**Doctoral School in Medical Sciences**

The manuscript title

U.D.C: *616.36-004-07:616.36-089.843:614.2[043.2]*

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# ANALYSIS OF CLINICAL-BIOLOGICAL MARKERS AND SCORING OF PATIENTS WITH LIVER CIRRHOSIS IN THE LIVER TRANSPLANT PROGRAM

**321.24 TRANSPLANTOLOGY**

**Summary of doctoral thesis in medical sciences**

**Chisinau, 2024**

The thesis was developed in the Laboratory of Scientific Surgery „Reconstructive Surgery of the Digestive Tract". IP State University of Medicine and Pharmacy "Nicolae Testemitanu" of the Republic of Moldova.

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Doctoral thesis defense will take place on 14th of February 2024, at 14:00, Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, 165, Stefan cel Mare si Sfant Ave, room 205, in the meeting of the Commission for public defense of the doctoral thesis, approved by the decision of the Scientific Council of the Consortium from 05th of December 2024 (minutes of the meeting no. 26).

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## CONCEPTUAL FRAMEWORK OF THE RESEARCH

**Actuality and importance of the researched problem:** Although recent years have seen a steady increase in the incidence of liver disease, which is a serious problem in modern medicine, viral liver cirrhosis is still certainly underestimated both nationally and globally. Currently, worldwide 844 million people are registered with chronic liver disease, with a mortality rate of 2 million deaths per year, including 1 million deaths due to complications of cirrhosis and 1 million due to viral hepatitis and hepatocellular carcinoma [1].

Liver disease is becoming more and more common lately and more alarming worldwide, as well as in the Republic of Moldova, 75% of deaths caused by pathology of the digestive system are due to liver cirrhosis [2].

Epidemiological analysis of viral liver cirrhosis showed a 3-fold increase in morbidity in 2019 compared to 2000. As a result of which, the number of patients with liver cirrhosis of viral etiology increased in 2019 to 5482 patients. Also, in the case of chronic viral hepatitis, the majority of patients were detected with hepatitis B virus. In the multi-year dynamics the prevalence index of HBV morbidity increased from 655 cases (15.3 cases per 100 thousand inhabitants) in 2000 to 2422 cases (68.32 cases per 100 thousand inhabitants) in 2019. The prevalence rate in liver cirrhosis caused by C virus increased practically 9-fold, from 229 cases (5.4 cases per 100 thousand inhabitants) in 2000 to 2240 cases (63.19 cases per 100 thousand inhabitants) in 2019. Viral liver cyonoses, other etiologies and those not specified, showed a slight decrease from 522 cases (12.2 cases per 100 thousand inhabitants) in 2000 to 420 cases (11.85 cases per 100 thousand inhabitants) in 2019 [3].

Thus, at this stage, viral liver cirrhosis and primary liver cancer represent one of the most serious problems for the population, due to their global spread, increased morbidity and mortality, and the high degree of disability caused by the rapid progression of these pathologies. Globally, approximately 257 million people are infected with chronic viral hepatitis B, while 71 million people are infected with chronic viral hepatitis C, mainly in less developed countries. In 2019, 10 thousand patients with liver cirrhosis were registered in the Republic of Moldova, as a result of which 70% of patients with cirrhosis developed primary liver cancer. Morbidity for viral etiology liver cirrhosis, caused by virus D, increased from 183 cases (4.3 cases per 100 thousand inhabitants) in 2000 to 400 cases (11.28 cases per 100 thousand inhabitants) in 2019. What denotes a higher prevalence for the Republic of Moldova is HDV viral liver cirrhosis, which has a more aggressive and rapid evolution compared to other viral liver cirrhosis [3].

Over the past two decades, efforts have focused on reducing mortality on the liver transplant waiting list without compromising post-transplant outcomes. However, it can be

difficult to identify candidates who are too ill for HT to prevent unnecessary transplants [39]. The implementation of the MELD score was the first and most important change in liver allocation, redirecting donor organs to the sickest patients and aiming to reduce waiting list mortality [4].

Notwithstanding the fact, that there is a need for continuous consolidation and development of new prognostic scores for the end-stage liver disease population on the waiting list for liver transplantation in the Republic of Moldova, the validation of new scores and in fact what defines the research problem at hand, which is predestined to improve and prolong the quality of life of patients on the waiting list within the national liver transplantation system.

Thus, based on the above, the aim of the scientific work is to: study the clinical-biological landmarks and analyze different prognostic scores on the population with viral liver cirrhosis from the waiting list for liver transplantation in the Republic of Moldova.

The following general research objectives were stipulated to achieve the aim:

1. Evaluation of clinical-biological landmarks in patients on the waiting list for liver transplantation
2. Analysis of prioritization factors of recipients for liver transplant waiting list
3. Comparison of predictive accuracy between MELD score, MELD Na, MESO-index on mortality in the first 3 months after liver transplant listing
4. Validation of the MELD 3.0 prognostic score for mortality in the first 3 months of recipients on the liver transplant waiting list
5. Development of the algorithm for enrolling patients with decompensated viral liver cirrhosis on the liver transplant waiting list based on the validated maximum predictive accuracy prognostic score

**Scientific research methodology**

The present work represents a stepwise, retrospective and analytical clinical study focused on the evaluation of clinical parameters, results of instrumental methods of diagnosis and monitoring of 265 patients with viral liver cirrhosis included in the waiting list for liver transplantation. With the application of prognostic scores to predict mortality rate in the first 90 days after listing for liver transplantation.

Statistical analysis was performed using SPSS software, version 23.0. Data are reported as mean±SD. Gaussian normal distribution was tested by applying normality tests (Shapirko-Wilk test); and homogeneity of variance was checked by Levene's test. Differences between groups were detected by performing the independent t-test for normally distributed homogeneous values and the Welch test for non-homogeneous normally distributed values. The Mann-Whitney

U test was applied for non-parametric data or for parametric data not following the normal distribution. Differences were considered significant at a p-value less than 0.05.

The PhD scientific project was favourably approved by the Research Ethics Committee of the IP USMF "Nicolae Testemitanu" (no. 47 of 17.06.2019).

**Novelty and scientific originality of the results obtained:** Taking into account the increasing number of patients on the waiting list with viral liver cirrhosis, the long waiting time, the rapid progression of the disease with increased mortality rate of patients, for the first time an interdisciplinary clinical and paraclinical study was conducted, with a complex evaluation of prognostic scores predicting mortality in the first 90 days of listing, with the creation of a monitoring system validated and adapted for the Republic of Moldova. Careful monitoring and re-evaluation of candidates at regular intervals has been implemented which can improve the success of the liver transplant programme and the overall patient outcome.

**Scientific and practical problem solved**

The scientific-practical problem solved in the research is the development of the rational algorithm for evaluation and triage of patients with liver cirrhosis of viral aetiology from the waiting list in various clinical situations and greater accessibility in the view of the liver transplant coordinator team.

**Theoretical importance and applicative value of the study**

The applicative value of the study is reflected in the scientific work - the analysis of the concepts of scientists in the country and abroad, the hypotheses and problematizations made, as well as the knowledge we have gained through our PhD research, will broaden the horizon of research of clinical-paraclinical features in patients with liver cirrhosis of viral etiology and the assessment of prognostic scores of short-term mortality risk for patients included in the waiting list for liver transplantation. New scores have been proposed that exceed the predictive value of the MELD score and would facilitate the inclusion of patients on the liver transplant waiting list depending on the severity of the disease, so that patients with end-stage liver disease in severe disease are given priority for liver transplantation. Also in teaching activity - the conclusions and recommendations presented in the paper can be used in the training process of students/residents; practical activity - the acquired knowledge and the proposed recommendations will improve the work of clinics.

**Implementation of research results.**

The practical impact of the present study is the external validation of the new MELD 3.0 score on the population with viral liver cirrhosis from the waiting list for liver transplantation in the Scientific Surgical Laboratory ,,Reconstructive Surgery of the Digestive Tract" Nicolae

Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. In addition, the results obtained (validation of the new prognostic mortality score in the first 90 days after listing) were presented to medical students during the classes at the Department of Surgery No. 2.

**Approval of scientific results.** The results obtained were discussed and presented at the following scientific forums: the National Congress of Surgery, Sinaia, 2022, the National Congress of the Romtransplant Association, edition 2022, the scientific-practical conference with international participation ,,Hepatobiliary-pancreatic surgery, abdominal parietal defects, advanced laparoscopic surgery", Chisinau, 2022, the annual scientific conference ,,Research in biomedicine and health: Quality, Excellence and Performance" dedicated to the 77th anniversary of the founding of Alma Mater. National Conference ,,Days of the CF Clinical Hospital Iasi", edition 2022, Scientific Conference with international participation dedicated to the Medical Days of the Municipal Clinical Hospital ,,Saint Archangel Michael" 1st edition, 21.11.2022, International Scientific Conference ,,Tissue and Cell Transplantation. Actualități și perspective", National Scientific Conference on BPH Surgery, 20.04.2023 - 23.04.2023, Bucharest, Congress Balkan Medical Week, XXXVII edition Perspectives of Balkan Medicine in the post COVID-19 era, 7-9 June 2023, Chisinau, Republic of Moldova, National Congress of Surgery. The XIVth Congress of the Association of Surgeons ,,Nicolae Anestiadi" of the Republic of Moldova. 21-23 September 2023.

**Publications on the research topic.** 29 scientific papers have been published on the subject of the thesis, of which: 10 articles in scientific journals, 9 theses, 1 abstract in SCOPUS journal. 1 patent, active participations in national and international scientific conferences and congresses in total 10 participations confirmed by programs and certificates of participation. Of which, international communications - 2, national - 8.

**Thesis structure.** Thesis includes annotations in Romanian, Russian and English, list of abbreviations, introduction, 4 chapters with general conclusions, practical recommendations. The paper is followed by the list of bibliographical references with 222 sources and the author's CV. The introduction part of the paper reflects the topicality and scientific-practical importance of the problem addressed in the thesis, the aim, objectives, scientific novelty, theoretical importance and applied value of the research, approval of the results of the study.

**Keywords:** waiting list, liver transplantation, prognostic scores, viral liver cirrhosis, donor, MELD score, risk factors, complications, acute liver failure.

## THESIS CONTENT

# 1. FUNDAMENTAL CONCEPTS AND MODERN VIEWS OF DECOMPENSATED LIVER CIRRHOSIS

Although recent years have seen a steady increase in the incidence of liver disease, which is a serious problem in modern medicine, viral liver cirrhosis is still certainly underestimated both nationally and globally. Currently, worldwide 844 million people are registered with chronic liver disease, with a mortality rate of 2 million deaths per year, including 1 million deaths due to complications of cirrhosis and 1 million due to viral hepatitis and hepatocellular carcinoma [6]. Liver disease is becoming increasingly common in recent times and increasingly alarming worldwide, as well as in the Republic of Moldova, 75% of deaths caused by pathology of the digestive system are due to liver cirrhosis [1, 5].

*Pre-MELD transplant prioritization.* Understanding the evolution of the MELD score is key to learning liver transplant allocation policy. Prior to the implementation of the Model for End-stage Liver Disease (MELD) score, priority on the liver transplant waiting list was based on hospitalization status, time on the waiting list, and ultimately, the Child-Turcotte-Pugh (CTP) score and its complications. However, these prioritization methods allowed manipulation of the system through loopholes, leading to unfair prioritization of patients on the waiting list. For example, it allowed patients to be admitted to hospital to increase their priority on the waiting list even without a true indication for admission. In addition, the subjective components of the CTP score, namely the presence and degree of ascites or encephalopathy, led to inadequate assessment of a patient's severity.

In 2000, the Final Rule, which was designed by the U.S. Department of Health and Human Services, sought to ensure fairness by equitably allocating organs across geographic regions and prioritizing transplantation based on medical urgency defined by standardized criteria [6]. The Final Rule prompted the need for a validated objective score for prioritizing liver transplantation in order to avoid failures.

*MELD score in transplant allocation.* The MELD score was first developed in 2001 to predict survival in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt [7]. Its use has been extended to predict disease severity and survival in cirrhosis even more accurately than the CTP score [8]. Its objectivity and increased accuracy led to the endorsement of the use of the MELD score for transplant allocation and prioritization in 2002. MELD has increased transplant rates for patients with more severe disease and reduced waiting list mortality while maintaining post-transplant survival. Shortly thereafter, sodium levels were shown to be an independent predictor of mortality in cirrhosis and were then incorporated into the MELD score,

further enhancing its ability to predict mortality [9]. Although the MELD Na score is the most widely adopted prediction model in liver transplantation, it also has some limitations.

*MELD Na score limits.* Despite its improved predictive ability of mortality in cirrhosis, MELD Na still has limitations. It is a dynamic score that changes over time. Recent studies demonstrate a predictive ability to reduce the MELD Na score as the epidemiology of liver disease changes. The MELD Na score was developed when hepatitis C was the most common indication for transplantation. As the prevalence of hepatitis C decreases and the incidence of nonalcoholic fatty liver disease and alcohol-associated liver disease increases, the discriminative ability of MELD Na to predict mortality has decreased [10].

The inclusion of serum creatinine in the score inaccurately reflects true renal function [11, 12]. Individuals with lower muscle mass (i.e. sarcopenia) may have lower serum creatinine levels, inaccurately reflecting true renal function [13]. Similarly, women have less muscle mass compared to their male counterparts and therefore have lower creatinine levels, disadvantaging the prioritization of the MELD Na score on the waitlist [14].

In fact, a study of over 90,000 patients found that women are 20% less likely to be transplanted than men, despite having a higher mortality rate. In addition, the limitation of serum creatinine levels in the MELD Na score has been questioned as it is limited to 4 mg/dL, implying similar mortality among those with higher creatinine values and regardless of whether they are on dialysis [15].

## 2. MATERIAL AND METHODS OF STUDY

The work was carried out in the Scientific Research Laboratory ,,Reconstructive Surgery of the Digestive Tract", Department of Internal Medicine (Gastroenterology and Hepatology Discipline) of IP USMF "Nicolae Testemitanu", in the Hepatobiliopancreatic Surgery Department of IMSP Republican Clinical Hospital ,, Timofei Mosneaga" and National Transplant Agency.

This is a single-center study including all patients with viral etiology liver cirrhosis on the waiting list (n=265) listed for liver transplantation between 2013 and 2022, who were either transplanted during that time frame, deceased or active.Obiectivul principal al studiului a fost validarea de noi scoruri prognostic pe lista de așteptare pentru transplant de ficat.

Paediatric patients younger than 18 years were not included in the study. To improve the accuracy of the research, a number of inclusion and exclusion criteria were followed, thus allowing the study to be better defined and focused on a specific representative group.

**Criteria for inclusion in the research group :**

1. Patients with liver cirrhosis of viral aetiology with or without HCC.
2. Patients with serum viral markers: HBsAg; anti-HBc; anti HDV positive, anti HCV at least 6 months.
3. Patients aged 18-65 years.
4. Patients who have read and signed the informed consent of the study.
5. Patients with communication skills with the researcher, understanding and compliance with the research requirements.

**Exclusion criteria were:**

1. Patients with liver pathology of viral etiology other than B, D and C (other hepatotropic viruses), metabolic (Wilson's disease, hemochromatosis, alpha1 antitrypsin deficiency), drug, vascular, cholestatic, autoimmune.
2. Patients under 18 years of age.
3. Patients with lack of informed consent or request to withdraw from the study.
4. Patients with a history of immunodeficiency disease, primary immunodeficiency, including a positive HIV antibody test result.
5. Patients with severe associated pathologies affecting the progression of liver cirrhosis.
6. Patients with advanced malignant pathology of other systems and organs.

The analyses endeavoured to facilitate a comparison of areas under the receiver-operating characteristic curves (AUROC) for predicting mortality in the first 90 days with prognostic models investigated using data from the full cohort, as well as clinically relevant sub-cohorts, of waiting list candidates with specific indications for liver transplantation. The secondary objective of the study was to compare the prognostic models investigated using the mean scores of the quality criteria assessment scores provided.

In addition, we used detailed statistical methods to comparatively assess both discrimination and calibration of the models in the overall cohort and in specific subgroups. We also identified model boundaries to stratify those at higher risk of death. We found that variables associated with mortality in our cohort did not deviate from the literature data. The study design (Figure 1).

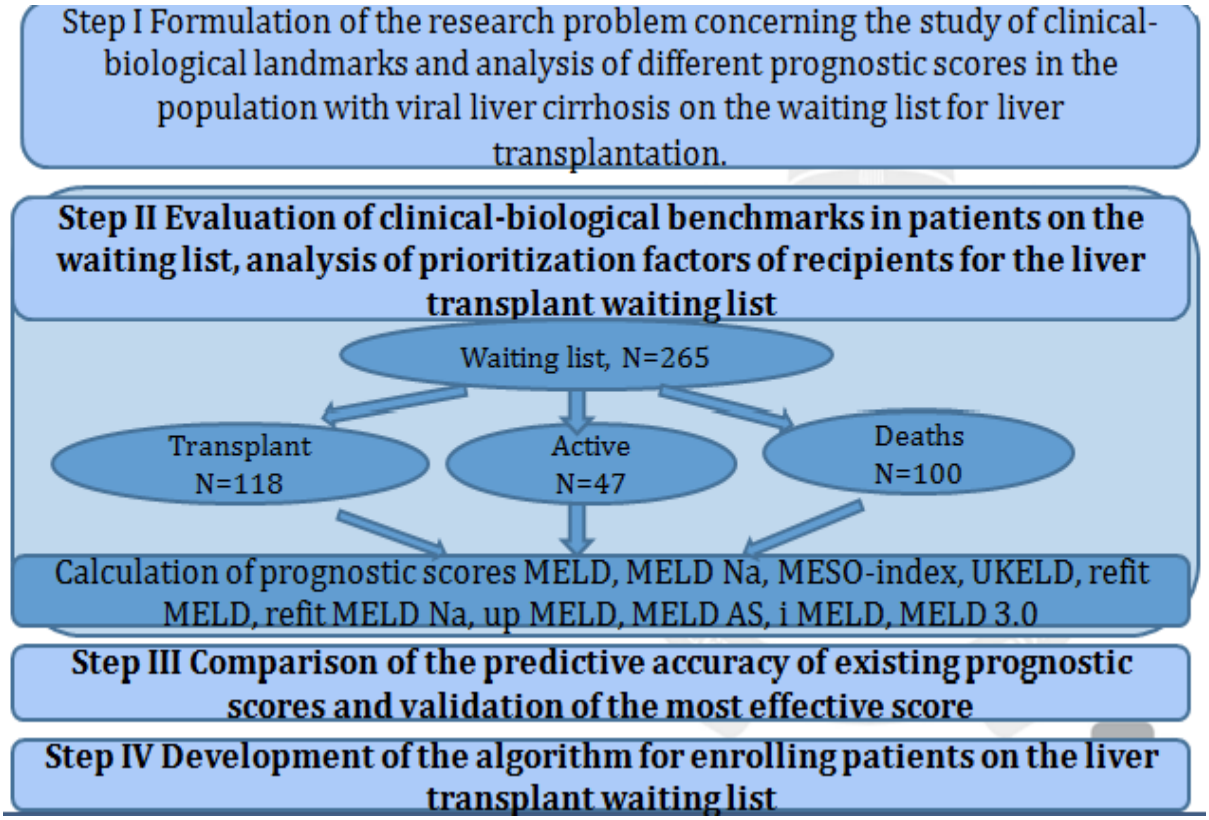

Figure 1. **Overall study design**

Validation of a prediction model essentially boils down to comparing predicted risks with actual observed outcomes in a patient population. There are different methods that can be used to compare them to assess predictive performance. For researchers planning an external validation study, transparent reporting of a multivariable prediction model is recommended for the Individual Prediction or Diagnosis checklist, explanatory and elaboration document [10]. The validation methods of the two most commonly used regression models in prediction, namely logistic and Cox proportional hazards.

## 3. CLINICAL AND EVOLUTIONARY CHARACTERISTICS OF PATIENTS ON THE WAITING LIST FOR LIVER TRANSPLANTATION.

### 3.1 Evaluation of clinical-biological landmarks in patients on the waiting list for liver transplantation

The cross-sectional clinical cohort study included 265 patients with viral liver cirrhosis aged 18-65 years on the waiting list for HT between February 2013 and January 2022. In 2013 when the liver transplant programme started, 35 patients were registered. Taking into account the shortage of transplants and technical shortcomings at the level of patient registration at the National Transplant Agency, the number of recipients on the waiting list is decreasing. With the onset of the COVID - 19 pandemic a low patient listing rate is maintained (in 2020 there were 8

patients and in 2021 there were 15 patients). The waiting list for HT has increased in dynamics in the last decade in the context of a huge shortage of organs, resulting in increased mortality rate on the waiting list, longer waiting times and lack of emergency supply of HT [16]. The mean age of the patients in the study group was 50.00 ± 9.97 years. The youngest patient was 18 years old and the oldest was 65 years old. Dividing them by age groups, it can be seen that most patients included in the waiting list were aged 46-55 years (39.31%), with statistically significant differences between the age groups compared (11.45% aged 18 (Figure 2).

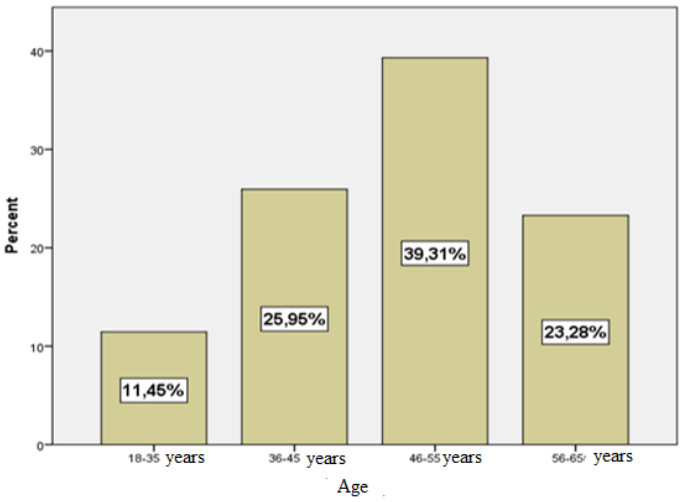


Figure 2. **Age distribution of patients on the waiting list (%)**

Thus, we note that 35 years vs 39.31% - those aged 46- 55 years , p<0,001).

The majority of patients (76.7%) on the waiting list are of working age (<55 years), which has an important socio-economic impact and explains the need to optimise the national transplant programme in order to increase the number of liver transplant surgeries.

The gender distribution in the study group showed an approximately equal share of men and women: women - 111 (41.88%) (95% CI - 35.9 - 48.1), reflecting the fact that end-stage liver disease affects both sexes equally.

Distribution by geographic area, more than half of the patients evaluated were from the Central 151 area (57%), explained by the higher accessibility of patients from this geographic area to medical centers, information and dynamic patient records. This is followed by the Southern area 64 (24.2%), the Northern area 41 (15.5%) and a smaller number from Transnistria 9 (3.4%), which again reflects the accessibility to medical services (p<0,001). Most patients listed for HT were from the urban area 172 - 64.9% (95% CI - 58.8-70.6), which notes better information, evidence, awareness and accessibility of the population to medical centres in the urban area. The most common patients on the waiting list were patients with viral cirrhosis type D 66.8% (177) (Figure 3), equally distributed were patients with viral etiology type B and C

12.8% (34) and 14.7% (39) of in the liver transplant program in the Republic of Moldova, HDV viral liver cirrhosis is predominant, has a more rapid and aggressive evolution compared to other viral liver cirrhosis.

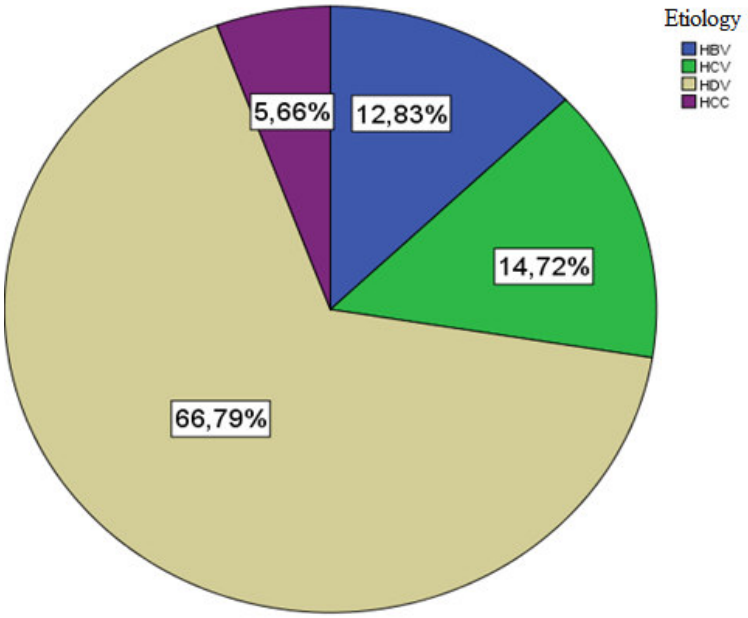


Figure 3. **Structure of patients by aetiology of liver disease (%)**

Whereas in the United States the prevalence of HCC in the waiting list is increasing reaching 30% of patients. Another increasing trend is non-alcoholic steatohepatitis, being 32% of the waiting list for liver transplantation [16]. Effective treatment of viral hepatitis C, has significantly transformed the landscape of chronic liver disease in the Republic of Moldova, viral hepatitis B and D, alcohol-associated liver disease still has clinical significance and is a considerable economic burden. Lack of effective treatment of HBV and HDV etiology liver diseases, alcohol-associated liver disease, contributes to the increasing severity of this disease among patients, leading to an evolution towards liver cirrhosis, especially decompensated liver cirrhosis requiring liver transplantation, in this context it is welcome to evaluate the etiology of liver disease among adults waiting for HT in the Republic of Moldova.Durata medie de așteptare în dependență de etiologia boli (figura 4) a fost cea mai

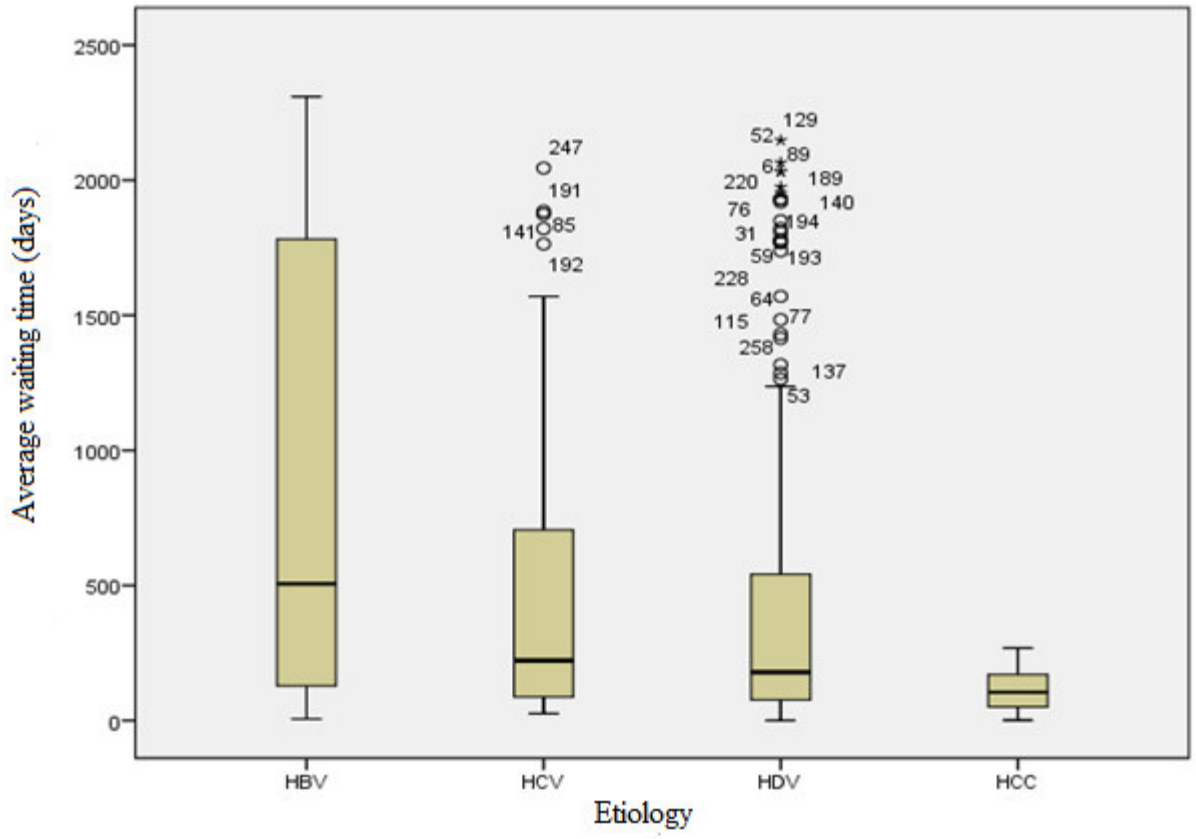


Figure 4. **Average waiting time on the liver transplant list depending on the aetiology of liver pathology**

The average waiting time for liver transplantation was 21.41 months in patients with HBV cirrhosis, 15.15 months in patients with HCV, 12.16 months in patients with HDV, and a much shorter period in patients with HCC of 4 months.

*Quality assessment of prognostic scores in patients included in the study*

In our study, to assess the quality of prognostic scores, laboratory data was applied, following which ten prognostic scores were calculated in the patients in the study group: MELD, MELD-Na, MELD 3.0, iMELD, MELD-AS, MESO-Index, UKELD, refit MELD, refit MELD Na, up MELD. Quality assessment of the prognostic models investigated was performed using the quality assessment tool for prognostic models for the first 90 days after liver transplant listing.

When assessing the MELD score the median in patients included in the study (Table 1), was 16.14±5.15 (7.79-37.72 points). The mean MELD-Na score was 19.17±5.38 (9.36-38.46 points). The value of the MELD 3.0 score determining the discrepancy between males and females was 17.46±6.68 (6.49-40.24 points). The i MELD score which also takes into account the age of the recipient obtained a higher mean compared to MELD and MELD Na, being 72.40±11.37 (34.84-106.22 points). MELD-AS score values were also higher due to the coefficients in the formula

26.11±6.07 (16.79-46.71 points). The lowest mean score was reported for the MESO-Index: 1.18±0.41 (0.59-2.97 points), taking into account its calculation formula with modified coefficients.

Table 1. **Prognostic scores calculated in patients on the waiting list for LT.**

| **Prognostic scores (points), median ± SD, (min-max)** | **Values** |
|---|---|
| MELD | 16,14±5,15 (7,79-37,72) |
| MELD-Na | 19,17±5,38 (9,36-38,46) |
| MELD 3.0 | 17,46±6,68 (6,49-40,24) |
| i MELD | 72,40±11,37 (34,84-106,22) |
| MELD-AS | 26,11±6,07 (16,79-46,71) |
| MESO-Index | 1,18±0,41 (0,59-2,97) |
| UKELD | 56,20±4,45 (46,27-71,35) |
| refit MELD | 16,49±4,99 (7,88-36,38) |
| refit MELD-Na | 14±4,17 (12,42-22,73) |
| up MELD | 3,78±0,69 (2,78-6,65) |

The UK version of the MELD score - the UKELD obtained a mean value of 56.20±4.45 (46.27-71.35 points). The refit MELD score showed a value of 16.49±4.99 (7.88-36.38 points). The up MELD score was 3.78±0.69 (2.78-6.65 points).

### 3.2 Analysis of prioritisation factors for recipients on the waiting list for liver transplantation.

For the analysis of the prioritisation factors of the recipients on the waiting list for liver transplantation, we performed the characterisation of patients according to their status.

Out of 265 patients included in the baseline group, 118 patients were transplanted (subgroup 1 Transplanted), 47 patients at the time of inclusion in the study were actively waiting for liver transplantation (subgroup 2 Active) and 100 waiting list patients included in the baseline group died during the study and constituted subgroup 3.

Analyzing the socio-demographic data (Table 2) we found that in the sublot of transplant recipients 66 (55.9%) were male, in the sublot of those waiting for liver transplantation (active), 30 (63.8%) male, in the sublot of those who died during the study showed 58 (58%) male, the sublots analyzed did not show statistically significant differences based on gender ($p>0.005$).

Table 2. **Comparative analysis of socio-demographic data of transplanted, deceased and active liver disease patients.**

| | **Together, n=265** | | |
|---|---|---|---|
| | **Transplant n= 118** | **Active n= 47** | **Deaths n= 100** |
| **Sex** M, n(%) | 66 (55,9%) | 30 (63,8%) | 58 (58%) |
| F, n(%) | 52 (44,1%) | 17 (36,2%) | 42 (42%) |
| **Age (years), median±SD** | 49 ± 9,16 | 48 ± 12,62 | 51 ±9,38 |
| **Age distribution (years), n(%)** | | | |
| 18-35 (ani) | 12 (10,2%) | 10 (21,3%) | 11 (11%) |
| 36-45 (ani) | 33 (28%) | 11 (23,4%) | 24 (24%) |
| 46-55 (ani) | 51 (43,2%) | 16 (34%) | 36 (36%) |
| 56-65 (ani) | 22 (18,6%) | 10 (21,3%) | 29(29%) |
| **Geographical distribution, n(%)** | | | |
| North, n(%) | 21 (17,8%) | 2 (4,3%) | 18 (18%) |
| Centre, n(%) | 61 (51,7%) | 29 (61,7%) | 61 (61%) |
| South, n(%) | 29 (24,6%) | 15 (31,9%) | 30 (30%) |
| Transnistria, n(%) | 7 (5,9%) | 1 (2,1%) | 1 (10%) |
| **Environment, n(%)** | | | |
| Urban, n(%) | 82 (69,5%) | 27 (57,4%) | 63 (63%) |
| Country side, n(%) | 36 (30,5%) | 20 (42,6%) | 37 (37%) |

*Note: Values are presented as median ± standard deviation for numerical data;*

Distribution of patients depending on aetiology (Table 3), thus patients with liver cirrhosis of HBV aetiology constituted the transplanted vs active vs deceased subgroup: 14 (11.9% vs 14 (29.8) vs 6 (6%), there is statistically significant difference between active and deceased (p<0,001); for HCV were: 17 (14.4%) vs 8 (17.0%) vs 14 (14%), but with no true statistical difference (p=0.08); HDV were: 83 (70.3%) vs 25 (53.2%) vs 69 (69%), there are statistically significant differences between transplanted and active sublots (p<0,001); HCC consisted of: 4 (3.4%) vs 0 (0%) vs 11 (11%), there are statistically significant differences between transplanted and deceased (p<0,001).

Table 3. **Assessment of patients with liver disease according to aetiology**

| **Etiology, n(%)** | **Together, n=265** | | |
|---|---|---|---|
| | **Transplant n=118** | **Active n=47** | **Deaths n= 100** |
| HBV, n(%) | 14 (11,9%) | 14 (29,8%) | 6 (6%) |
| HCV, n(%) | 17 (14,4%) | 8 (17%) | 14 (14%) |
| HDV, n(%) | 83 (70,3%) | 25 (53,2%) | 69 (69%) |
| HCC, n(%) | 4 (3,4%) | 0 (0%) | 11 (11%) |

Depending on the waiting time (Table 4), statistically significant differences were found (p<0,01) in transplanted patients 6.64±6.96 months with active ones (29.17±16.22 months), and for deceased - 13.78±15.31 months, which shows that the waiting time for liver transplantation is quite long.

Table 4. **Distribution of patients with liver disease by length of wait.**

| | **Together, n=265** | | | ***p*** |
|---|---|---|---|---|
| | **Transplant n=118** | **Active n=47** | **Deaths n= 100** | |
| **Waiting time (months) median±SD** | 6,64±6,96 | 29,17±16,22 | 13,78±15,31 | *p*<0,001 |

**Evaluation of prognostic models calculated in study patients.**

The MELD score showed a median of 15.85±4.50 points in subgroup 1 of the study, 14.61±1.60 points in subgroup 2 of the study, while a higher score existed in subgroup 3 of the study 18.49±5.94 points, with statistically significant differences (p<0,005). The MELD Na score in sublot 1 study consisted 19.10±4.56 points, in sublot 2 study it was 16.33±1.66 and much higher score in sublot 3 study 22.65±5.94 points, there was statistically significant difference (p<0,005). The i MELD score determined 71.25±9.86 points in sublot 1 study, 66.78±12.94 points in sublot 2 study and 77.19±10.34 points in sublot 3 study, there was statistically significant difference (p<0,005). Also there was statistically significant difference of MELD-AS score in sublot 1 of study determined 25.03±15.10 points, in sublot 2 of study found 22.88±9.09 points, and in sublot 3 of study showed 27.87±13.46 points. The MESO-Index score in study sublot 1 showed 1.17±0.35 points, in study sublot 2 1.05±0.11 points, and in study sublot 3 1.42±0.47 points, there was statistically significant difference (p<0,005).

For the UKELD score in sublot 1 study found 55.96±3.77 points, in sublot 2 showed 54.07±1.40 points, and in sublot 3 study determined 58.92±4.92, also there was statistically significant difference (p<0,005).

The Refit MELD score showed in subgroup 1 study 16.21±4.32 points, in subgroup 2 study 14.63±1.82 points, while in subgroup 3 study 19.17±5.67 points, there was statistically significant difference (p<0,005). The Refit MELD-Na score showed 14.28±3.40 points in study sublot 1, 13.16±1.49 points found in study sublot 2, and 13.82±5.52 points in study sublot 3, with no statistically significant difference (p>0.005). The MELD up score showed values of 3.77±0.40 points in study subgroup 1, 3.59±0.23 points in study subgroup 2, and 4.11±0.79 points in study subgroup 3, there was a statistically significant difference (p<0,005). MELD 3 score. 0 score was 17.19±5.68 points in subgroup 1 study, 13.37±2.79 points in subgroup 2

study, and much higher in subgroup 3 study 21.94±7.19 points, also there was statistically significant difference (p<0,005).

**3.3 Comparison of predictive accuracy between MELD score, MELD Na score and MESO-index score on mortality in the first 3 months after listing for liver transplantation**

The MELD Na index (Table 5) had a better and significant correlation with the MESO Index (r=0.912; respectively p<0.001).

Table 5. **Correlation between MELD score, MELD Na score, MESO index.**

| Correlation coefficient | **Together, n=265** | | |
|---|---|---|---|
| | MELD | MELD Na | MESO Index |
| MELD | 1,000 | ,855** | ,990** |
| MELD Na | ,855** | 1,000 | ,912** |
| MESO Index | ,990** | ,912** | 1,000 |

Thus, using the c-statistic and 3-month mortality as an endpoint, the AUC (Figure 5) was 0.762 for the MELD score, 0.772 for the MELD Na and 0.767 for the MESO index, respectively.

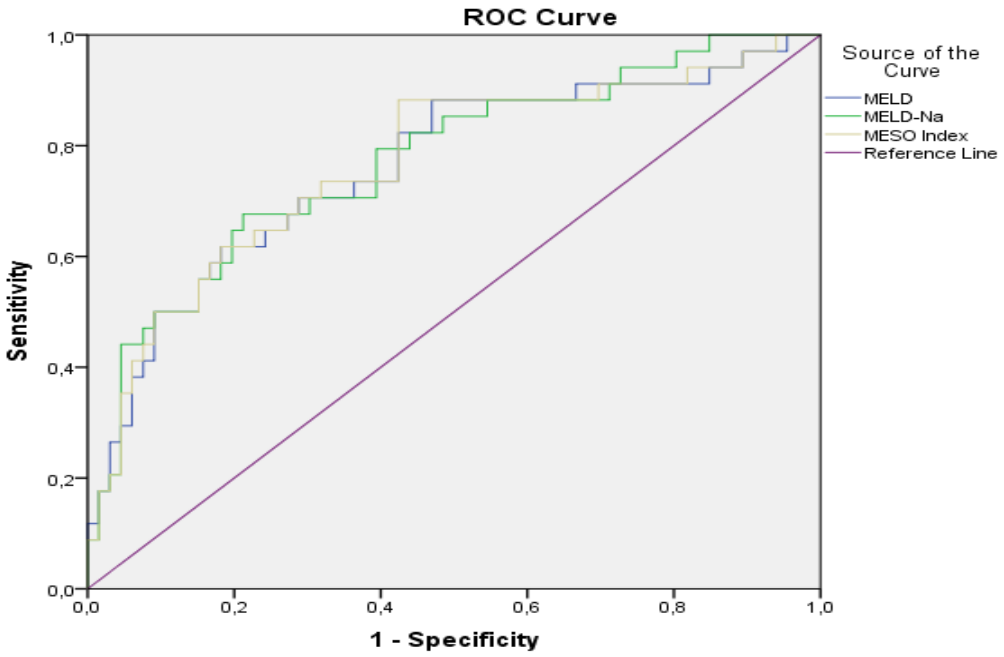


Figure 5. **ROC curve of MELD score, MELD Na, MESO INDEX for prognostic mortality at 3 months after enrolment in the waiting list for LT.**

Dilutional hyponatremia in liver cirrhosis occurs as a result of reduced clearance of free water caused by non-osmotic secretion of antidiuretic hormone secondary to circulatory dysfunction and decreased effective volume [18]. Surprisingly, although not statistically significant, MELD Na remained the best prognostic predictor of 3-month mortality compared to

MELD score and MESO index in the population of patients on the waiting list for liver transplantation in the Republic of Moldova.

### 3.4 Comparison of predictive accuracy between MELD, MELD Na, MESO-index, UKELD, refit MELD, refit MELD Na, up MELD, MELD AS, i MELD, MELD 3.0 score on mortality in the first 3 months after listing for liver transplantation

Thus, following the ROC curve analysis (Table 6), for the 10 scores the largest area under the ROC curve was observed for the MELD 3.0 score (Figure 6) 0.790 (0.694-0.885) p-value being less than 0.005 which means that the model is good for application in clinical practice and is statistically significant, being a score that excludes the discrepancy between male and female gender, thus ensuring a better distribution of liver grafts.

Table 6. **Evaluation of prognostic scores for early mortality to LT**

| Variable ± SD | Areea | Standard deviation | 95% IÎ | *p* |
|---|---|---|---|---|
| MELD 3.0 | 0,790 | 0,049 | 0,694 - 0,885 | *p*<0,005 |
| UKELD | 0,778 | 0,050 | 0,679 - 0,877 | *p*<0,005 |
| refit MELD | 0,776 | 0,051 | 0,676 - 0,877 | *p*<0,005 |
| MELD Na | 0,772 | 0,051 | 0,673 - 0,872 | *p*<0,005 |
| up MELD | 0,769 | 0,053 | 0,665 - 0,873 | *p*<0,005 |
| MESO Index | 0,767 | 0,052 | 0,665 - 0,870 | *p*<0,005 |
| MELD | 0,762 | 0,052 | 0,658 - 0,866 | *p*<0,005 |
| i MELD | 0,711 | 0,055 | 0,603 - 0,603 | *p*<0,005 |
| MELD-AS | 0,373 | 0,057 | 0,261 - 0,484 | *p=0,037* |
| refit MELD Na | 0,352 | 0,062 | 0,231 - 0,474 | *p=0,016* |

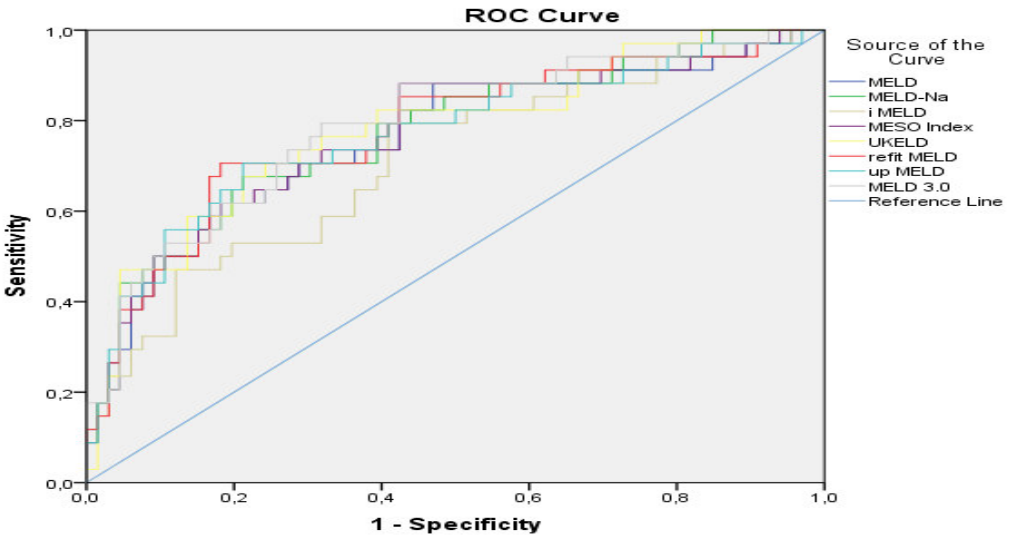


Figure 6. **ROC curve for prognostic mortality at 3 months after enrolment on the waiting list for LT.**

Next was the UKELD score which stood out as the second statistically significant score in the given study calculated by ROC analysis, AUC - 0.778 (0.679-0.877), p<0,005. Scorul refit MELD a obținut o AUC de 0,776 (0,676-0,877), *p*<0,005. For the MELD score Na area showed 0.772 (0.673-0.872), p<0.005. The upMELD area score determined 0.769 (0.665-0.873), p<0,005. The MESO Index score showed area of 0.767 (0.665-0.870), p<0,005. The MELD score scored 0.762 (0.658-0.866), p<0,005. iMELD scored 0.711 (0.603-0.820), p<0,005.

The MELD AS score obtained a value of 0.373 (0.261-0.484), its p-value of 0.037 being statistically insignificant. The MELD Na refit score obtained the lowest area 0.352 (0.231-0.474) and its p-value was 0.016, being statistically insignificant.

### 3.5. Validation of the new mortality prediction score for patients on the liver transplant list in the Republic of Moldova

The MELD 3.0 score (Figure 7) achieved the best average sensitivity of -88.2%, out of 34 patients who died in less than 90 days. The cut-off for the MELD 3.0 score was 17.42<4.77. Out of 34 patients who died within 90 days of listing - 30 had MELD 3.0 score greater than 17.42. Specificity of MELD 3.0 score was 50%, out of 66 patients who died later than 90 days - 33 had MELD 3.0 score less than 17.42. PPV for MELD 3.0 was 47.6%, out of 100 patients who died 63 had MELD 3.0 score greater than 17.42; of which 30 patients died within 90 days. NPV was 89.2%, out of 37 patients who had MELD 3.0 score less than 17.42 - 33 patients died later than 90 days.

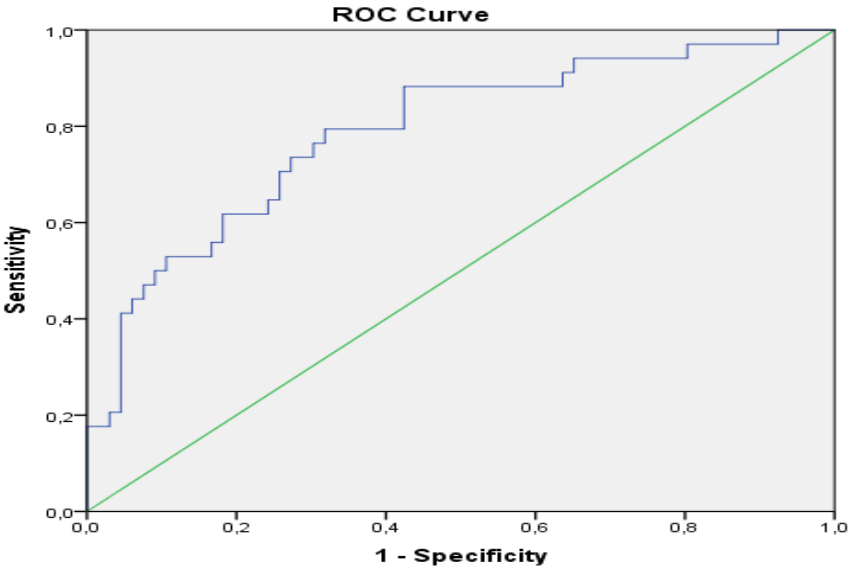


Figure 7. **ROC curve for prognostic mortality at 3 months after listing based on MELD 3.0 score**

Thus, in our prognostic score validation study, the MELD 3.0 score was significantly better at predicting mortality in the first 90 days on the waiting list compared to the other scores. The AUROC curve for 3-month mortality approached 0.80 indicating that it is a good prognostic test for predicting short-term mortality on our waiting list.

Reclassification of liver transplant candidates was demonstrated (Table 7) between MELD Na and MELD 3.0 score in the validation set was, the distribution of MELD Na and MELD 3.0 score was considered correct in 79.62% of cases (211 out of 265 patients), and 153 were < 20 and 120 were correct.

But of the patients who represented MELD Na and MELD 3.0 < 20 correctly classified were 78.43%. While more patients were subcategorized 35 (13.21%) than overcategorized 19 (7.17%). Out of 100 deceased patients 79 (79%) remained in the same category, while 10 (10%) were incorrectly reclassified with category decrease and 11 (11%) were correctly reclassified with overcategorization increase, with net increase of 1 (1%) patient.

Table 7. **Reclassification of liver transplant candidates between MELD Na and MELD 3.0 in the validation set.(A) number of patients, (B) number of deaths**

| A. Patients (n) | | MELD 3.0 | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | 6-9 | 10-19 | 20-29 | 30-39 | 40+ | |
| MELDNa | 6-9 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 10-19 | 1 | 120 | 0 | 0 | 5 | 126 |
| | 20-29 | 0 | 9 | 62 | 0 | 13 | 84 |
| | 30-39 | 0 | 0 | 0 | 24 | 1 | 25 |
| | 40+ | 1 | 22 | 1 | 1 | 5 | 30 |
| Total | | 2 | 151 | 63 | 25 | 24 | 265 |

| B.Deaths (%) | | MELD 3.0 | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | 6-9 | 10-19 | 20-29 | 30-39 | 40+ | |
| MELD Na | 6-9 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 10-19 | 0 | 24 | 0 | 0 | 0 | 24 |
| | 20-29 | 0 | 5 | 34 | 0 | 11 | 50 |
| | 30-39 | 0 | 0 | 0 | 19 | 0 | 19 |
| | 40+ | 1 | 3 | 0 | 1 | 2 | 7 |
| Total | | 1 | 32 | 34 | 20 | 13 | 100 |

The most significant change was in patients who were registered with MELD-Na of 20-29 (n=84), 50 died and 30-39 (n=19) 25 patients died. Deceased MELD 20-29 were MELD-Na

(n=50), MELD 3.0 (n=34), MELD 30-39 with MELD-Na were (n=25), and with MELD 3.0 (n=20). The proportion of deaths was higher in patients who had a higher category and of the (n=35) who were subcategorized lower 28.57% patients died (n=10). Of the patients over-categorised (n=19) 11 patients died. The proportion of patients who died was higher in overcategorised patients and lower in undercategorised patients compared to those whose score was not changed.

Thus, the discrepancy between these two scores is more significant when increasing, (n=19) 7.7% of patients who were offered enough points to be recategorised to the 40+ category, i.e. these patients had a greater chance of receiving the organ and possibly avoiding death.

The proportion of patients who died who were categorised above or below was higher than those who were correctly categorised. Following evaluation of the literature data [11, 12, 18] and the results of the present study we developed an algorithm for diagnosis and surveillance of patients with viral liver cirrhosis on the waiting list for HT (Figure 8).

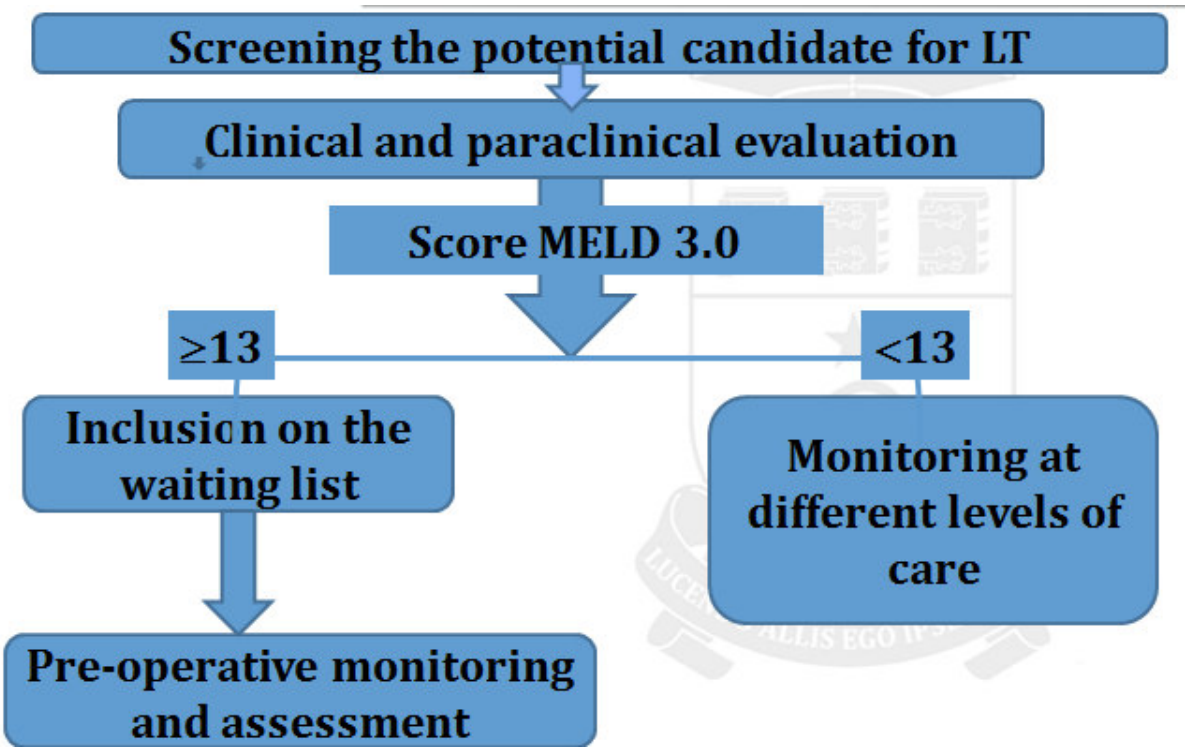


Figure 8. **General algorithm for liver transplant recipient management**

## GENERAL CONCLUSIONS

1. Clinical-evolutionary characterization of patients with decompensated viral liver cirrhosis on the waiting list for liver transplantation revealed that the average age was around 50 years and the majority of patients (76.7%) on the waiting list were of working age (□55 years). 70% of cases were with Delta viral liver cirrhosis. The average waiting time for liver transplantation was around 13 months. The majority of patients presented with cholestatic, cytolytic, hepatoproliferative syndrome and hyperspenism. Median MELD Na score at listing was 20.58±5.39. Ascites (90.6%) and encephalopathy (74.3%) were the most common complications of liver cirrhosis in patients in the study. In 46% of patients on the waiting list there was at least 1 episode of upper GI bleeding from varices.

2. Analysis of prioritization factors of recipients on the waiting list for liver transplantation established that the presence of end-stage liver pathology caused by Delta virus (70% of transplant recipients); the presence of upper GI bleeding episodes from esophageal varices (33% of transplant recipients); median MELD Na score in transplant recipients 18.81±4.57; and MELD Na prognostic score in active recipients (16.60±1.67).

3. Comparison of the predictive accuracy of the MELD score, MELD Na and MESO-index demonstrated that MELD Na was one of the most effective predictors of prognostic mortality at 3 months compared to the MELD score and MESO-index in the study population (AUROC MELD vs MELD Na vs MESO-index - 0.762 vs 0.772 vs 0.767).

4. External validation revealed that 90-day mortality was predicted by the MELD 3 score. 0 cut-off > 17, with a sensitivity (88.2%) and specificity (50%) AUROC curve 0.790 (95% IÎ 0.694-0.885) higher compared to the rest of the prognostic scores analysed and may in fact serve for enrolling patients in the liver transplant waiting list in the national programme, as a score for the future, being a useful prognostic predictor for both short and long term survival, with more equitable allocation of grafts to different populations and avoiding inequity between men and women on the waiting list.

5. Taking into account the waiting period of 29.17±16.22 months, an algorithm for enrolling patients with decompensated viral liver cirrhosis and inclusion in the waiting list for liver transplantation was developed, using validation of the MELD 3.0 prognostic score with cut-off 13, which will assess the cut-off time for access to a graft and timely prioritization to ensure the best chance of survival for all recipients on waiting lists for liver transplantation.

## RECOMMENDATIONS

In order to facilitate the solution of the problems highlighted in the study we propose the following recommendations:

- At the level of practice medicine (healthcare providers):

1. Application of MELD 3.0 score to patients with viral liver cirrhosis at primary care level (score >13 is an indication for referral to family physician, hepatologist, infectious disease specialist, surgeon).

- At the level of decision makers (Ministry of Health and Liver Transplant Agency):

1. To introduce the algorithm developed for patients with viral liver cirrhosis into the national clinical protocol ,,Liver transplantation".

- At the level of prospective scientific research:

1. Considering the average waiting time of 29.17±16.22 months and the 50% mortality rate in the waiting list for liver transplantation, it is obvious that the coordination and monitoring method in favour of recipients needs to be revised in order to improve the prioritisation factors.

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**a. international**

22. **Pîrvu V**. Analiza și validarea diferitor scoruri prognostice pe populația cu ciroză hepatică din programul de transplant hepatic din Republica Moldova. *National Congress of Surgery.* Sinaia, România, 8-11 iunie.
23. **Pîrvu V.** Evaluation of clinical and biological features in patients with liver cirrhosis in the liver transplant program. The 9 th International Medical Congress for Students and Young Doctors, MedEspera. Chișinău, 12-14 mai 2022.

**b. national**

24. **Pîrvu V.**, Hotineanu A., Toacă I., Ivancov G., Iurciuc V., Buga D. et al. Assessment of early complications afterwards liver transplantation. *Congresul consacrat aniversării a 75-a de la fondarea USMF „NicolaeTestemițanu”.* Chișinău, 21-23 octombrie 2020.
25. Toacă I., Hotineanu A., **Pîrvu V.**, Peltec A., Buga D., et al. Complications of liver transplantation. *Congresul consacrat aniversării a 75-a de la fondarea USMF „Nicolae Testemițanu”.* Chișinău, 21-23 octombrie 2020.
26. **Pîrvu V.** Evaluation of clinical and biological features in patients with liver cirrhosis in the liver transplant program. *Conferinţa ştiinţifică anuală "Cercetarea în biomedicină şi sănătate: calitate, excelenţă şi performanţă".* Chișinău, 20-22 octombrie 2021.

27. **Pîrvu V.**, Hotineanu A., Peltec A., Pîrvu C. Evaluation of MELD score in liver transplant allocation. *Conferința Națională Științifică cu Participare Internațională „Transplantul de celule și țesuturi. Actualități și perspective”.* Chișinău, 17-18 martie 2023.
28. **Pîrvu V.**, Hotineanu A., Peltec A. New prognostic scores for liver transplant waiting list. *The 8$^{TH}$ Congress on urology, dialysis and kidney transplant from the Republica Moldova with international participation „New horizon in urology’’*. Chișinău, 7-9 iunie 2023.
29. **Pîrvu V.**, Hotineanu A., Peltec A., Ivancov G. Noi scoruri, noi oportunități de evaluare a pacienților cu ciroză hepatică în lista de așteptare pentru transplant hepatic. *Al XIV-lea Congres al Asociației Chirurgilor „Nicolae Anestiadi” și al IV-lea Congres al Societății de Endoscopie, Chirurgie miniminvazivă și Ultrasonografie ”V.M.Guțu” din Republica Moldova*. Chișinău, 21-23 septembrie 2023.

**ANNOTATION**

**Pîrvu Victor**

**Analysis of clinical-biological landmarks and the prioritization of patients with liver cirrhosis in the liver transplant program.**

**Doctoral thesis in medical sciences, Chisinau, 2024**

The thesis is presented on 146 pages and includes: introduction, 3 chapters, synthesis of the obtained results, conclusions, recommendations, bibliography comprised of 222 titles, 25 tables, 16 figures. The obtained results arepublished in 29 scientific papers.

**Key words:** waiting list, liver transplantation, prognostic scores, viral liver cirrhosis, donor, MELD score, risk factors, complications, acute liver failure.

**Field of study: 321.24 – transplantology**

**The purpose of the study:** Study of clinical-biological landmarks and analysis of different prognostic scores in the population with viral liver cirrhosis on the waiting list for liver transplantation in the Republic of Moldova.

**Objective of the study:** 1. Evaluation of clinical-biological milestones in patients on the waiting list for liver transplantation. 2. Analysis of recipient prioritization factors for the liver transplant waiting list. 3. Comparison of predictive accuracy between MELD score, MELD Na, MESO-index on mortality in the first 3 months after listing for liver transplantation. 4. Validation of the MELD 3.0 prognostic score on mortality in the first 3 months of recipients on the liver transplant waiting list. 5. Development of the algorithm for enrolling patients with liver cirrhosis of decompensated viral etiology from the liver transplant waiting list based on the validated prognostic score with maximum predictive accuracy.

**Scientific novelty:** A comprehensive assessment of the criteria for inclusion on the waiting list for liver transplantation was carried out with the creation of a validated monitoring system adapted for the Republic of Moldova.

**The solved scientific problem:** A new score has been proposed that exceeds the predictive value of the MELD score and would facilitate the inclusion of patients in the waiting list for liver transplantation depending on the severity of the disease, so that patients with severe end-stage liver disease are given priority for liver transplantation.

**Applicative value of the study:** An algorithm was developed to validate the MELD 3.0 prognostic score with a cut-off of 13, which will assess the cut-off moment for access to a graft and prioritization in a timely manner to ensure the highest possible chances of survival for all recipients on the lists of waiting for a liver transplant.

**Implementation of the results:** The scientific results and practical recommendations are implemented in the didactic process of the Department of Surgery No. 2 USMF "Nicolae Testemitanu", surgical and therapeutic sections of Republican Clinical Hospital "Timofei Mosneaga".

**ADNOTARE**

**Pîrvu Victor**

**Analiza reperelor clinice-biologice și scorificarea pacienților cu ciroză hepatică în programul de transplant de ficat**

**Teza de doctor în științe medicale, Chișinău, 2024**

Teza este expusă pe 146 pagini și include: introducere, 3 capitole, sinteza rezultatelor obținute, concluzii, recomandări, bibliografie din 222 titluri, 25 tabele, 16 figuri. Rezultatele obținute sunt publicate în 29 lucrări științifice.

**Cuvinte cheie:** lista de așteptare, transplant hepatic, scoruri prognostice, ciroză hepatică de etiologie virală, donator, scorul MELD, factori de risc, complicații, insuficiență hepatică acută.

**Domeniul de studiu: 321.24 – transplantologie**

**Scopul lucrării:** Studierea reperelor clinice-biologice și analiza diferitor scoruri prognostice pe populația cu ciroză hepatică de etiologie virală din lista de așteptare pentru transplant de ficat din Republica Moldova.

**Obiectivele lucrării:** 1. Evaluarea reperelor clinice-biologice la pacienți din lista de așteptare pentru transplant de ficat. 2. Analiza factorilor de prioritizare a recipienților pentru lista de așteptare pentru transplant hepatic. 3. Comparația acurateței predictive între scorul MELD, MELD Na, MESO-index privind mortalitatea în primele 3 luni de la listare pentru transplant de ficat. 4. Validarea scorului prognostic MELD 3.0 privind mortalitatea în primele 3 luni a recipienților din lista de așteptare pentru transplant de ficat. 5. Elaborarea algoritmului de înrolare a pacienților cu ciroză hepatică de etiologie virală decompensată din lista de așteptare a transplantului de ficat în baza scorului de prognostic cu acuratețe predictivă maximală validat

**Noutatea științifică:** A fost realizată o evaluare complexă a criteriilor de includere în lista de aşteptare pentru transplant de ficat cu crearea unui sistem de monitorizare validat şi adaptat pentru Republica Moldova.

**Problema științifică soluționată:** A fost validat nou scor prognostic care depășește valoarea predictivă a scorului MELD și care ar facilita includerea pacienților în listă de așteptare pentru transplant de ficat în dependență de severitatea bolii, astfel pacienții cu boala hepatică în stadiul terminal în stare gravă să aibă prioritate în beneficierea de transplant hepatic.

**Valoarea aplicativă a lucrării:** S-a elaborat un algoritm de validare a scorului prognostic MELD 3.0 cu cut-off-ul 13, care va aprecierea momentul limită pentru accesul la o grefă şi prioritizarea în timp util pentru a asigura şanse cît mai mari de supravieţuire a tuturor recipienților aflaţi pe listele de aşteptare pentru transplant hepatic.

**Implementarea rezultatelor științifice:** Rezultatele științifice și recomandările practice sunt implementate în procesul didactic al Catedrei de chirurgie nr. 2 USMF „Nicolae Testemițanu”, secțiile de profil chirurgical și terapeutic al IMSP Spitalul Clinic Republican „Timofei Moșneaga”.

# АННОТАЦИЯ

**Pîrvu Victor**

**Анализ клинико-биологических ориентиров и определение приоритетности пациентов с циррозом печени в программе трансплантации печени**

**Диссертация на соискание ученой степени, Кишинев, 2024**

Диссертация состоит из 3 глав, обзора результатов, выводов, рекомендаций, списка литературы, которая состоит из 222 источников, 146 страниц базового содержания, 25 таблиц, 16 фигур. Полученные результаты были опубликованы в 29 научных работах.

**Ключевые слова:** лист ожидания, трансплантация печени, прогностические баллы, вирусный цирроз печени, донор, балл MELD, факторы риска, осложнения, острая печеночная недостаточность.

**Специальность: 321.24 – трансплантология**

**Цель работы:** изучение клинико-биологических особенностей и анализ различных прогностических показателей в популяции с вирусным циррозом печени, находящейся в листе ожидания трансплантации печени в Республике Молдова.

**Задачи исследования:** 1. Оценка клинико-биологических показателей у больных, стоящих в очереди на трансплантацию печени. 2. Анализ факторов приоритетности реципиентов в листе ожидания трансплантации печени. 3. Сравнение точности прогнозирования между оценкой MELD, MELD Na, MESO-индексом смертности в первые 3 месяца после включения в лист для трансплантации печени. 4. Валидация прогностической шкалы MELD 3.0 смертности в первые 3 месяца реципиентов в списке ожидания трансплантации печени. 5. Разработка алгоритма включения больных декомпенсированным циррозом печени вирусной этиологии в лист ожидания трансплантации печени на основе валидизированного прогностического балла с максимальной прогностической точностью.

**Научная новизна исследования**: Была проведена комплексная оценка критериев включения в лист ожидания на трансплантацию печени с созданием валидированной системы мониторинга, адаптированной для Республики Молдова.

**Решена научная задача:** Предложена новая оценка, которая превосходит прогностическую ценность оценки MELD и позволит включать пациентов в лист ожидания на трансплантацию печени в зависимости от тяжести заболевания.

**Практическое значение научной работы:** Был разработан алгоритм для проверки прогностического показателя MELD 3.0 с пороговым значением 13, который позволит оценить момент отсечения для доступа к трансплантату и своевременно расставить приоритеты, чтобы обеспечить максимально возможные шансы на выживание для всех реципиентов на списки ожидающих трансплантации печени.

**Внедрение научных результатов:** Научные результаты и практические рекомендации внедряются в учебный процесс кафедры хирургии № 2 ГУМФ им. «Николае Тестемицану», секций хирургического и терапевтического профиля Республиканской клиники им. «Тимофей Мошняга».