Republic of Moldova, which serve as clinical bases of the Department of Gastroenterology of the Nicolae Testemițanu State University of Medicine and Pharmacy. According to the study design, several stages were conducted: identification of the scientific hypothesis, patient screening, and implementation of the specific research methods, culminating in results and conclusions. Longitudinal surveillance assessment involved the analysis of qualitative indicators, such as hospital readmissions correlated with regular follow-up visits aimed at preventing decompensation. The evaluation of remote surveillance included the administration of the Chronic Liver Disease Questionnaire (CLDQ) as a component of health-related quality of life assessment at hospital discharge, and at 3 and 6 months post-discharge, using the

Viber application. Preventively, each patient was asked to provide consent for this method of communication. The results obtained through statistical analysis generated the study outcomes and formed the basis for the development of a stratified surveillance and monitoring algorithm for patients with HDV-related liver cirrhosis.

Within the doctoral program, the research received a positive approval from the Research Ethics Committee (Protocol No. 5, dated 17 June 2022) and was conducted based on the decision of the Scientific Council of the Consortium No. 2/4.6, dated 29 March 2023.

Scientific novelty of the study. The first national primary evaluation of the impact of surveillance and monitoring in hepatitis delta virus–related liver cirrhosis conducted through the proposed study represents the initiation of a patient-centered analytical approach and offers perspectives for influencing healthcare policy decision-makers. The study also analyzed barriers to reduced surveillance, which contribute to increased morbidity and mortality of HDV-related liver cirrhosis in the Republic of Moldova. The research identified a series of determinants influencing survival in patients with HDV-related liver cirrhosis, dependent on both patient-related and healthcare provider–related factors. Predictive factors for liver cirrhosis decompensation were identified, as well as the burden of advanced liver disease measured using DALYs. In addition, patient quality of life was longitudinally assessed using the CLDQ. For the first time, the effectiveness of remote surveillance in preventing hepatic decompensation and reducing hospital readmissions among study patients was demonstrated. Consequently, the applicability of remote surveillance is justified, particularly given the high level of patient satisfaction observed in this study as a result of teleconsultation use. This study is relevant to the national healthcare system as it documents inadequate surveillance in hepatitis delta virus–related liver cirrhosis associated with significant socioeconomic impact and proposes strategies to improve surveillance through the use of a risk index and the CLDQ in patient monitoring. For the first time, a surveillance and monitoring algorithm for patients with compensated and decompensated HDV-related liver cirrhosis was developed, integrating remote surveillance methods such as teleconsultation.

Theoretical significance and applicative value of the study. The obtained results are oriented toward improving survival in patients with hepatitis delta virus–related liver cirrhosis. The primary outcome of interest was mortality caused by complications of liver cirrhosis in patients with HDV-related disease. This study investigated the benefit of decompensation surveillance in terms of survival among patients with compensated liver cirrhosis and identified factors associated with surveillance effectiveness in reducing mortality. The results enabled integration of patient education into liver disease monitoring and early alerting at the first signs of decompensation, thereby transforming the patient with liver cirrhosis into a co-participant in medical care. Furthermore, the research demonstrated that the CLDQ is a valid instrument to be incorporated into the management of patients with HDV-related liver cirrhosis and may be considered part of quality-of-life assessment. Patient surveillance in HDV-related liver cirrhosis also includes teleconsultation, as demonstrated in this research, reflected by high patient satisfaction with this component. The practical value of the study lies in the development

of an integrated surveillance protocol for patients with hepatitis delta virus–related liver cirrhosis, incorporating quality-of-life questionnaires and teleconsultation as monitoring and surveillance methods.

Approval of research results. The initial and final results of the study were presented and discussed at national and international forums (Moldova, Romania, Slovenia, Japan).

–Slovenian Congress of Gastroenterology and Hepatology, 6th edition (Ljubljana, Slovenia, 2025);

–Congress of Gastroenterology, Hepatology and Digestive Endoscopy, 43rd edition (Cluj Napoca, Romania, 2024);

–International Medical Congress for students and young specialists MedEspera, 10th edition (Chisinau, Republic of Moldova, 2024) ;

–Annual Congress of the Asian-Pacific Association for the study of liver diseases (APASL), 33rd edition (Kyoto, Japan, 2024);

–JuniorRoMedINF Conference, first edition, (Timisoara, Romania, 2024) ;

–Congress of Internal Medicine, 4th edition (Chisinau, Republic of Moldova, 2024);

–Update course in Hepatology 2023: Liver Diseases Rare – Transition of medical care from pediatrics to adulthood, 4th edition (Chisinau, Republic of Moldova, 2023) ;

– Balkan Medical Week: Congress - Perspectives of Balkan Medicine in the post COVID-19 era, 37th edition (Chisinau, Republic of Moldova, 2023);

–Congress of Gastroenterology, Hepatology and Digestive Endoscopy 42th edition (Iasi, Romania, 2023);

– Update Course in Hepatology -New Frontiers in Hepatology, 3rd edition (Chisinau, Republic of Moldova, 2022);

–Annual Scientific Conference - Research in Biomedicine and Health: Quality, Excellence and Performance. USMF „Nicolae Testemitanu" (Chisinau, Moldova, 2022);

–International Medical Congress for students and young specialists MedEspera, 9th edition (Chisinau, Republic of Moldova, 2022);

– Update course in Hepatology: Precision hepatology; second edition (Chisinau, Republic of Moldova, 2021);

The thesis was discussed, approved and recommended for support at the defense at the meeting of the Gastroenterology Discipline, Department of Internal Medicine, (verbal process no.2 from 10.12.2025) and at the meeting of the Profile Seminar for specialties 321.General Medicine/Specialty: 321.01. Internal Medicine (Gastroenterology,

Hepatology); 321.02. Endocrinology; 321.08 Dermatology and Venerology (verbal process no. 1 of 2.02.2026).

Publications on the research topic.

The materials of the thesis were presented in various scientific publications, including: articles in journals from the National Register (4), articles in ISI journals, SCOPUS (1), abstracts/communications at international conferences (11), abstracts/communications at national conferences (1).

The research resulted in: 2 innovation certificates, 2 implementation acts, Gold Diploma and Certificate of Excellence at the International Exhibition INVENTCOR, Deva, Romania, Romania , Diploma and Silver Medal at the European Exhibition of Creativity and Innovation EUROINVENT, Iasi, Romania.

Summary of the thesis structure . The thesis is presented on 153 pages of Romanian language text, with content that includes the list of abbreviations, the list of tables and figures, introduction, 5 chapters, general conclusions, practical recommendations, the list of bibliographic references with 160 sources, annexes, the statement on assuming responsibility, the list of publications/participations at scientific forums and the candidate CV. The illustrative material contains 15 tables, 27 figures and 9 annexes.

Key words: cirrhosis of the liver, HDV, surveillance, DALY, CLDQ, hepatic decompensation, telemedicine, teleconsultation.

THE CONTENT OF THESIS

1.THE ROLE OF SURVEILLANCE AND MONITORING IN DELTA VIRAL LIVER CIRRHOSIS

This chapter reflects information regarding the mechanisms and factors of decompensation in delta viral liver cirrhosis, the social impact viewed through the global burden of disease indicators—disability-adjusted life years (DALY) and years of life lost due to premature mortality (YLL), remote surveillance through telemonitoring and prevention of hepatic decompensation, as well as the identification of indicators reflecting patient-reported outcomes related to the quality of care in cirrhosis.

2. MATERIALS AND METHODS

2.1. General characteristic of the research

In order to achieve the proposed objectives, the research was conducted in three dimensions: **Study 1.** The main scientific component, an observational longitudinal study conducted during 2021–2025, including 131 patients with delta viral cirrhosis (CH VHD) forming the research sample. It involved assessing the disease burden of CH VHD through DALY analysis. **Study 2.** An analytical observational study including two

independent equal cohorts of VHD patients: a derivation cohort (100 patients with CH VHD) and a validation cohort (100 patients). Medical data from the derivation cohort were used to develop the index predicting hepatic decompensation, while validation was performed on the second cohort. **Study 3.** A prospective longitudinal study in which a qualitative method of patient surveillance was applied using the Chronic Liver Disease Questionnaire (CLDQ) at three time points, enabling the assessment of changes in quality of life among patients monitored both physically and remotely. The efficiency of tele-consultation in post-discharge follow-up or after the first in-person visit to the specialist was also investigated. To evaluate patient satisfaction with tele-consultation, surveys were conducted during the first month after the tele-consultation was completed. The Telemedicine Satisfaction Questionnaire (TSQ) was used to assess overall patient satisfaction.

Research Instruments: The study collected socio-demographic, clinical, and paraclinical data (via the patient's personal file capturing demographic information, anamnesis, paraclinical and clinical findings, and disease progression), as well as standardized tools for evaluating quality of life (CLDQ), already translated and approved for use in Romania and the Republic of Moldova.

For a better accuracy and sensitivity of the research, the study group was defined according to certain criteria.

The inclusion criteria were:

1.Age over 18 years

2. Confirmed diagnosis of delta viral liver cirrhosis ,regardless of disease duration and severity

3. Patient or legal representative consent for study participation

Exclusion criteria from the research group:

1.Age < 18 years

2.Hepatic encephalopathy stage III-IV (for study 3- telemonitoring study)

3.Liver transplantation (for studies 2 and 3)

4.Lack of patient or legal representative consent

The research involved a step towards setting priorities in the period 2021 – 2025.

Stage I. **Formulating the scientific hypothesis** . This was based on reviewing publications on trends in delta viral cirrhosis research (Web of Science Core Collection, 2021–2022) , consulting biostatistical data of delta viral cirrhosis in the Republic of Moldova, to understand what could be the research group, according to the objectives. As a result, the concept of the study was created and the goals of the research were drawn up.

Stage II. **Defining the research sample**. The cohort included 131 patients with CH VHD subject monitored over a defined period (12 months). After obtaining the informed consent, the participants completed at the first visit: socio-demographic questionnaires and were trained for further visits. The research started with the clinical and paraclinical evaluation of the patient at the time of presentation, calculating the burden of cirrhosis by assessing DALY and identifying the predictive parameters of suboptimal surveillance (study 1). An index of decompensation risk was developed, validated, and calibrated , allowing patients to be stratified into three risk groups (study 2). Subsequently, the cohort of patients with CH VHD was selected, having previously undergone pre-screening, which excluded patients who did not have access to the internet, or without the ability or willingness to connect online with specialists, or those lost to follow-up for unknown reasons. At this stage, time tracking of these patients was initiated, through 2 methods: offline and online (study 3). Surveillance was carried out in three sequences: at discharge, 3 months after discharge, 6 months after discharge, and at 12 months the tele-consultation satisfaction assessment was evaluated. All patients with delta viral cirrhosis who were included in the study were assessed for quality of life by applying the CLDQ .

Stage III. **Data analysis and conclusions** The obtained results and conclusions served as the foundation for practical recommendations in clinical practice and formed the basis for further scientific hypotheses.This stage involved data processing and statistical analysis. Key points of the study were identified and later compared with existing literature. Several limitations of the study were also highlighted and discussed.

Ethical Considerations. After confirming eligibility, patients with delta viral liver cirrhosis were fully informed about the study's purpose, benefits, and risks. Participants received an information sheet, with explanations provided as needed, and subsequently expressed written consent.Confidentiality was ensured throughout the study. All collected data were stored in a password-protected database with restricted access, in compliance with the Research Ethics Committee of the "Nicolae Testemițanu" University (VP no. 5, dated 17.06.2022)

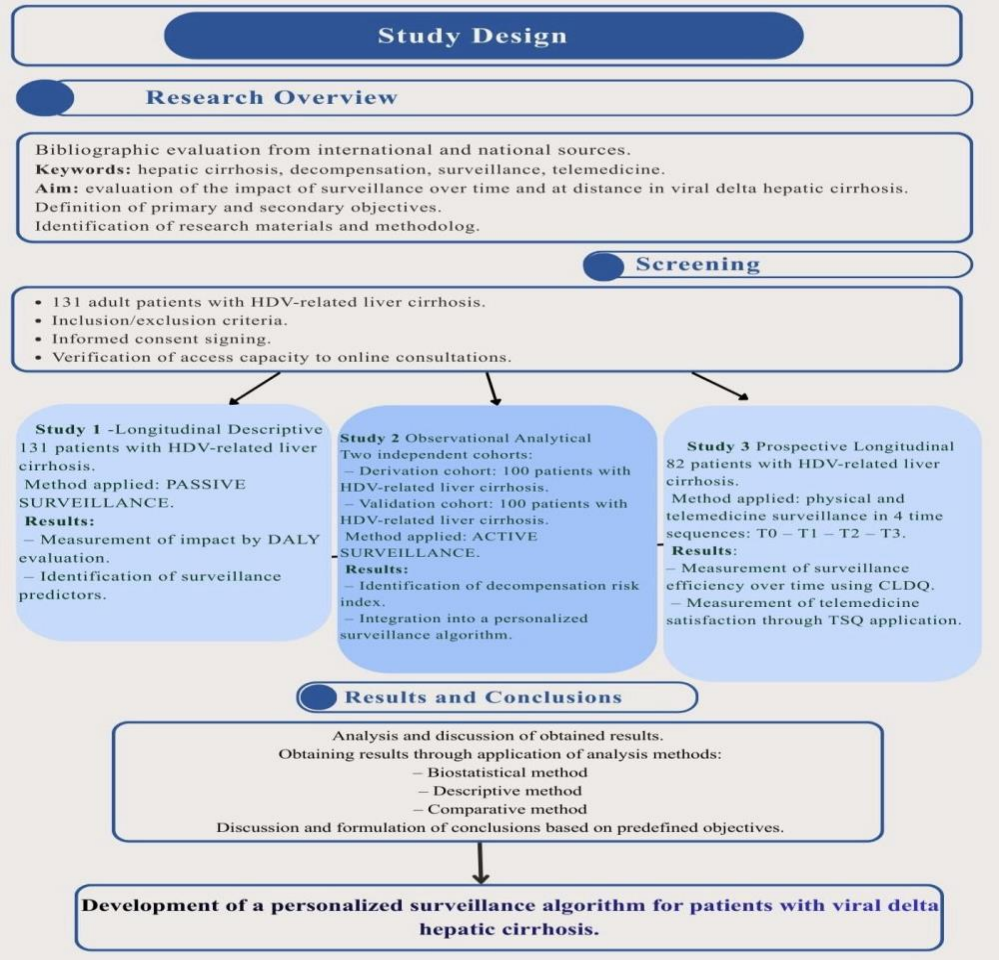

Figure 1: The study design

2.2.Research methods applied in the study

In the present study, patients' medical data were interpreted and subsequently analyzed from multiple perspectives, including demographic status, socio-economic status, clinico-evolutionary status, and quality of life in patients with viral delta liver cirrhosis. Quality of life was assessed using the Chronic Liver Disease Questionnaire (CLDQ). Data were collected using standardized forms specifically developed for patients with viral delta liver cirrhosis, including the primary patient assessment form, the CLDQ, and the Telemedicine Satisfaction Questionnaire (TSQ).

The socio-demographic profile included variables such as age, sex, ethnicity, place of birth, area of residence, access to specialist medical care, frequency of outpatient specialist visits, and the patients' general knowledge regarding their disease.

The clinico-evolutionary status comprised information on the presence or absence of symptoms characteristic of compensated or decompensated liver cirrhosis, including potential complications related to parenchymal and/or portal decompensation. Disease history data included age at diagnosis of hepatitis B virus (HBV) and hepatitis D virus

(HDV) infection, disease progression, prescribed therapy and its effectiveness, as well as the occurrence of initial decompensation events.

The biological profile included hematological examination, hepatic biochemical parameters, assessment of liver synthetic function, viral markers for HBV, HDV, and hepatitis C virus (HCV), as well as hepatic autoimmune markers when clinically indicated. Instrumental investigations consisted of ultrasonography, upper gastrointestinal endoscopy, non-invasive fibrosis scores (APRI, FIB-4), transient elastography (FibroScan), and advanced imaging modalities (MRI or multiphase CT) when indicated.

In this study, the survival indices of the delta viral cirrhosis patient were measured using the DALY score. Disabled years of life (DALY) were calculated by the formula: DALY = YLL + YLD. The share of disability has been measured on a scale from zero to one, where zero equals a state of full health, and one equals death. Disability weights (DW) were selected from the GBD Global Burden of Disease (Global Disease Population) sets for comparable clinical conditions .The estimated values of the study for liver-related health conditions are: Compensated cirrhosis: Low DW (12pecial. 0.039), Decompensated cirrhosis (Ascite): DW moderate to high (12pecial. 0.178), Hepatic encephalopathy: High DW (may exceed 0.400 in severe forms), Hepatocarcinoma (Heat cancer): very high DW (12pecial. 0.450 – 0.540). The Child-Pugh degree was used to estimate the remaining years of life, and this number was subtracted from the ideal age-specific life expectancy to obtain YLL. All categorical variables were presented as percentages and frequency, while all continuous variables were documented as mean and standard deviation. The Pearson correlation was used to evaluate the possible association between continuous variables. Questionnaires used. CLDQ was developed by Yonossi et al. in 1999 [18] and is the only tool validated for varying degrees of severity of chronic liver disease. The Romanian version includes 29 questions that are reflected in six areas: Abdominal symptoms (AS), Fatigue (FA), Systemic symptoms (SS), Activity (AC), Emotional function (EF) and Concern (PO). The domains SA and AT have 3 items each; FA, SS and PO have 5 items each; while EF comprises 8 items. Each item is rated on a 7-point Likert scale. The higher questionnaire score indicates minimal symptoms and the lower score indicates more pronounced symptoms. CLDQ is an internationally validated tool for patients with cirrhosis of the liver. We used the Romanian version, previously available and used in clinical research in the Romanian-speaking space. Since the population of the Republic of Moldova is linguistically compatible, a full revalidation of the instrument was not required, but the score was subject to internal consistency verification and analysis of domain correlations within the sample studied [19]. A threshold of CLDQ score was determined to evaluate HRQoL based on the literature being researched:

- Average CLDQ score ≥5 were considered to represent an increased quality of life (HRQoL),
- A CLDQ score of average<5 involved poor quality of life.

At the end of the first consultation, each patient completed the CLDQ questionnaire, but was also asked if he wanted to be consulted online later using the viber application, thus creating a group of participants tracked and consulted remotely. The ability to access tele-consultation was assessed using several questions adapted for people with cirrhosis of the liver, but also for those with low incomes. Participants were asked whether they had access to a device that could be used for tele-consultation (mobile phone, digital tablet or computer), whether they used any of their devices for joint telephone/internet-related activities (video calls/meetings, watching movies/videos/television programs, social networks, ordering food/products/services, and remote work. The consultation was considered resolved by telemedicine when adequate follow-up was obtained without the need to refer the patient to specialized ward. To assess patient satisfaction with tele-consultation, surveys were conducted at the end of the research on Telemedicine satisfaction questionnaire (TSQ) reflecting adhesion by responding to 14 items.

Data Processing and Statistical Analysis. The primary study data were processed using a personal computer with the functions and modules of Microsoft Office Excel 2023. Each category within the patient record required the coding of relative values assigned to each individual parameter to facilitate statistical analysis. All study groups used identical coding schemes for measurable and non-measurable parameters, ensuring statistical comparability.Data were centralized in a Microsoft Excel database. Objectives No. 1 and No. 2 were achieved using the personal patient record and DALY calculation, while Objective No. 4 employed the CLDQ and TSQ questionnaires.

Variables included nominal (categorical), quantitative (age, disease duration, ALT, AST, INR), and interval variables (age intervals for DALY calculations). Statistical significance was defined as $p < 0.05$ (two-tailed, 95% confidence interval). Data were presented using tables and graphical methods. Receiver Operating Characteristic (ROC) curve analysis was used to determine the decompensation index. Model performance was assessed using the area under the curve (AUC), where 1.0 indicates perfect discrimination and 0.5 indicates random performance.

3. RESEARCH RESULTS

Results of study 1.

3.1 Quantification of the Burden of Delta Viral Liver Cirrhosis in Terms of Years Lived with Disability

To assess the social and clinical impact of delta viral liver cirrhosis, the Disability-Adjusted Life Year (DALY) metric approved by the World Health Organization was applied to the study cohort DALY (concept proposed in 1990) [20]. Disease progression, complications, and mortality were analyzed over a 12-month monitoring period in 131 patients. There were analyzed aspects of the natural progression of the disease with the progression to cirrhosis of the liver, taking into account further installed complications that may affect the quality of life, such as ascites, hepatic encephalopathy, variceal bleeding, hepatocarcinoma development or death. In the context of delta viral liver

cirrhosis, the DALY indicator provides an integrated picture of activity-level health loss (service): years of life living with disability (YLD) + years of life lost through premature death (YLL). The main results obtained in the research cohort (in 131 patients with CH VHD) monitored for the 12-month period revealed multiple directions of interest. Using a conservative definition of YLD (decompensated if there is one or more events, such as ascites, HDS or hepatic encephalopathy at evaluation; DW=0.178; 1.0 year duration)[21] and estimating YLL from the difference between standard life expectancy and age at death, we obtained: total YLD = 13.17 years, total +YLL = 716.80 years, total DALY = 729.97 years (absolute, total value for the entire population and the entire period studied), that is, about 467.9 years/100 person-year at YLD of 8.4; YLL 459.5/100 person-year (per 100/person-year is a relative value, relative to a standard unit, 100 people in 1 year, necessary to allow comparisons (figure 2). DW (Disability Weight) or disability weight coefficient measured how much loss of health a given condition produces: 0.00 = perfect health (no deficit), 1.00 = equivalent to death (total loss of health). In our cohort it is visible that the burden of cirrhosis is overwhelmingly dominated by mortality (98% of DALY). In practical figures, each death marked an average of 31 years of standard life expectancy, explaining the magnitude of YLL

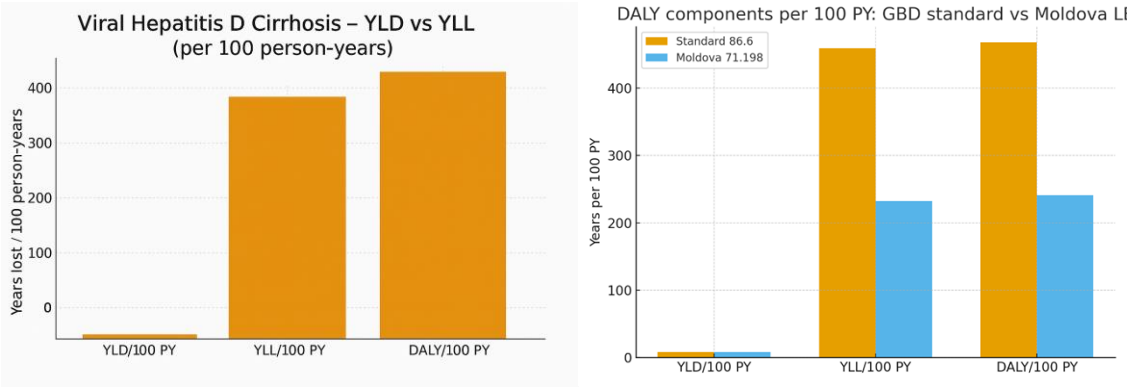

Figure 2. DALY components in patients with delta viral liver cirrhosis

Recalculation using national life expectancy data for the Republic of Moldova [22] reduced total DALY to 240.85 per 100 person-years, without altering the clinical interpretation that mortality is the dominant contributor to disease burden (table 1).The difference between the global and national standards does not change the clinical meaning: mortality remains the main driver of the burden; it only changes the reported magnitude, which is useful for communicating with local decision makers.

Table 1: DALY in patients with delta viral liver cirrhosis

Indicators	**Standard Life expectancy 86.6, GBD, 2019**	**Standard Life expectancy in Republic of Moldova 71.198 (2023)**
YLD (years)	13.17	13.17
YLL (years)	716.8	362.55
DALY (years)	729.97	375.73

YLD /100 PY	8.44	8.44
YLL /100 PY	459.49	232.41
DALY /100 PY	467.93	240.85

In the studied cohort, DALY is dominated by YLL, which reflects a high lethal burden and justifies the implementation without delay of meticulous, risk-differentiated surveillance with early post-discharge contact, telemonitoring and operational triggers (biological, and PRO tools). From the clinical and workplace management perspective, the decrease of DALY/100 persons – year becomes the central objective and tangible measure for the success of the surveillance intervention in VHD cirrhosis.

3.2 Evaluation of Socio-Demographic and Clinico-Evolutionary Factors in Patients with Delta Viral Liver Cirrhosis

The study cohort comprised 131 patients diagnosed with viral delta liver cirrhosis. The mean age of the entire cohort was 54.85 ± 9.55 years. In the compensated cirrhosis group, the mean age was 56.39 ± 8.80 years, whereas in the decompensated group the mean age was 54.26 ± 9.80 years. Approximately half of the patients (48.46%) were of working age, according to World Health Organization criteria. A slight predominance of male patients was observed (51.84%). Sex had a statistically significant influence on the age at which cirrhosis was diagnosed, with men being diagnosed at significantly different ages compared to women ($t = 2.70$, $p = 0.008$). The mean age at diagnosis of HDV-related liver cirrhosis was 47.25 ± 10.54 years. More than 50% of patients originated from the central region of the country (predominantly Chișinău, Ialoveni, and Hîncești), while approximately one third of patients were from the southern regions (Cahul, Cantemir, Comrat).

Clinico-evolutionary characteristics were further explored using unsupervised K-means clustering ($k = 2$), based on clinical and biological variables including AST, ALT, bilirubin, albumin, INR, serum sodium, platelet count, creatinine, and the presence of portal vein thrombosis (PVT). Cluster separation quality was assessed using the silhouette score (0.319), indicating moderate but acceptable separation for exploratory analysis. The "hepato-inflammatory" cluster was characterized by serum sodium levels of 135.8 ± 10.7 mmol/L, INR of 1.33, albumin levels of 31.2 ± 1.8 g/L, and significantly elevated cytolytic markers (ALT 91.2 ± 11.7 U/L, AST 112.1 ± 19.3 U/L) as well as cholestatic markers (γ-GTP 87.8 ± 21.3 U/L). Portal vein thrombosis was absent in this cluster, and the mean Child–Pugh score was 6 ± 1.6 points. The "hepato-vascular" cluster was characterized by lower serum sodium levels (131.8 ± 6.18 mmol/L, $p < 0.05$), higher INR values (1.70, $p < 0.05$), lower albumin concentrations (26.5 ± 3.4 g/L, $p < 0.01$), and a high prevalence of portal vein thrombosis (37%). Cytolytic and cholestatic markers showed only minimal, non-significant elevations. This cluster exhibited a more

progressive clinical course and a substantially higher rehospitalization rate (86.7% vs. 42%). The odds ratio for decompensation per cluster was OR = 1.46 (95% CI: 0.45–4.71, p = 0.782).

From a clinical management perspective, for two patients with identical severity scores, assignment to the "hepato-vascular" cluster may justify shorter intervals between follow-up visits, more frequent laboratory monitoring, and intensified management of portal hypertension–related complications.

Table 2. Clinico-evolutionary correlations in the study cohort (131 patients with HDV-related liver cirrhosis)

Variables – correlations	**Statistical results**
Albumin (g/l) – Ascites	34,0 vs cu 27,5; p<0,001, OR 0,40 (IC95% 0,26–0,63), **p<0,001**
Albumin (g/l) - Hepatic Encefalopathy	34,0 vs 27,0; **p<0,001**, OR 0,34 (0,21–0,55), p<0,001
Na seric (mmol/l) – Ascites	140,0 vs 137,0; p=0,002, OR 0,09 per SD (0,01–0,54), p=0,037
Na seric (mmol/l) - Hepatic Encefalopathy	140,0 vs 137,0; p=0,003
INR – Ascites	1,27 vs 1,42; **p=0,001**, OR 1,72 (1,13–2,61), p=0,042
INR – Hepatic Encefalopathy	1,24 vs 1,40; **p<0,001** OR 2,06 (1,30–3,26), p=0,010
MELD-Na - Ascites	med 10,0 vs 15,0; p<0,001, OR 2,22 (1,47–3,36), **p=0,001**
MELD-Na - Hepatic Encefalopathy	med 10,0 vs 15,0; **p<0,001**, OR 2,44 (1,58–3,77), **p<0,001**
scorul Child-Pugh - Ascites	7,0 vs 9,0**; p<0,001**, OR 1,47 (1,23–1,76), p<0,001
scorul Child-Pugh - Hepatic Encefalopathy	7,0 vs 9,0; **p<0,007**, OR 1,64 (1,34–2,00), p<0,001
Low platelets ($\times 10^9$/L) – Hepatic Encefalopathy	103,0 vs 75,0; **p=0,017**

Lower albumin levels were strongly associated with hepatic decompensation, with each standard deviation decrease significantly reducing the odds of remaining complication-free (OR < 1). Serum sodium also demonstrated a protective effect, with higher values associated with a lower risk of decompensation. Elevated INR was clearly associated with an increased risk of decompensation. Analysis of composite severity scores, including MELD-Na and Child–Pugh, demonstrated a stepwise increase in the risk of liver-related complications with increasing scores. Among hematological

parameters, only thrombocytopenia showed a significant association with hepatic encephalopathy (p = 0.017) (table 2). Patients presenting with hypoalbuminemia, hyponatremia, elevated INR, and high MELD-Na or Child–Pugh scores should be prioritized for intensive monitoring, either through early in-person visits or telemonitoring, regardless of age or sex, which were not independent predictors.

3.3 Definition of Surveillance Criteria in Patients with Delta Viral Liver Cirrhosis

Decompensation and rehospitalization represent key criteria for defining the effectiveness of surveillance in patients with viral delta liver cirrhosis. A central objective of the present analysis was to determine the impact of structured surveillance and monitoring on rehospitalization rates in this patient population. The analysis of the study cohort yielded consistent results supported by multiple statistical approaches, including classical and ridge-penalized logistic regression, Negative Binomial regression for the number of hospital admissions, Spearman and point-biserial correlation analyses, and evaluation of model discrimination using the area under the receiver operating characteristic curve (AUC).

Table 3. Factors associated with rehospitalization in delta viral liver cirrhosis

	Variables	**IRR**	**CI 95% (lower)**	**CI 95% (** upper)	**P value**
1	Sex (1=male)	1.662	0.956	2.891	0.072
2	Age (years)	1.003	0.951	1.059	0.9
3	Age at diagnosis, years	0.977	0.93	1.026	0.35
4	Child-Pugh Score (numeric)	0.93	0.751	1.152	0.507
5	MELD-Na	1.028	0.948	1.114	0.506
6	Portal vein thrombosis (1=yes)	1.868	0.868	4.019	0.11
7	Lower platelets (1=yes)	1.736	0.73	4.129	0.212
8	HCC (1=yes)	1.232	0.585	2.598	0.583
9	Ascites (1=yes)	0.825	0.442	1.542	0.547
10	Hepatic Encefalopathy (1=yes)	1.607	0.852	3.031	0.143
11	Variceal bleeding(1=yes)	0.556	0.289	1.07	0.079

In the Negative Binomial regression model, designed to analyze the number of rehospitalizations, severity-related factors (MELD-Na and Child–Pugh scores) and clinical events, including ascites and hepatic encephalopathy, were associated with a significant increase in rehospitalization rates. Each additional point in the Child–Pugh score increased the rehospitalization rate by approximately 15%, while severe thrombocytopenia (<50 × 10^3/mm^3) was associated with an incidence rate ratio (IRR) of 1.5, underscoring the substantial burden placed on hospital resources (table 3, figure 3).

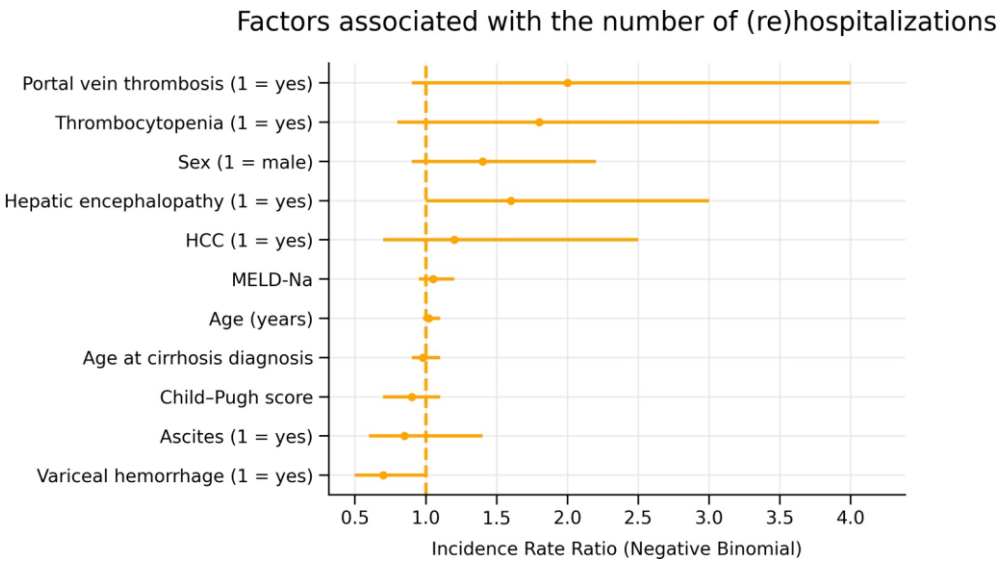

Figure 3. Factors associated with the number of rehospitalizations in patients with HDV liver cirrhosis

Severe thrombocytopenia demonstrated an inverse correlation with the number of rehospitalizations, while longer disease duration increased the cumulative burden on the healthcare system through repeated admissions. Male sex was associated with a higher utilization of healthcare services, reflecting more frequent decompensation episodes. Decompensation itself showed a strong positive correlation with rehospitalization frequency. These findings support the need for differentiated surveillance strategies in patients with viral delta liver cirrhosis.

Table 4. Significant correlations between predictor variables for re-hospitalization

Variable 1	**Variable 2**	**Correlation coefficient (ρ)**
Age	Decompensation	+0.24
Disease duration	Number of rehospitalizations	+0.31
Platelet count	Number of rehospitalizations	–0.35
Sex (male)	Number of rehospitalizations	+0.28
Decompensation	Number of rehospitalizations	+0.38

Factors affecting the severity of delta viral liver cirrhosis. Analysis of factors influencing the severity of disease evolution demonstrated that male sex was associated with an approximately eightfold increased risk of decompensation compared with female sex (OR = 8.05; 95% CI: 2.01–213.66), suggesting an independent role of sex in disease progression. Portal vein thrombosis emerged as a major determinant of decompensation (OR = 142.54; 95% CI: 1.03–552.00), while thrombocytopenia was associated with a nearly tenfold increased risk (OR = 10.41; 95% CI: 1.88–232.53). The presence of hepatocellular carcinoma was also significantly associated with decompensation, increasing risk by more than 600-fold (OR = 665.05; 95% CI: 1.00–5383.48), although the wide confidence interval suggests an influence of small case numbers (table 5).

In contrast, patients' age, age at cirrhosis diagnosis, and Child-Pugh and MELD-Na scores did not demonstrate a statistically significant association with decompensation in the cohort analysed. Contrary to data from the international literature, where these parameters are considered established predictors of the prognosis in cirrhosis, in patients with VHD the clinical profile seems to be particularized, with the predominance of vascular and oncological complications.

Table 5. Relevant factors for hepatic decompensation

	Variable	**OR**	**CI 95% (Lower)**	**CI 95% (Upper)**	**p**
0	Sex (male)	8.048	2.011	213.655	0.083
1	Age (years)	1.106	0.951	1.599	0.431
2	Age at diagnostic of cirrhosis (years)	0.892	0.644	1.014	0.349
3	Child-Pugh score	1.466	0.879	3.589	0.267
4	MELD-Na score	0.992	0.767	1.367	0.952
5	Portal Vein Thrombosis	142.541	1.027	552.001	0.017
6	Trombocitopenie	10.406	1.883	232.531	0.063
7	HCC	665.048	1	5383.489	0

The probability that the model correctly discriminates between a patient with and without decompensation was 89.9% (figure 4), indicating very good predictive performance. This finding supports the integration of these factors into a risk stratification algorithm with direct clinical implications for personalized monitoring and management of patients with viral delta liver cirrhosis.

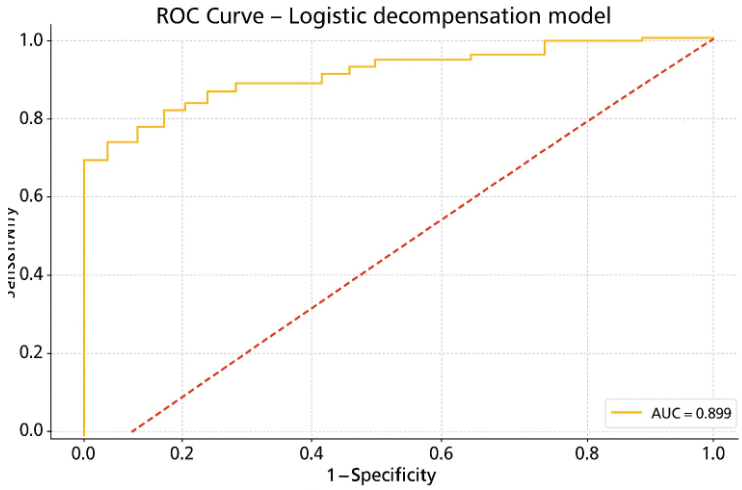

Figure 4. ROC curve for prediction of hepatic decompensation in patients with HDV liver cirrhosis

Results of study 2.

3.4 Derivation and validation of a decompensation index (Risk Index)

The derivation and validation of a decompensation index (Risk Index), based on the most influential predictors identified through penalized logistic regression, represented the next step of the research and constituted the foundation of Study 2. Initially, decompensated status was defined as a composite variable encompassing any decompensation event, including variceal hemorrhage, ascites, or hepatic encephalopathy.Two cohorts of patients with viral delta hepatitis–related liver cirrhosis were evaluated: a derivation cohort (100 patients with HDV-related cirrhosis extracted from the research sample) and a validation cohort (100 patients with HDV-related cirrhosis extracted from the institutional registry of patients with HDV-induced liver disease).

Clinical Characteristics of the Cohorts - ***Derivation cohort.*** The median age was 56.0 years (49.0–61.8), with an even sex distribution (51.5% male). The biological profile revealed hypoalbuminemia (mean albumin 30.0 [26.0–35.0] g/L), thrombocytopenia (platelets 86.0 [57.0–129.0] $\times 10^9$/L), INR 1.3 (1.2–1.6), AST 72.0 (46.0–120.0) U/L, ALT 61.0 (40.0–118.0) U/L, and total bilirubin 49.0 (41.0–57.0) µmol/L.Disease severity was expressed by MELD-Na 11.0 (9.0–17.0) and Child-Pugh score 9.0 (7.0–10.0) points. Complications were frequent: ascites 44.6%, hepatic encephalopathy 46.9%, variceal bleeding 22.3%, and hepatocellular carcinoma (HCC) 17.2%. The age at HDV diagnosis was 44.5 (35.0–55.0) years, and the age at cirrhosis diagnosis was 49.0 (41.0–57.0) years. The mean interval between HDV diagnosis and cirrhosis diagnosis was 5.8 ± 8.9 years. ***Validation cohort.*** This cohort included 100 patients with HDV cirrhosis, with a mean age of 55.7 ± 8.8 years and a median of 55.0 (46.0–59.1); 50.8% were male. Biologically, the profile was somewhat milder compared with the derivation cohort: albumin 35.0 (29.9–39.0) g/L, platelets 106.5 (80.5–142.2) $\times 10^9$/L, INR 1.3 (1.1–1.4), AST 56.8 (41.0–

94.6) U/L, ALT 58.0 (42.0–95.5) U/L, and total bilirubin 46.4 (11.3–56.1) µmol/L.Complications at inclusion were: ascites 24.0%, hepatic encephalopathy 28.0%, variceal bleeding 11.0%, and HCC 8.0%. Disease severity scores were MELD-Na 13.0 (10.0–16.0) and Child-Pugh 8.0 (6.0–10.0) points.

Outcome and Index Derivation. The primary outcome of this validation was the assessment of the 12 month decompensation rate, defined as composite decompensation, including one or more events and at least one (re)hospitalization and/or the occurrence of a major complication (ascites, hepatic encephalopathy, variceal bleeding, HCC).For index derivation, penalized logistic regression (ridge regression) was used, incorporating an extended set of clinical and biological predictors. Based on predictors with strong clinical relevance and statistical stability, a Risk Index (also termed a "bedside score") was constructed. The initial model included 10 items, subsequently reduced to 7 binary items with fixed point values, allowing easy calculation at discharge. The selected items included:MELD-Na ≥ 15 (+2 points), Child-Pugh B/C ≥ 7 (+2 points), Albumin < 30 g/L (+2 points), Sodium < 130 mmol/L (+2 points), Platelets < 50 ×10⁹/L (+2 points), Ascites/hepatic encephalopathy/variceal bleeding (+1 point), Male sex (+1 point)(table 6). Three predefined risk categories were established:< 5 points – low risk, 5–7 points – intermediate risk, ≥ 7 points – high risk. The same rules (identical items, thresholds, and risk categories) were applied to the validation cohort.

Table 6. Integration of the decompensation index into the discharge sheet

Parameter	**Threshold**	**Points***
MELD-Na score	≥ 15	2
Child-Pugh score	B sau C	2
Hepatic Encefalopathy	present	2
Ascites	present	1
Variceal bleeding	present	1
Platelets	< 50 mii/mm³	2
INR	≥ 1,5	1
Total Bilirubin	≥ 34 µmol/L	1
Portal vein thrombosis	present	1
HCC	present	2

*Point values reflect the relationships derived from the model.

The discharge summary should include a dedicated section titled "Decompensation Risk Index", with Yes/No checkboxes or values, total score, and interpretation:

- 0–4 points (low risk): follow-up with general practitioner and specialist every 6 months
- 5–7 points (intermediate risk): specialist consultation recommended every 3 months
- ≥ 7 points (high risk): specialist evaluation recommended every 1–3 months

Model Performance and Validation. This index provides a rationale idea for continuous surveillance. Patients classified as "intermediate" and "high" risk account for approximately 80% of decompensation events; mandatory scheduling at discharge plus follow-up at 3 or 6 months reduces the likelihood of missing the therapeutic window. Discrimination was assessed using ROC analysis (logistic regression with the score as the sole predictor), calibration by observed-to-predicted ratios across deciles, and event rates by risk category. Outcomes of interest included the frequency and rate of decompensation events. In the validation cohort (100 patients), the 12-month decompensation rate was 39%. The bedside decompensation score demonstrated an AUC of 0.933, indicating excellent discrimination between patients with and without decompensation.

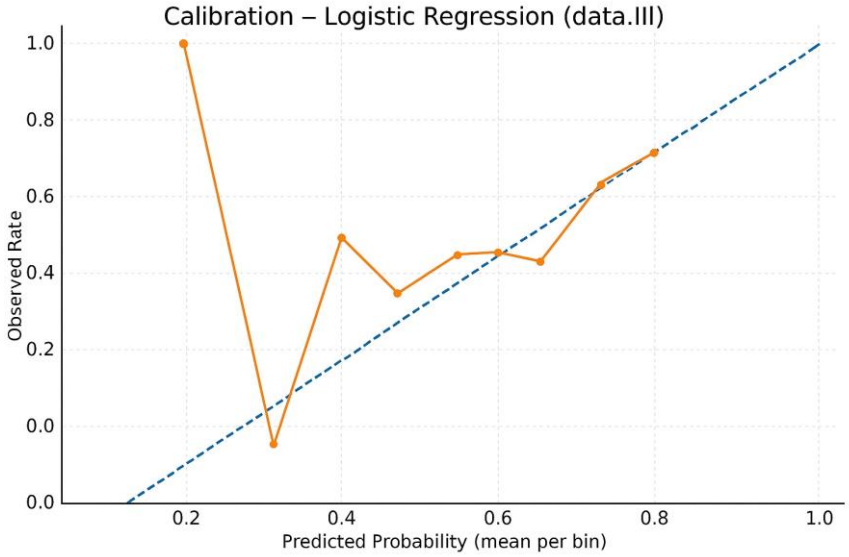

Figure 5. Calibration curve for the risk index

To enable scientific and clinical application, calibration of the index was required. The calibration curve demonstrated good agreement between predicted and observed risk for patients in the intermediate and high-risk categories, confirming the clinical applicability of the score. Deviations observed at lower probabilities suggest local under- or overestimation, possibly influenced by the smaller sample size in this category. These findings confirm that the index exhibits both excellent discrimination (AUC = 0.89) and satisfactory calibration (figure 5), making it suitable for integration into risk stratification algorithms.

Table 7. Performance of the Decompensation index

Variable	**Derivation cohort (100 p.)**	**Validation cohort (100 p.)**
AUC (95%CL)	0.84	0.93
Accuracy	89%	87%
Negative predictive value	100%	76%
Positive predictive value	64%	95%

This external validation (figure 6, table 7) confirms that the decompensation risk index generalizes to an independent cohort of patients with HDV cirrhosis, maintaining excellent discrimination and adequate calibration. The results support integration of the score into the discharge summary to guide follow-up frequency (1–3 months for high risk, 3 months for intermediate risk, and 6 months for low risk).

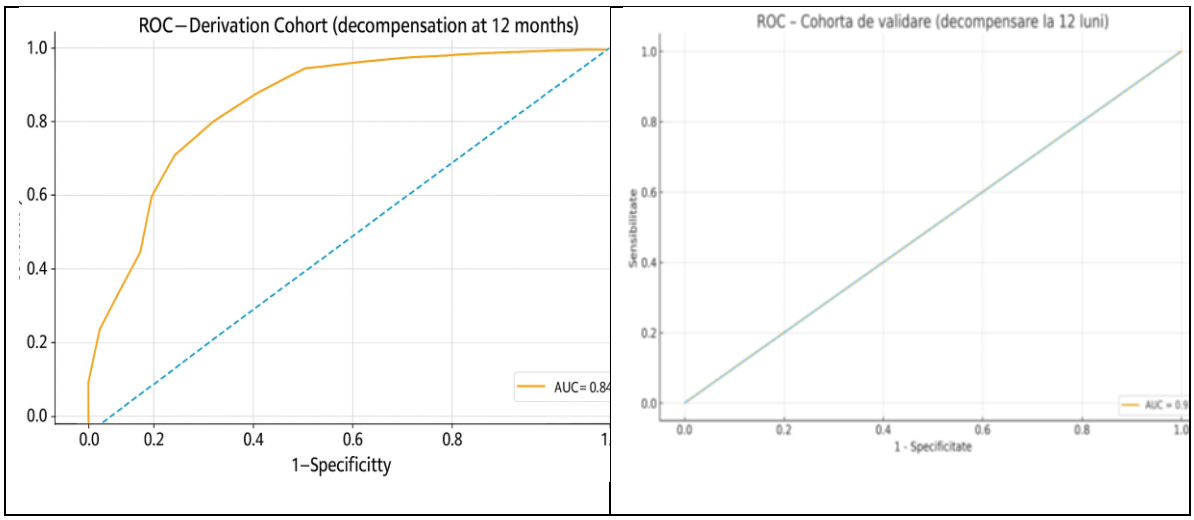

Figure 6. **ROC Curve for the Derivation Cohort and ROC Curve for the Validation Cohort**

The risk index provides excellent discrimination of 12-month decompensation risk in patients with HDV cirrhosis and is easy to implement at discharge. Its integration, together with symptom self-reporting (CLDQ) and a minimal laboratory panel, offers a practical framework for prioritizing follow-up and reducing decompensation events and (re)hospitalizations.

Results – Study 3

3.4 Patient-Reported Outcome (PRO) Instruments in Assessing the Effectiveness of Surveillance in Patients with Delta Viral Related Liver Cirrhosis

Patient-reported outcomes (PROs) are widely accepted by both patients and clinicians and have demonstrated potential to improve prognosis when integrated into routine clinical care, particularly through early identification of clinical deterioration and timely adjustment of therapeutic interventions. The Chronic Liver Disease Questionnaire (CLDQ) is one of the most extensively validated disease-specific PRO instruments in hepatology. It has undergone cross-cultural translation and validation, showing good validity and reliability across multiple etiologies, including liver cirrhosis. The primary objective of this study was to compare the efficacy and feasibility of telemonitoring (TM) versus conventional in-person visits (IPV) using the CLDQ instrument. The predefined outcomes were: (a) adherence to the follow-up program; (b) changes in quality of life as assessed by CLDQ; and (c) incidence of decompensation events and/or

(re)hospitalizations at 12 months. This was a prospective, longitudinal, pragmatic study conducted between 2021 and 2025, comparing telemonitoring with conventional in-person follow-up. Two cohorts of patients with hepatitis delta virus–related liver cirrhosis were included: a telemonitoring group (n = 52) and an in-person visit group (n = 30). Patients were excluded if they lacked access to a telephone and/or internet (for the telemonitoring group), presented with grade III–IV hepatic encephalopathy, or were listed for liver transplantation.

Intervention and Follow-up Protocol. Clinical assessment and CLDQ completion were performed at four predefined time points: T0 (discharge), T1 (3 months), T2 (6 months), and T3 (12 months).

***T0 (discharge):** patients received standardized training for CLDQ completion, completed the questionnaire, underwent specialist consultation, and had relevant medical data extracted from clinical records.

***T1 (3 months):** patients in the telemonitoring group completed the CLDQ online and participated in a 10–15 minute video consultation conducted by the investigator, focusing on clinical evaluation and identification of alarm signs suggestive of hepatic decompensation. Patients in the in-person visit group underwent a physical examination and completed the CLDQ on paper.

***T2 (6 months) :** patients in the telemonitoring group completed the CLDQ online and participated in a 10–15 minute video consultation conducted by the investigator, focusing on clinical evaluation and identification of alarm signs suggestive of hepatic decompensation. Patients in the in-person visit group underwent a physical examination and completed the CLDQ on paper. CLDQ online; video call 10-15 min. Physical presence (physical examination) + CLDQ on paper.

***T3 (12 months):** patient satisfaction with teleconsultation was assessed exclusively in the telemonitoring group using the Telemedicine Satisfaction Questionnaire (TSQ)

Clinical Trigger and Outcome Measures. A common clinical trigger was applied in both groups: a decrease of ≥2 points in any CLDQ domain or the occurrence of alarm symptoms (e.g., signs of hepatic encephalopathy or clinical deterioration) prompted classification as hepatic decompensation and urgent referral for hospitalization.
The mean difference in CLDQ score (ΔCLDQ) between baseline (T0) and 12 months (T3) was calculated. A positive ΔCLDQ indicated improvement in quality of life, whereas a negative ΔCLDQ indicated deterioration. The main outcomes included adherence to scheduled visits, mean ΔCLDQ (T0–T3), and number of hospitalizations.

The advanced practical hypothesis: telemonitoring reduces absenteeism and allows for earlier interventions.

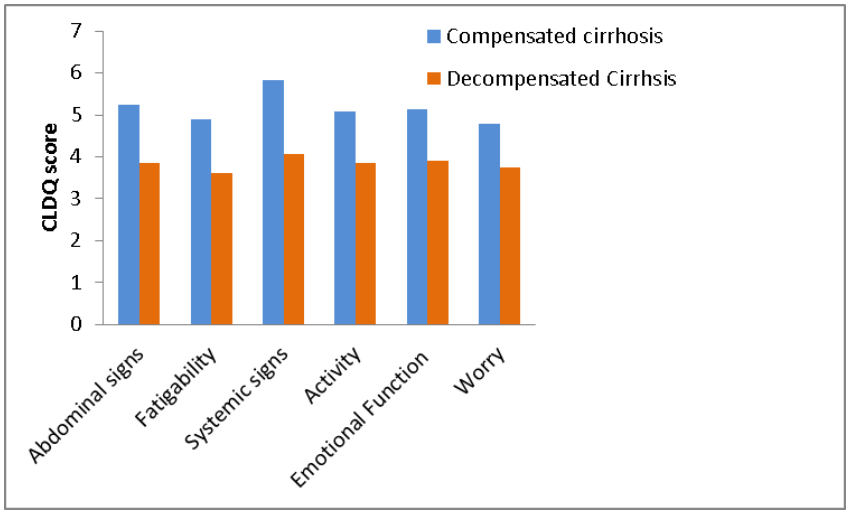

Figure 7. CLDQ domain characteristics in patients with hepatitis HDV liver cirrhosis.

Sex-related differences significantly influenced CLDQ domain scores. Female patients exhibited greater impairment in the Systemic Symptoms (SS), Activity (AC), Emotional Function (EF), and Worry (WO) domains, while fatigue (FA) impairment was comparable between sexes. Male patients demonstrated relatively more severe impairment related to physical disability, contributing to an increased burden in the management of hepatitis delta virus–related liver cirrhosis. Baseline clinical severity at discharge (T0) showed significant negative correlations with the total CLDQ score and all individual domains (Spearman's ρ, false discovery rate adjusted). Greater disease severity was consistently associated with poorer self-reported quality of life, particularly in the fatigue and emotional function domains. These findings support the sensitivity of the CLDQ as a patient-reported outcome instrument and its utility for clinical risk stratification in patients with hepatitis delta virus–related liver cirrhosis.

Analysis of the interrelationships between liver disease severity (stage T0 variable) and CLDQ domains reported the presence of negative correlations between cirrhosis clinical stage with all CLDQ domains and total score (Spearman ρ , adjusted FDR). Thus, CLDQ_total T0: ρ = −0,585, p_FDR < 0,001, Domains: FA = −0,653, EF ρ = −0,621, WO ρ = −0,515, SS = −0,505, AS ρ = −0,404, AC = −0,412 (all FDR < 0,011). The trend is observed that the higher the initial severity, the lower the self-reported quality of life in all dimensions, especially fatigue and emotional function. This validates CLDQ as severity-sensitive PRO and supports its use in risk stratification.

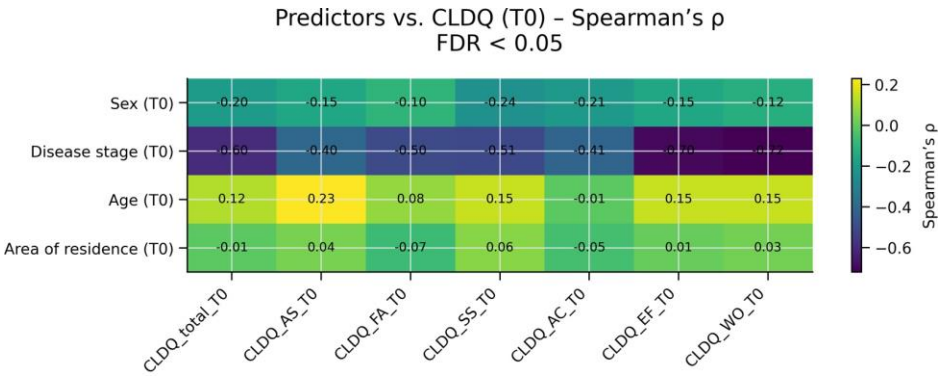

Figure 8. Predictors of liver disease severity and correlation with CLDQ

Several clinical predictors correlating with CLDQ domains (figure 8) have also been identified. Baseline clinical severity at discharge (T0) showed significant negative correlations with the total CLDQ score and all individual domains (Spearman's ρ, false discovery rate adjusted). Greater disease severity was consistently associated with poorer self-reported quality of life, particularly in the fatigue and emotional function domains.

More severe patients report a lower quality of life from discharge, in particular to FA, EF, SS and PO.

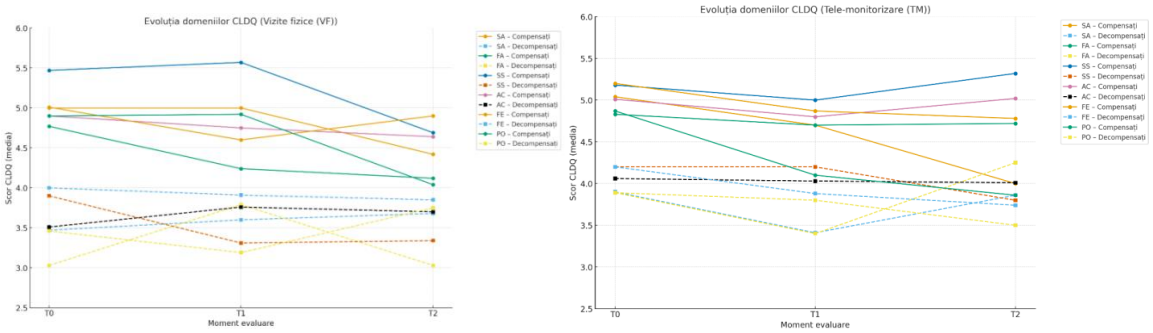

Figure 9. Temporal evolution of CLDQ domains in telemonitoring versus in-person follow-up groups.

In patients with delta virus–related liver cirrhosis, CLDQ scores showed a tendency toward better preservation of quality of life in the telemonitoring (TM) group compared with the in-person visit (IPV) group. Follow-up adherence differed substantially between groups. In the IPV group (30 patients), major losses to follow-up were observed, with 9 patients lost at T1 and an additional 7 patients at T2. In contrast, the TM group (52 patients) experienced fewer losses, with 3 patients lost at T1 and 1 patient at T2. Regarding rehospitalizations, 2 patients in the IPV group were rehospitalized at T1 and 4 patients at T2. In the TM group, only 1 patient was rehospitalized at T1, with no rehospitalizations recorded at T2. Overall, loss from the follow-up program reached 53.3% in the IPV group and only 7.7% in the TM group, indicating more than sevenfold higher adherence with telemonitoring. Rehospitalizations and clinically significant decompensation events occurred in 13.3% of patients followed through in-person visits compared with 1.9% in the telemonitoring group (figure 12). Patients monitored remotely

benefited from easier access to the medical team and earlier clinical interventions, without the burden of travel. This resulted in two major effects: substantially higher retention within the follow-up program and markedly fewer hospital admissions. These advantages were directly reflected in CLDQ scores, which demonstrated better stability or even improvement in the telemonitoring group, whereas quality of life progressively deteriorated in the in-person visit group.

Further analyses evaluated the impact of surveillance on quality of life at 3 months (T1) and 6 months (T2) after discharge, using a patient-centered timeline reflecting perceived clinical manifestations, abdominal and systemic symptoms, and overall health status.

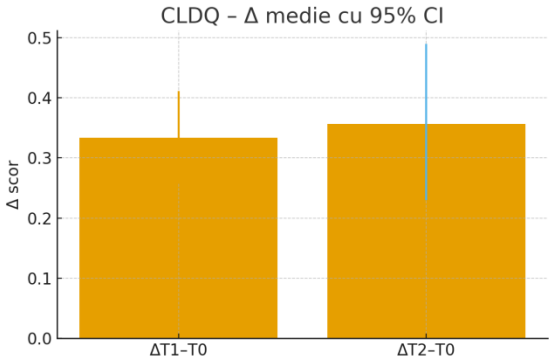

Figure 10. Temporal differences in CLDQ characteristics in patients with HDV related liver cirrhosis

Total CLDQ score has evolved over time as follows: Δ T1–T0: +0.333 (95% CI 0.257–0.406; N=54) and Δ T2–T0: +0.357 (95% CI 0.229–0,485; N=50) (Figure 10). Thus, the self-reported quality of life improves at 3 months and keeps or even modestly increases at 6 months.

Satisfaction with Telemedicine in HDV-related Cirrhosis. Patient satisfaction with telemedicine was assessed using the Telemedicine Satisfaction Questionnaire (TSQ), consisting of 14 items rated on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). The questionnaire captures patient feedback regarding accessibility, usability, and the perceived impact of telemonitoring on disease evolution.A total of 48 patients completed the TSQ. Among them, 31 patients had decompensated HDV-related cirrhosis, with a mean age of 51.84 ± 10.75 years, 46.87% were male, and 56.25% originated from the central region. The compensated cirrhosis subgroup included 17 patients, who were older on average (58.38 ± 7.83 years) and predominantly male (61.1%).The overall mean TSQ item score was 3.18 (SD = 0.32) (figure 11). In univariate analyses, higher TSQ summary scores were significantly associated with greater satisfaction ($p < 0.05$). In multivariable models, higher TSQ summary scores remained independently associated with greater satisfaction ($\beta = 0.01$; $p = 0.02$), while older age and disease decompensation or associated complications were linked to lower satisfaction scores.

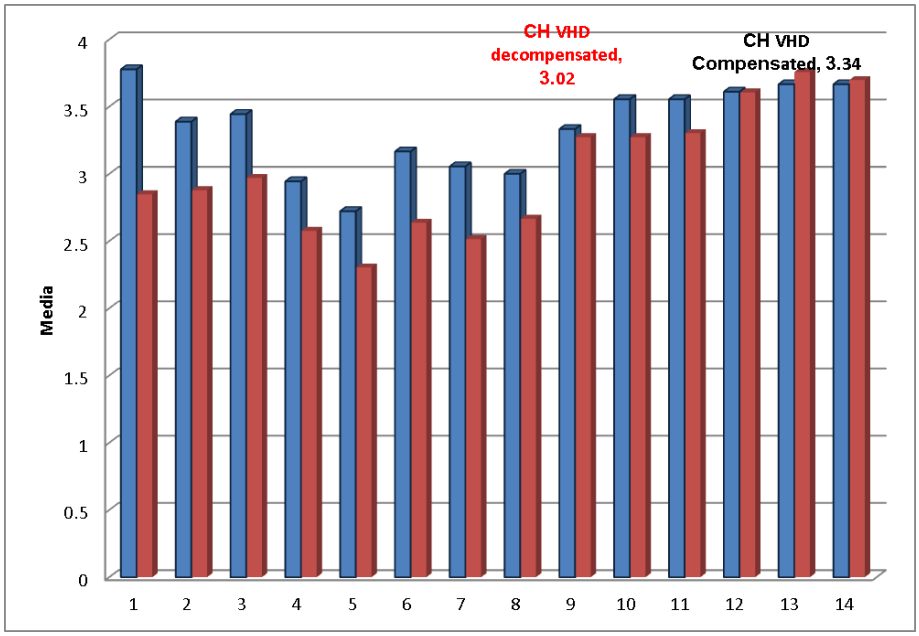

Figure 11. Telemedicine Satisfaction Questionnaire (TSQ) responses according to disease compensation status

Patients with decompensated disease reported significantly lower scores across all items related to accessibility, usefulness, and satisfaction with telemedicine services. Mean scores in the decompensated group were lower by approximately 0.4–1.0 points for most items. Given the sample size and magnitude of differences, these findings are likely statistically significant (estimated Welch t-values 2.3–4.0, $p < 0.05$).

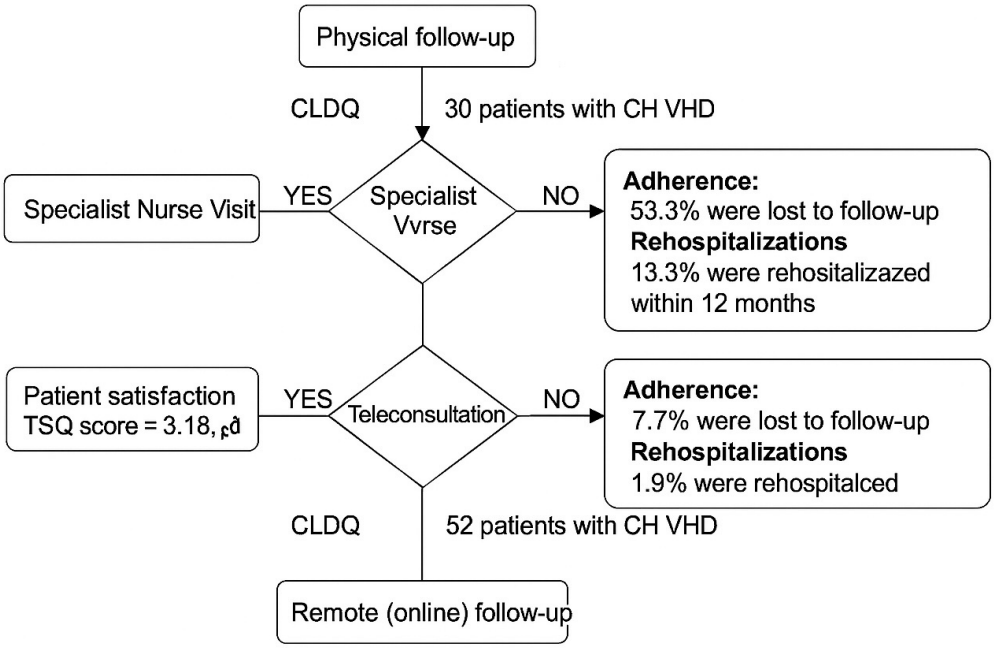

Figure 12. Temporal evaluation outcomes through teleconsultation versus in-person follow-up in patients with delta virus–related liver cirrhosis

3.5 Development of a Surveillance and Monitoring Algorithm for Patients with Hepatitis Delta Virus–Related Liver Cirrhosis

The results of our study highlight the role of remote surveillance in hepatitis delta virus (HDV)–related liver cirrhosis by integrating qualitative measures for the early identification of hepatic decompensation and the occurrence of cirrhosis-related complications into the surveillance strategy. Accordingly, the proposed surveillance algorithm incorporates a decompensation risk index, based on which patients with HDV-related liver cirrhosis are stratified into three risk categories. Subsequent clinical and paraclinical evaluation intervals are recommended according to the assigned risk category.According to this algorithm (figure 13), surveillance represents a practical and essential component of the management of patients with HDV-related liver cirrhosis, contributing to the prevention of morbidity and mortality, as well as to the improvement of health-related quality of life. For patients classified as low risk, surveillance every 6 months is recommended and includes consultation by a general practitioner, minimal laboratory testing, completion of the Chronic Liver Disease Questionnaire (CLDQ), and abdominal ultrasound for the detection of focal liver lesions. For patients in the intermediate-risk category, specialist evaluation every 3 months is recommended, together with completion of the CLDQ and laboratory testing including serum albumin, serum sodium, and platelet count, as well as ultrasound-based surveillance for hepatocellular carcinoma (HCC). In patients classified as high risk, close monitoring is advised at intervals of 1–3 months, including specialist consultations, comprehensive laboratory assessment, CLDQ completion every 3 months, and evaluation for liver transplantation.

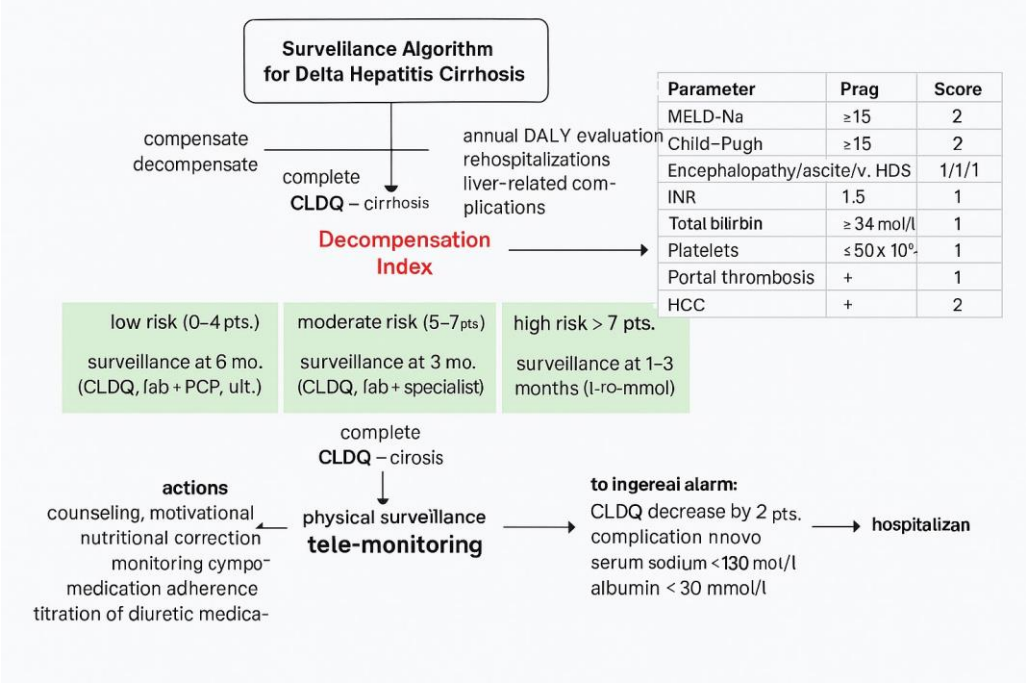

Figure 13. Surveillance algorithm delta viral liver cirrhosis

The algorithm also highlights predefined alarm triggers, including a decrease in CLDQ score of ≥2 points, the occurrence of a new cirrhosis-related complication, serum sodium levels below 130 mmol/L, and serum albumin levels below 30 g/L. The presence of these triggers mandates hospitalization or urgent specialist assessment. Patients presenting with hypoalbuminemia, hyponatremia, elevated international normalized ratio (INR), and increased MELD-Na or Child–Pugh scores should be prioritized for intensive monitoring, either through early in-person visits or telemonitoring, irrespective of age or sex, which were not identified as independent predictors.Our analysis has several strengths, as well as certain limitations. Key strengths include the integration of a comprehensive set of biological markers and clinical events into an extended logistic model, the development and internal validation (AUC) of a practical risk index that can be easily implemented in routine clinical records, and the consideration not only of disease progression but also of access to care and follow-up adherence, thereby providing a holistic perspective on surveillance.

Limitations of this study include its single-center design, albeit conducted in a tertiary care setting. In addition, contextual socioeconomic variables (such as income level and educational status) and healthcare resource factors (including the availability of hepatology specialists) were not captured, although these factors may influence surveillance effectiveness and adherence. This study demonstrates that the burden of HDV-related liver cirrhosis on the healthcare system is substantial and that current surveillance strategies do not adequately prioritize patients at the highest risk of decompensation and (re)hospitalization. Implementation of the proposed risk index at hospital discharge, combined with differentiated follow-up protocols (at discharge, 3 months, and 6 months) and systematic use of quality-of-life instruments such as the CLDQ, has the potential to significantly reduce complications and healthcare costs, thereby fulfilling the study objectives of burden assessment and surveillance optimization.Based on these findings, targeted interventions may be proposed, including the routine application of post-discharge telemonitoring and periodic training programs for specialists aimed at improving adherence to surveillance protocols.

4. General Conclusions

1. Quantification of the burden of liver disease through the analysis of years of life lost (YLL) and years lived with disability (YLD) demonstrates that, in the study sample, the burden of cirrhosis is overwhelmingly dominated by mortality (98% of DALYs), with a total disease burden of approximately 240.9 years per 100 person-years.

2. The clinical profile of patients with liver cirrhosis is predominantly characterized by males with a mean age of 56 years, originating mainly from the central and southern regions of the country, with cirrhosis diagnosed at a mean age of 47 years. The hepato-vascular cluster was identified as a clinical phenotype associated with a high rate of decompensation (OR = 1.46, 95% CI 0.45–4.71, p = 0.782).

3. The decompensation risk index (AUC = 0.84) and the rehospitalization rate (AUC = 0.772) were identified as indicators of insufficient surveillance in patients with hepatitis delta virus–related liver cirrhosis. The most influential predictors were male sex (OR = 8.05; 95% CI: 2.01–213.66), presence of portal vein thrombosis (OR = 142.54; 95% CI: 1.03–552.00), and thrombocytopenia (OR = 10.41; 95% CI: 1.88–232.53).

4. Significant negative correlations were established between the clinical stage of cirrhosis and the total CLDQ score ($\rho = -0.585$, $p < 0.001$), as well as across all CLDQ domains: fatigue (FA) $\rho = -0.653$, emotional function (EF) $\rho = -0.621$, worry (WO) $\rho = -0.515$, systemic symptoms (SS) $\rho = -0.505$, activity (AC) $\rho = -0.412$, and abdominal symptoms (AS) $\rho = -0.404$ (all $p < 0.01$). These findings validate the CLDQ as a severity-sensitive patient-reported outcome and support its use in risk stratification.

5. The ΔCLDQ reported via teleconsultation reflected an improvement in self-reported quality of life at 3 months, which was maintained or modestly increased at 6 months: ΔT1–T0 = +0.333 (95% CI 0.257–0.406) and ΔT2–T0 = +0.357 (95% CI 0.229–0.485). Telemonitoring demonstrated superior program adherence ($p < 0.05$), fewer rehospitalizations ($p < 0.05$), and greater stability of quality of life (ΔCLDQ), particularly among patients with compensated cirrhosis (4.98 vs. 4.6).

6. The development of a patient follow-up algorithm for HDV-related liver cirrhosis, integrating the decompensation risk index, CLDQ assessment, and temporal telemonitoring, represents a viable and effective tool for personalized surveillance of both compensated and decompensated cirrhosis patients.

Practical Recommendations

1. Quantification of the burden of liver cirrhosis using DALYs provides a tangible measure of surveillance effectiveness in HDV-related cirrhosis and supports the implementation of meticulous, risk-stratified follow-up with early post-discharge contact.

2. Use of the decompensation risk index at hospital discharge in patients with HDV-related liver cirrhosis allows stratification according to decompensation risk and provides a rationale for determining surveillance periodicity.

3. Implementation of a national remote surveillance protocol (telehepatology) for patients with hepatitis delta virus–related liver cirrhosis, integrated into national eHealth platforms.

4. Integration of the CLDQ questionnaire as a standardized tool for quality-of-life assessment in patients with liver cirrhosis, complementary to clinical and paraclinical evaluations. Its periodic use enables early detection of subjective health changes that may precede objective clinical deterioration.

5. Active involvement of nursing staff in the administration, monitoring, and preliminary interpretation of the CLDQ questionnaire, considering the essential role of nurses in the continuous surveillance of patients with HDV-related liver cirrhosis.

6. Promotion of patient medical education and continuous professional training for specialists in the use of telemonitoring technologies for chronic liver diseases.

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of Ms. Ecaterina Cebanu, PhD graduate, Discipline of Gastroenterology, Department of Internal Medicine, " Nicolae Testemițanu" State University of Medicine and Pharmacy of the Republic of Moldova, completed within the doctoral thesis entitled:
"The impact of remote surveillance in delta viral liver cirrhosis",
Internal Medicine Specialty (Gastroenterology, Hepatology).

SCIENTIFIC PUBLICATIONS

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