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CLINICAL COURSE OF LIVER CIRRHOSIS OF VIRAL B AND DELTA ETIOLOGY IN THE PRE- AND POST-TRANSPLANT STAGE

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INTRODUCTION

Relevance and importance of the topic. The Republic of Moldova is a European endemic focus of hepatitis Delta virus (HDV) infection. Liver cirrhosis is the third leading cause of death at the national level. The course of chronic HDV infection is usually aggressive, with rapid progression to decompensated cirrhosis. A national study documented liver cirrhosis in 58.4% of patients with hepatitis Delta.

Viral Delta cirrhosis is one of the most frequent indications for liver transplantation in the Republic of Moldova and accounted for 59.5–62% of inclusions on the waiting list. Patients are listed with relatively moderate MELD scores, but their subsequent course is frequently marked by severe decompensation and death. The classical prognostic scores therefore do not fully reflect the risk of these patients. National data on their course in the pre- and post-transplant stages remain limited, which justifies the present research.

The aim of the study is to establish the clinical, biological, evolutionary and prognostic particularities of liver cirrhosis of viral Delta etiology, with a view to implementing modern strategies for monitoring patients on the liver transplant waiting list and transplant recipients.

Research objectives:

1. To determine the clinical, biological and virological particularities of patients with liver cirrhosis of viral Delta etiology included in the liver transplant programme.
2. To identify the clinical and biological phenotypes of patients with liver cirrhosis of viral Delta etiology by applying cluster analysis.
3. To assess the course of patients with liver cirrhosis of viral Delta etiology on the liver transplant waiting list, through the analysis of competing events (death on the list and liver transplantation).
4. To evaluate the prognostic factors on the waiting list using cause-specific Cox and Fine-Gray models and to develop a Delta prognostic score.
5. To assess the early and late outcomes of liver transplantation in patients with liver cirrhosis of viral Delta etiology.
6. To develop strategies for monitoring patients with viral Delta liver cirrhosis, aimed at preventing and delaying the onset of complications.

Scientific novelty and the scientific problem solved. According to the literature identified, the study is the first systematic, ambispective analysis of the entire national cohort of liver transplant candidates in the Republic of Moldova (2013–2025, 313 adult patients). Clinical and biological phenotypes were described by PAM cluster analysis. The course on the waiting list was analysed within the competing risks framework, on both hazard scales. The Delta Prognostic Score was developed and temporally validated. The TransplantCare digital application was developed and recognised by Innovator Certificate No. 6463.

The scientific problem solved consists in characterising the course and prognosis of patients with liver cirrhosis of viral Delta etiology in the national liver transplant programme, for whom no systematised data existed. The results substantiate risk stratification and the monitoring strategy for these patients in the pre- and post-transplant stage.

Theoretical importance and applied value of the study. The study characterises the course of liver cirrhosis of viral Delta etiology in an endemic country, where HBV/HDV coinfection is much more frequent than in European centres. It shows that the effect of etiology differs on the

cause-specific scale and on the subdistribution scale when transplantation, as a competing event, is unevenly distributed between groups.

The applied value concerns clinical practice, the organisation of the transplant programme and digital monitoring. The Delta Prognostic Score is calculated at the bedside and has an indicative role until external validation. The results may substantiate the revision of the National Clinical Protocol PCN-347 "Liver transplantation" and the completion of the national registry with perioperative variables. The TransplantCare prototype calculates the score automatically and signals a change in risk category.

Approval of the scientific results. The results were presented at nine national and international scientific forums. These include the Romtransplant National Congress (Iași, 2023), The 37th Balkan Medical Week (Chișinău, 2023), the 11th Update on Hepatology Course (Bucharest, 2024), the 4th International Meeting Delta Cure (Hanover, 2025) and the 6th National Congress of Gastroenterology and Hepatology of the Republic of Moldova (Chișinău, 2025). The results were implemented in the clinical activity of the "Timofei Moșneaga" Republican Clinical Hospital and in the teaching process of "Nicolae Testemițanu" SUMPh.

Publications on the thesis topic. On the thesis topic, 24 scientific works and materials were produced. These include one article in the World Journal of Hepatology, 8 articles in national category B journals, 3 abstracts, 5 oral presentations, 4 posters, one innovator certificate, one management guide and one national clinical protocol.

Summary of the thesis chapters. The thesis comprises the introduction, five chapters, the discussion, the general conclusions and practical recommendations, a bibliography of 142 titles and two annexes. The main text has 112 pages, 35 tables and 28 figures.

Keywords: hepatitis Delta, liver cirrhosis, liver transplantation, HBV/HDV coinfection, waiting list, MELD score, Delta Prognostic Score, competing risks, clinical phenotypes, post-transplant survival.

1. THEORETICAL AND EPIDEMIOLOGICAL BACKGROUND OF LIVER CIRRHOSIS OF VIRAL DELTA ETIOLOGY

The chapter summarises the data on the burden of liver cirrhosis and HDV infection in the Republic of Moldova. It analyses the accelerated progression of fibrosis and the increased risk of decompensation and hepatocellular carcinoma in HBV/HDV coinfection. It examines the prognostic scores used on the waiting list, the outcomes of liver transplantation in HDV cirrhosis and the principles of post-transplant monitoring. In decompensated HDV cirrhosis, a hepatocellular phenotype and a portal-vascular phenotype are described.

2. MATERIAL AND RESEARCH METHODS

2.1. Design and stages of the research

The research is a nationwide observational, ambispective, cohort clinical study. It covers the period 01.01.2013–31.12.2025 and spans the entire duration of operation of the national liver transplant programme. The study was conducted within the Discipline of Gastroenterology of "Nicolae Testemițanu" SUMPh, with its clinical base in the Hepatology Department of the "Timofei Moșneaga" Republican Clinical Hospital. Data on the waiting list and on transplants were provided by the Transplant Agency. In-country transplants were performed at the Clinic of Biliopancreatic Surgery and Liver Transplantation of the same hospital.

The research went through four stages. The first comprised the formulation of the hypothesis and of the protocol, based on the analysis of the literature in the Web of Science, PubMed and Scopus databases. The second comprised the definition of the cohorts and of the eligibility criteria and data collection. The third comprised statistical processing and analysis. The fourth comprised the development of the TransplantCare digital application.

2.2. Study cohorts and inclusion/exclusion criteria

The research was organised into two studies, corresponding to the pre-transplant stage (Study A) and the post-transplant stage (Study B).

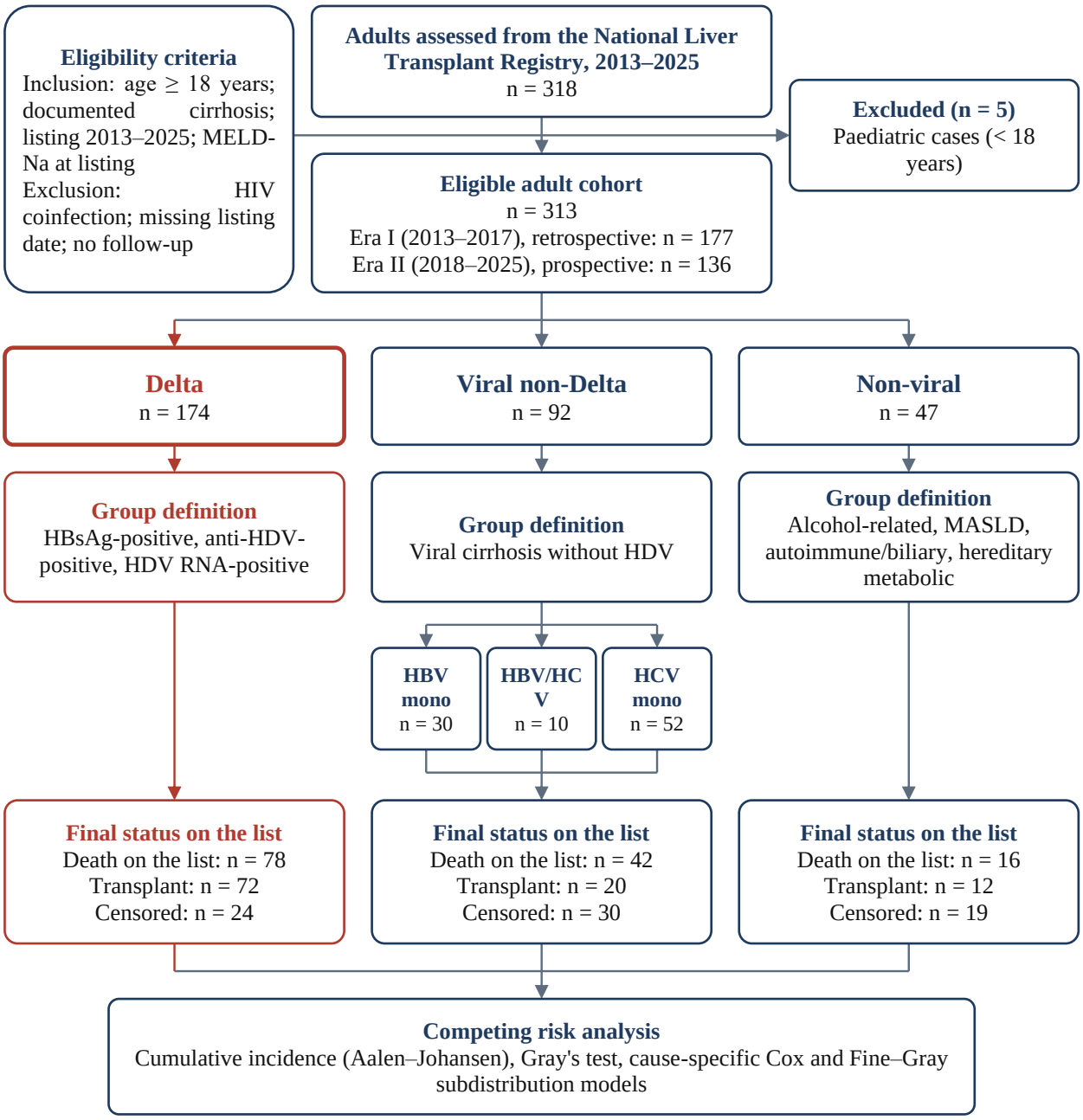

Figure 1. Flow diagram of the pre-transplant cohort (N = 313)

Cohort A included all adult patients with liver cirrhosis, regardless of etiology, registered in the Transplant Agency Registry during the study period (N = 313) (figure 1). Of these, 174 (55.6%) had HBV/HDV coinfection, 30 (9.6%) had HBV monoinfection and 109 (34.8%) had other etiologies. For the comparative analyses, patients were stratified into the HDV subgroup (n = 174)

and the non-HDV subgroup (n = 139). To verify the stability of the prognostic score over time, the cohort was divided into Era I (2013–2017, n = 177) and Era II (2018–2025, n = 136).

The inclusion criteria were age of at least 18 years, a diagnosis of liver cirrhosis, registration on the national waiting list and availability of data for calculating the MELD-Na score at listing. The exclusion criteria were documented HIV infection, age under 18 years, insufficient data for calculating the MELD-Na score and a missing date of inclusion on the list. The etiology of cirrhosis was established as the dominant etiology, and associated cofactors were recorded as descriptive variables.

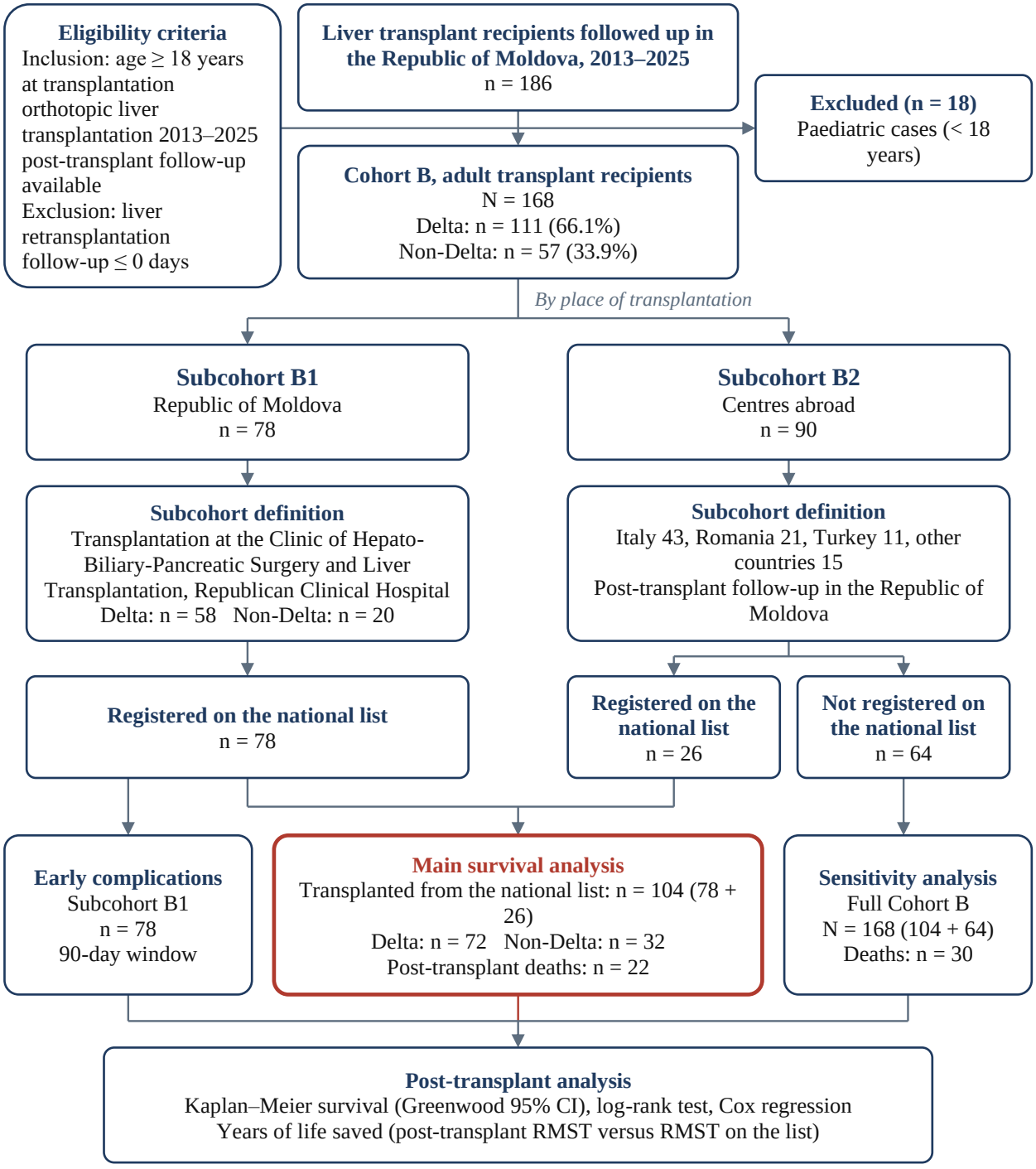

Figure 2. Flow diagram of the post-transplant cohort (N = 168)

Cohort B included 168 adult liver transplant recipients (figure 2). Subcohort B1 comprises 78 patients transplanted in the Republic of Moldova, previously registered on the national list. Subcohort B2 comprises 90 patients transplanted in centres abroad and subsequently followed up in the country. The two cohorts partially overlap, since 104 patients from Cohort A were transplanted during follow-up. The inclusion criteria were age of at least 18 years at transplantation, orthotopic liver transplantation performed during the study period and available follow-up data. Paediatric cases and retransplantation were excluded.

For Cohort A, the minimum sample size was calculated using the formula for estimating a proportion, with a 95% confidence interval and a maximum admissible error of ±5%. The calculated minimum size was 288 patients. The events-per-variable criterion was met for the multivariable models (136 deaths, EPV ≈ 27). Cohort B is an exhaustive cohort, without sampling. The main analysis of post-transplant survival was performed on the 104 patients transplanted from the national list, the only ones with a documented MELD-Na score at listing. The full Cohort B was used in the sensitivity analyses.

2.3. Variables collected and assessment methods

Data were collected using an individual form structured by domains. The demographic component comprised age, sex, area of origin and region of residence. The clinical component comprised the complications of cirrhosis at the time of listing, namely ascites, hepatic encephalopathy, variceal gastrointestinal bleeding, hepatorenal syndrome and spontaneous bacterial peritonitis. The biological profile comprised the complete blood count, liver tests, renal function and electrolytes. The etiological diagnosis used the serological and molecular markers of hepatitis B and Delta viruses, determined during the pre-transplant assessment.

Disease severity was quantified by the MELD, MELD-Na, MELD 3.0 and Child-Turcotte-Pugh scores. The scores were calculated from the values at inclusion on the waiting list and were used as fixed variables. For transplant recipients, the donor type, transplant centre, immunosuppression protocol, prophylaxis of viral recurrence, complications and death were recorded. Morbidity was reported at 90 days and perioperative mortality at 30 days.

2.4. Handling of missing data and completeness of the analytical sets

Availability of the MELD-Na score at listing was an inclusion criterion, so that its component variables have 100% completeness. The 73 patients without an event by the follow-up cut-off date are censored observations, not missing data. The proportion of censored observations was lower in the Delta group than in the non-Delta group (13.8% versus 35.3%, $p < 0.001$), as a result of the higher transplant rate. Multiple imputation was not required.

2.5. Methods of statistical analysis

Continuous variables were described by the median and interquartile range, and categorical variables by frequencies. Comparisons used the Mann-Whitney U, χ^2 and Fisher tests, and the magnitude of differences was expressed by the standardised mean difference (SMD). The clinical and biological phenotypes were identified by the PAM algorithm with Gower distance, in 290 patients. The number of clusters was established by silhouette analysis, and the stability of the solution by bootstrap with 1,000 iterations and the Jaccard index.

The course on the waiting list was analysed within the competing risks framework. Death on the list was the event of interest, liver transplantation was the competing event, and patients active on the list and those delisted were censored observations. The Delta group was compared at three levels, with all non-Delta etiologies (n = 139), with non-Delta viral cirrhosis (n = 92) and

with HBV monoinfection (n = 30). Cumulative incidence was estimated by the Aalen-Johansen method and compared by Gray's test.

The effect of covariates was estimated on two hazard scales. Cause-specific Cox regression estimates the effect on the instantaneous rate of the event in patients still at risk (csHR). Fine-Gray regression estimates the effect on the absolute probability of the event and keeps patients with a competing event in the risk set (sHR). The main models were prespecified and included HDV infection, age, sex, the MELD-Na score at listing and the era of inclusion. The proportional hazards assumption was verified using Schoenfeld residuals. Robustness was assessed through four sensitivity analyses, namely restricted comparators, replacement of MELD-Na with MELD 3.0, the extended model and exclusion of transplants in the first 30 and 90 days.

The Delta Prognostic Score was constructed in two steps, on the entire Cohort A. In the first step, the equivalent of Delta coinfection in MELD-Na points was estimated as the ratio between the coefficient of the HDV variable and the coefficient of the MELD-Na score in the cause-specific Cox model for death. In the second step, the equivalent was converted into a categorical score. Performance was assessed by univariable cause-specific Cox models, Harrell's concordance index and the time-dependent area under the ROC curve at 1, 3 and 5 years. Stability was verified across the two eras of inclusion. A temporal validation was also performed, with derivation on Era I and application on Era II, in which calibration was also assessed.

Post-transplant survival was estimated by the Kaplan-Meier method, with Greenwood confidence intervals, and compared by the log-rank test. Factors associated with mortality were assessed by univariable Cox regression. The association between Delta coinfection and death at 30 days was estimated by logistic regression adjusted for the MELD-Na score at listing and for donor type. Transplant benefit was expressed in years of life saved (YLS), as the difference between the restricted mean survival time after transplantation and that estimated on the waiting list, at 5 and 10 years. The analyses were performed in R version 4.5.2.

2.6. Ethical aspects and approvals

The research complied with the principles of the Declaration of Helsinki and the national regulations on biomedical research. The study was approved by the Research Ethics Committee of “Nicolae Testemițanu” SUMPh (approval No. 40 of 12.02.2018). For the prospective component, written informed consent was obtained from each patient. The retrospective component used anonymised data. Data were processed under conditions of confidentiality.

3. CLINICAL PROFILE AND COURSE ON THE WAITING LIST OF PATIENTS WITH DELTA LIVER CIRRHOSIS IN THE PRE-TRANSPLANT STAGE

3.1. General characteristics of the national cohort of liver transplant candidates

The final cohort included 313 adult patients with advanced chronic liver disease, registered on the waiting list between 1 January 2013 and 31 December 2025. Of these, 177 (56.5%) were included in Era I, with retrospectively collected data, and 136 (43.5%) in Era II, with prospectively collected data. HBV/HDV coinfection was the most frequent cause of cirrhosis, in 174 patients (55.6%). A further 92 patients (29.4%) had non-Delta viral cirrhosis, of whom 52 had HCV monoinfection, 30 had HBV monoinfection and 10 had HBV/HCV coinfection. The remaining 47 patients (15.0%) had cirrhosis of non-viral etiology.

The median age at inclusion was 50.0 years (IQR 42.0–56.0). The cohort included 181 men (57.8%) and 132 women (42.2%). A total of 164 patients (52.4%) came from rural areas. At inclusion on the list, the liver disease had been known for a median period of 6.0 years.

At inclusion, the most frequent manifestations were esophageal varices (81.5%) and splenomegaly (75.2%). Ascites was present in 57.5% of patients, jaundice in 54.6%, hepatic encephalopathy in 36.2% and hemorrhagic syndrome in 25.6%. Portal vein thrombosis was present in 6.4% of patients and hepatocellular carcinoma in 49 patients (15.7%). More than half of the patients therefore had decompensated cirrhosis at inclusion on the list.

The median MELD score was 14.0 points (IQR 11.0–17.0), MELD-Na 15.0 (IQR 11.0–18.0) and MELD 3.0 16.0 (IQR 12.0–19.0). More than 80% of patients were therefore included on the list with a MELD-Na score below 20, which limits the ability of the score to differentiate risk among them.

3.2. Characteristics of patients with Delta coinfection compared with non-Delta viral cirrhosis and with HBV monoinfection

The Delta group was compared successively with two more homogeneous groups (table 1). The first consists of patients with non-Delta viral cirrhosis. The second consists only of patients with HBV monoinfection and differs from the Delta group only by the absence of the D virus.

Table 1. Baseline characteristics of the Delta group compared with the comparison groups

Characteristic	Delta (n = 174)	Non-Delta viral (n = 92)	p	HBV (n = 30)	p
Age, years	48.0 (42.0–54.0)	53.0 (48.0–58.0)	<0.001	52.0 (47.0–57.8)	0.037
Female sex, n (%)	78 (44.8%)	30 (32.6%)	0.072	6 (20.0%)	0.019
Body mass index, kg/m²	24.8 (22.8–27.1)	26.4 (24.5–28.1)	<0.001	27.1 (24.7–30.4)	0.004
Time on the list, days	247.5 (102.5–631.0)	601.5 (173.5–1936.5)	<0.001	281.0 (135.2–762.2)	0.593
Leukocytes, ×10⁹/L	3.4 (2.4–4.8)	4.5 (3.4–5.5)	<0.001	4.6 (3.8–5.9)	0.002
Platelets, ×10⁹/L	72.0 (49.0–103.5)	97.8 (71.5–124.2)	<0.001	98.0 (68.5–161.3)	0.005
ALT, U/L	58.1 (39.3–93.1)	48.3 (27.0–77.6)	0.005	43.3 (26.9–64.2)	0.009
Albumin, g/L	28.0 (24.9–31.9)	30.8 (25.7–36.0)	0.004	29.4 (24.0–35.6)	0.643
Ascites, n (%)	110 (63.2%)	46 (50.0%)	0.051	15 (50.0%)	0.242
Hepatic encephalopathy, n (%)	68 (39.3%)	25 (27.2%)	0.067	10 (33.3%)	0.676
Hepatocellular carcinoma, n (%)	31 (17.8%)	18 (19.6%)	0.854	8 (26.7%)	0.375
MELD	15.0 (12.0–17.0)	14.0 (10.0–17.0)	0.249	15.5 (11.0–17.0)	0.992
MELD-Na	15.0 (12.0–18.8)	15.0 (10.0–17.2)	0.074	15.5 (11.0–18.0)	0.510
MELD 3.0	16.5 (13.0–20.0)	15.0 (11.0–18.2)	0.029	16.5 (12.0–19.0)	0.652

Note. *Values are median (IQR) or n (%). The p values were not adjusted for multiple comparisons. IQR, interquartile range. ALT, alanine aminotransferase. HBV, hepatitis B virus. MELD, Model for End-Stage Liver Disease. MELD-Na, MELD score with serum sodium.*

Five parameters differed significantly in both comparisons. Patients with Delta infection were younger at inclusion, with a median of 48.0 years, versus 53.0 years in the non-Delta viral group and 52.0 years in the HBV group. The platelet count was lower (72.0 versus 97.8 and 98.0 ×10⁹/L), as was the leukocyte count (3.4 versus 4.5 and 4.6 ×10⁹/L). The body mass index was lower and ALT was higher. Thrombocytopenia and leukopenia are consistent with more pronounced hypersplenism.

Other parameters differed from the non-Delta viral group, but not from the HBV group. Albumin was lower than in the non-Delta viral group (28.0 versus 30.8 g/L, p = 0.004), but the difference disappeared in comparison with the HBV group (28.0 versus 29.4 g/L, p = 0.643). Time

on the list was much shorter than in the non-Delta viral group (247.5 versus 601.5 days, $p < 0.001$), but similar to that in the HBV group. Ascites and hepatic encephalopathy were more frequent in the Delta group, without significant differences. At a comparable MELD score and on the same background of HBV infection, patients with Delta infection therefore do not have lower hepatic synthetic function. They do, however, have more pronounced signs of hypersplenism, at a younger age.

The MELD-Na score did not differ significantly either from the non-Delta viral group ($p = 0.074$) or from the HBV group (15.0 versus 15.5, $p = 0.510$). The MELD 3.0 score was higher than in the non-Delta viral group (16.5 versus 15.0, $p = 0.029$), but not in comparison with the HBV group ($p = 0.652$). Compared with the HBV group, none of the three scores differed significantly. At the same time, patients with Delta infection were four years younger and had 26 $\times 10^9$/L fewer platelets. These differences are not reflected by the MELD scores. This observation underlay the construction of a score that also includes Delta etiology. The conclusion needs to be confirmed, because the HBV group has only 30 patients.

3.3. Identification of clinical and biological phenotypes by PAM analysis

PAM analysis was applied to 290 patients. The best solution had three clusters, with a mean silhouette width of 0.283, a value indicating moderate separation. Bootstrap stability was good, with a Jaccard index of 0.82 for C1, 0.81 for C2 and 0.87 for C3.

Phenotype C1, with relatively preserved liver function (n = 98, 33.8%), includes the patients with the least advanced disease. The median MELD-Na score was 14, albumin 31.6 g/L and platelets 100 $\times 10^9$/L. Only 20% of these patients had Delta infection.

Phenotype C2, hepatocellular (n = 89, 30.7%), is characterised by hepatic encephalopathy in all patients. Ascites was present in 87% of patients and portal vein thrombosis in 11%. Delta infection was present in 69% of patients. The picture is that of advanced hepatocellular failure.

Phenotype C3, portal-hypertensive (n = 103, 35.5%), comprises patients who appear only moderately ill according to the MELD-Na score. The median score was 16, and no patient had hepatic encephalopathy. Nevertheless, one-year mortality was 27%, the highest of the three clusters, and 53% of patients died on the list during follow-up. Delta infection was present in 76% of patients. This phenotype shows that the MELD-Na score may underestimate the risk of some patients. The proposed mechanism, a decompensation driven mainly by portal hypertension, remains a hypothesis, because the portal pressure gradient was not measured.

The distribution of phenotypes changed between the two eras of inclusion. The proportion of patients in C2 increased from 14% in Era I to 50% in Era II. The proportion of those in C1 decreased from 41% to 25%, and of those in C3 from 45% to 24% ($p < 0.001$). The change may be explained by better access to hepatological assessment and by later inclusion on the list. It is relevant for the interpretation of the temporal validation of the prognostic score.

3.4. Course on the waiting list and competing risk analysis

On the waiting list, death and transplantation are mutually exclusive. Their separate analysis by the Kaplan-Meier method would overestimate the risk of each event, which is why the competing risks framework was used.

Of the 313 patients, 136 (43.5%) died on the waiting list and 104 (33.2%) were transplanted, of whom 78 in the national programme and 26 in centres abroad. The remaining 73 patients (23.3%) were censored observations. No patient was lost to follow-up. The proportion of censored observations was 13.8% in the Delta group and 35.3% in the non-Delta group ($p < 0.001$), and the

transplant rate was 41.4% and 23.0%, respectively. Patients with Delta coinfection therefore left the list earlier and more frequently.

At 5 years, the cumulative incidence of death on the list was 42.6% (95% CI 37.3–48.0%) and that of transplantation 34.4% (95% CI 29.1–39.8%).

The crude cumulative incidence of death did not differ significantly between groups at any level of comparison (figure 3). Compared with all non-Delta etiologies, the difference at 5 years was 7.4 percentage points (45.9% versus 38.5%, p = 0.345). Compared with non-Delta viral cirrhosis, the values were 45.9% and 42.9% (p = 0.696). Access to transplantation, however, differed significantly at all three levels, in favour of the Delta group. At 5 years, the cumulative incidence of transplantation was 43.1% in the Delta group, versus 23.3%, 21.7% and 20.7% in the comparison groups. A group transplanted more frequently may have a lower cumulative incidence of death than would correspond to its death rate. The two components were separated by the multivariable models.

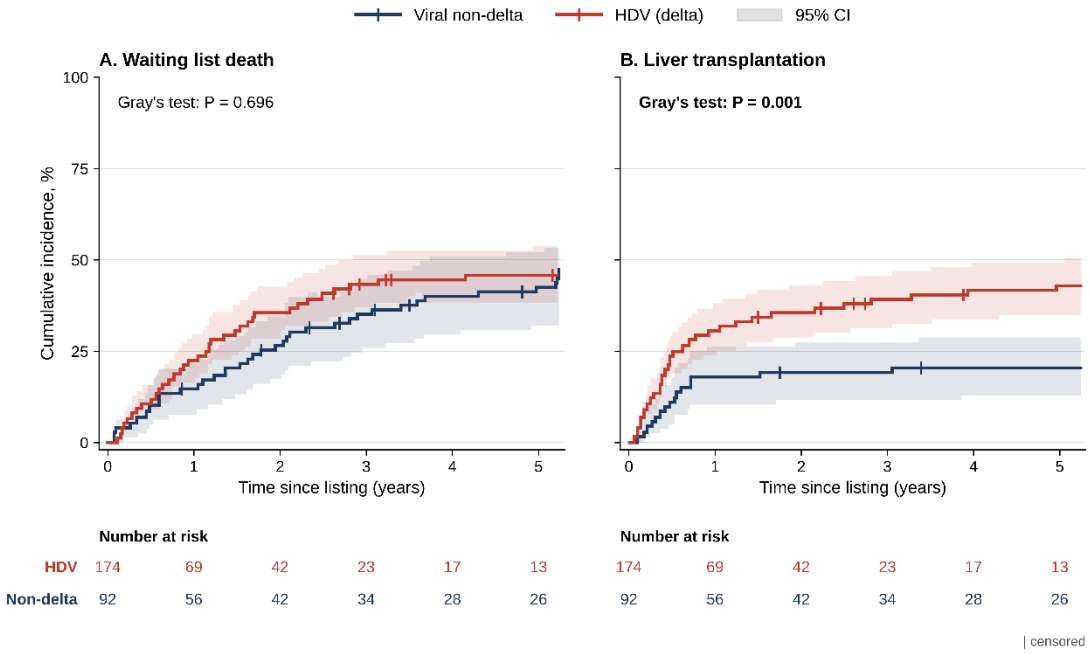

Figure 3. Cumulative incidence of death on the list and of transplantation, Delta compared with non-Delta viral cirrhosis

By phenotype, the cumulative incidence of death increased progressively. At 1 year, it was 13.1% in C1, 21.3% in C2 and 27.7% in C3. At 5 years, the values were 38.5%, 39.9% and 52.5% (Gray's test, p = 0.096). The portal-hypertensive phenotype had a 5-year mortality 14 percentage points higher than the phenotype with preserved function, although the median MELD-Na score differs by only two points.

On the cause-specific scale, HDV infection was associated with a twofold higher hazard of death on the waiting list (csHR = 2.01, 95% CI 1.40–2.89) (table 2). The effect persisted after adjustment for age, sex, the MELD-Na score and the era of inclusion. At the same time, HDV infection was associated with a hazard of transplantation of 2.41 (95% CI 1.56–3.73). Patients with Delta coinfection therefore die faster, but are also transplanted faster. Female sex was associated with a hazard of death reduced by almost half (csHR = 0.53, 95% CI 0.37–0.77), with no difference in access to transplantation.

Table 2. Cause-specific Cox and Fine-Gray models for death on the list and for transplantation

Covariate	Death, csHR (95% CI)	Transplantation, csHR (95% CI)	Death, sHR (95% CI)	Transplantation, sHR (95% CI)
HDV infection	2.01 (1.40–2.89)**	2.41 (1.56–3.73)**	1.20 (0.89–1.62)	1.89 (1.25–2.86)**
Age, per year	1.01 (1.00–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.02)	1.00 (0.98–1.02)
Female sex	0.53 (0.37–0.77)**	1.05 (0.71–1.56)	0.59 (0.44–0.81)**	1.24 (0.86–1.79)
MELD-Na, per point	1.07 (1.03–1.11)**	1.06 (1.02–1.11)**	1.04 (1.01–1.07)*	1.04 (1.00–1.08)
Era II versus Era I	1.00 (0.69–1.45)	1.30 (0.86–1.95)	0.79 (0.57–1.09)	1.15 (0.79–1.68)

Note. ** p < 0.05. ** p < 0.01. csHR, cause-specific hazard ratio. sHR, subdistribution hazard ratio. CI, confidence interval. HDV, hepatitis Delta virus. MELD-Na, MELD score with serum sodium.*

On the subdistribution scale, the effect of HDV infection on death on the list was attenuated and was no longer statistically significant (sHR = 1.20, 95% CI 0.89–1.62). The effect on access to transplantation remained significant (sHR = 1.89, 95% CI 1.25–2.86).

The difference between csHR = 2.01 and sHR = 1.20 arises for the same effect, in the same cohort and with the same covariates. The cause-specific hazard measures the rate of death in patients still on the list. The subdistribution hazard measures the absolute probability of death, after competition with transplantation. When the competing event is frequent and unevenly distributed between groups, the two estimates diverge. Patients with Delta coinfection leave the population at risk of death early, through transplantation. The result therefore does not indicate an allocation inequity. It suggests an additional risk, which the prioritisation tools do not measure directly. A possible explanation is the informal compensation of this risk through individual expediting.

The proportional hazards assumption was met for the cause-specific models (global test p = 0.819 for death and p = 0.408 for transplantation). In the Fine-Gray model for death, the interaction between HDV and time was significant (coefficient −0.22 per year, p = 0.036), which shows the attenuation over time of the effect on absolute probability.

The effect of HDV infection on death on the list was re-estimated in four sensitivity analyses. Restricting the comparator to non-Delta viral cirrhosis did not change the result (csHR = 2.12, 95% CI 1.38–3.24). Replacing the MELD-Na score with MELD 3.0 gave an almost identical estimate (csHR = 2.03). In the extended model, the effect persisted (csHR = 1.90, 95% CI 1.30–2.77), and hepatocellular carcinoma (csHR = 2.38, 95% CI 1.48–3.84) and ascites (csHR = 1.50, 95% CI 1.02–2.21) were independent predictors of mortality on the list.

The comparison with HBV monoinfection did not reproduce the effect, but did not refute it either. The cause-specific ratio was not significant (csHR = 0.82, 95% CI 0.49–1.35). The reference group has only 30 patients, of whom 19 died on the list, and the confidence interval is wide. The comparison is exploratory and represents a limitation of the main result.

The greater access to transplantation of the Delta group is not explained by early expediting. After exclusion of the 13 patients transplanted in the first 30 days, the effect on transplantation increased (sHR = 2.14, 95% CI 1.35–3.39). The analysis cannot rule out later expediting, which was not recorded as a formal allocation status.

3.5. Derivation, validation and clinical applicability of the Delta Prognostic Score

HDV infection was associated with a twofold higher cause-specific hazard of death at equal MELD-Na severity, and the allocation scores did not distinguish the Delta group from the etiologically homogeneous comparison groups. MELD-Na therefore does not capture the excess risk associated with Delta coinfection relative to non-Delta etiologies. Relative to HBV

monoinfection, this excess was not confirmed. The Delta Prognostic Score (DPS) was constructed to explicitly integrate HDV coinfection alongside MELD-Na.

The equivalent of Delta coinfection in MELD-Na points is the ratio between the coefficient of the HDV variable and that of the MELD-Na score. It shows how many additional MELD-Na points a patient without Delta coinfection would need in order to have the same risk of death as a patient with coinfection. The answer depends on the hazard scale. On the cause-specific scale, Delta coinfection is equivalent to approximately ten MELD-Na points, and the extended model confirms the order of magnitude (9.6 points). On the subdistribution scale, the equivalent decreases to approximately five points, because this scale includes the compensating effect of accelerated transplantation. The result is therefore reported as a range, of approximately five to ten MELD-Na points.

In the algorithm, this equivalent becomes a fixed supplement of 2 points (table 3). The MELD-Na categories used cover six points each on average, so that the cause-specific equivalent of 10.7 points corresponds to 1.8 categorical steps, a value rounded to 2. On the subdistribution scale, the equivalent would correspond to a single step. The choice of the upper limit is deliberate. For a tool intended for prioritisation, underestimating the risk in patients with Delta coinfection has more serious consequences than a moderate overestimation. Derivation by the ratio of coefficients has an indicative role, and the score is justified by its empirical performance.

Table 3. Algorithm for calculating the Delta Prognostic Score (DPS)

Step	Rule	Points
Step 1. MELD-Na categorisation	MELD-Na <12 (compensated disease)	0 points
	MELD-Na 12–17 (incipient decompensation)	1 point
	MELD-Na 18–24 (advanced dysfunction)	2 points
	MELD-Na >24 (critical stage)	3 points
Step 2. HDV coinfection	Absent (anti-HDV negative)	0 points
	Present (anti-HDV positive and detectable HDV RNA)	+2 points
Final DPS	Sum of the two components	0–5 points

Note. *MELD-Na, MELD score with serum sodium. HDV, hepatitis Delta virus. DPS, Delta Prognostic Score.*

Applied to the full cohort, the algorithm assigned 100 patients (31.9%) to the low-risk category (DPS 0–1), 154 (49.2%) to the intermediate-risk category (DPS 2–3) and 59 (18.8%) to the high-risk category (DPS 4–5). Almost half of the patients are therefore in the intermediate zone, in which the decision to expedite is the most difficult.

On the cause-specific scale, the hazard of death increased from one category to the next (table 4). Compared with the low-risk category, it was 1.56 times higher in the intermediate category and 3.43 times higher in the high category. Each additional score point increased the hazard by 41% (csHR = 1.41, 95% CI 1.23–1.61). On the cumulative incidence scale, the difference between categories did not reach statistical significance for death (Gray's test, $p = 0.071$), but was marked for access to transplantation ($p < 0.001$). The DPS therefore cannot be used to estimate the absolute probability of death on the list. It serves to rank patients according to the relative urgency of their need for transplantation.

Table 4. Stratification of the risk of death by DPS category

Risk category	n	csHR (95% CI)	p	Death at 1 year, %	Death at 3 years, %	Death at 5 years, %
Low (DPS 0–1)	100	reference	—	13.8	33.4	38.7
Intermediate (DPS 2–3)	154	1.56 (1.05–2.31)	0.028	17.2	37.7	40.9
High (DPS 4–5)	59	3.43 (2.12–5.54)	< 0.001	35.6	52.5	52.5
Per score point (0–5)	313	1.41 (1.23–1.61)	< 0.001	—	—	—

Note. *Univariable cause-specific Cox models, with transplantation treated as censoring. Death at 1, 3 and 5 years is estimated as cumulative incidence, with transplantation as a competing event. DPS, Delta Prognostic Score. csHR, cause-specific hazard ratio. CI, confidence interval.*

Discrimination was compared with that of the MELD-Na score using the time-dependent area under the ROC curve. When transplantation is treated as censoring, the DPS has numerically higher values at 3 and 5 years (0.707 versus 0.636 and 0.721 versus 0.644). The difference does not persist after correction for multiple comparisons ($p = 0.112$ and $p = 0.110$). The optimal threshold for predicting death at one year was DPS ≥ 4, with a sensitivity of 35.8% and a specificity of 88.3%. The main value of the DPS therefore does not lie in discrimination superior to the MELD-Na score. It lies in the explicit stratification of cause-specific risk into three categories and in the integration of Delta etiology into a tool that can be calculated at the bedside.

The gradient was reproduced in both eras of inclusion. The effect per score point was 1.32 in Era I and 1.64 in Era II, with widely overlapping confidence intervals. In the temporal validation, with derivation exclusively on Era I, Delta coinfection was independently associated with the cause-specific hazard of death (csHR = 1.76, 95% CI 1.14–2.73). Its equivalent was 8.8 MELD-Na points.

Calibration was assessed in the temporal validation. The calibration slope was 1.77 (95% CI 0.84–2.70) and did not differ significantly from the ideal value of 1 ($p = 0.106$). The one-year risk of death was, however, overestimated in the low category (13.6% predicted versus 6.3% observed) and underestimated in the high category (32.4% versus 67.6%). Calibration is therefore insufficient in the high-risk category. The score does not estimate absolute risk and may be proposed as a complementary stratification tool, after external validation.

4. POST-TRANSPLANT COURSE AND BENEFIT OF LIVER TRANSPLANTATION IN PATIENTS WITH LIVER CIRRHOSIS OF VIRAL DELTA ETIOLOGY

4.1. Post-transplant cohort and analysis sets

The complete series of adult transplants includes 168 patients, with a median age at surgery of 51 years (IQR 44–57). Of these, 111 (66.1%) had HBV/HDV coinfection and 57 (33.9%) had other etiologies. A total of 78 patients (46.4%) were transplanted in the Republic of Moldova. The graft came from a living donor in 37 patients (22.0%).

The analyses use three sets of patients. The main survival analysis relies on the 104 patients transplanted from the national list, of whom 78 were operated on in the country and 26 abroad. Only for these patients was disease severity recorded at listing, and follow-up starts at surgery. Early complications are analysed in subcohort B1 (n = 78), the only one with complete perioperative documentation. The full Cohort B is used in the sensitivity analysis. The 64 patients transplanted abroad without registration on the national list entered follow-up only after returning to the country, so that their perioperative deaths could not be captured.

The two etiological groups of the analytical cohort were comparable at the time of transplantation. Patients with Delta coinfection were approximately four years younger and had lower albumin, without the differences reaching statistical significance.

4.2. Early outcomes of transplantation (first 90 days)

In the analytical cohort, 14 patients (13.5%) died in the first 30 days and 16 (15.4%) in the first 90 days. Early mortality did not differ between the etiological groups. At 30 days, 13.9% of

patients with Delta coinfection and 12.5% of those with other etiologies had died. At 90 days, the proportions were 15.3% and 15.6%.

Complications in the first 90 days were analysed in the 78 patients operated on in the national programme. At least one complication was documented in 37 patients (47.4%), with no difference between the etiological groups (48.3% in Delta and 45.0% in non-Delta). None of the categories differed significantly between groups. Vascular and biliary complications were numerically more frequent in Delta patients, but the comparison group has only 20 patients.

The association between Delta coinfection and death at 30 days was estimated by a logistic model adjusted for the MELD-Na score at listing and for donor type. After adjustment, Delta coinfection was not associated with death at 30 days (OR = 1.00, 95% CI 0.26–3.81). A living donor graft was associated with the outcome (OR = 5.49, 95% CI 1.59–18.95, p = 0.007). The small number of events gives the estimates an indicative character.

4.3. Late outcomes of transplantation (after 90 days)

Late outcomes were analysed in the 85 patients alive and in follow-up at 90 days after transplantation, of whom 59 had Delta coinfection. Their median follow-up was 7.1 years (IQR 3.7–9.6). After day 90, 6 deaths were recorded, 4 in the Delta group and 2 in the non-Delta group. Survival conditional on passing the perioperative period was 97.5% at one year, 94.5% at five years and 92.9% at ten years. It did not differ between the etiological groups (log-rank test, p = 0.927). A patient who passes the perioperative period therefore has a favourable long-term prognosis, regardless of etiology. With only six events, the late outcomes are descriptive.

Virological monitoring was available in the patients operated on in the national programme. Of these, 62 were HBsAg-positive recipients, namely 58 with Delta coinfection and 4 with HBV monoinfection. No recurrence of HBV or HDV was recorded in any of them. The prophylactic protocol combines anti-HBs immunoglobulin with nucleos(t)ide analogues, administered indefinitely. Individual documentation of prophylaxis and of virological checks in the registry is incomplete.

4.4. Survival over the entire follow-up, by etiological group

Survival was estimated in the 104 patients of the analytical cohort. Median follow-up was 6.4 years, with a total of 574 person-years. During this interval, 22 deaths were recorded, of which 14 in the first 30 days, 16 in the first 90 days and 18 in the first year. Overall survival was 82.4% at one year, 81.3% at five years and 78.5% at ten years (table 5).

Table 5. Post-transplant survival by etiological group

Group	N	Deaths	1 year [95% CI]	5 years [95% CI]	10 years [95% CI]
Main analysis, overall	104	22	82.4% [75.3–90.1%]	81.3% [74.1–89.3%]	78.5% [70.6–87.2%]
Delta coinfection	72	15	81.6% [73.1–91.2%]	81.6% [73.1–91.2%]	79.6% [70.5–89.9%]
Other etiologies	32	7	84.1% [72.2–97.9%]	80.7% [67.9–95.9%]	75.9% [61.6–93.6%]
Full Cohort B, overall	168	30	88.0% [83.1–93.1%]	83.4% [77.8–89.5%]	80.6% [74.3–87.4%]
Delta coinfection	111	17	87.2% [81.2–93.7%]	86.2% [79.9–92.9%]	84.7% [77.9–92.0%]
Other etiologies	57	13	89.3% [81.6–97.8%]	78.6% [68.0–90.9%]	73.4% [61.7–87.3%]

Note. *Kaplan-Meier estimates. Log-rank test between etiological groups, p = 0.974 in the main analysis and p = 0.316 in the full Cohort B. CI, confidence interval.*

Survival did not differ between patients with Delta coinfection and those with other etiologies (figure 4). The hazard ratio for Delta coinfection was 0.98 (95% CI 0.40–2.42). With 22 deaths, the study could have detected only a hazard ratio of approximately 3.5 or greater. The data therefore do not show a survival disadvantage associated with Delta etiology, but neither do they demonstrate the equivalence of the two groups. On the waiting list, Delta coinfection was associated with a twofold higher cause-specific hazard of death. After transplantation, this difference is no longer found, an observation consistent with replacement of the native liver. In the sensitivity analysis on the full Cohort B, the conclusion remained the same (HR = 0.69, 95% CI 0.34–1.43).

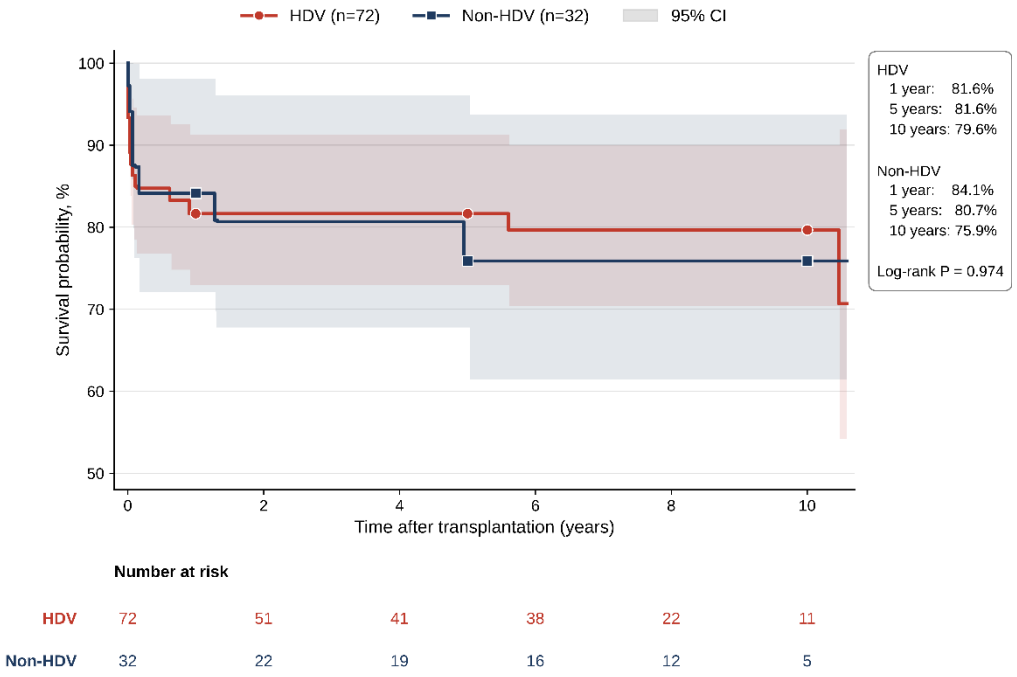

Figure 4. Post-transplant survival according to etiology (n = 104)

4.5. Other factors associated with post-transplant survival

Factors recognised as determinants of survival after transplantation were explored by univariable analysis. With 22 deaths, the analysis is exploratory. Hepatocellular carcinoma was documented in 20 patients (19.2%). Survival of these patients was 69.2% at one year and 63.5% at five years, versus 85.5% at both time points in patients without carcinoma (p = 0.027). Serum sodium and the MELD-Na score at listing were associated with survival, which supports transplantation before the onset of advanced decompensation. A living donor graft was associated with a one-year survival of 63.2%, versus 90.4% for a deceased donor graft. This association should be interpreted with caution.

4.6. Benefit of liver transplantation

Transplant benefit was expressed in years of life saved (YLS), as the difference between the mean survival observed after transplantation and the mean survival estimated in the absence of transplantation, over a 10-year horizon. The estimated mean benefit was 4.00 years of life per patient, that is 416 years for the entire analytical cohort. It was greater in patients with Delta coinfection (4.69 years) than in those with other etiologies (2.44 years). The difference does not arise from better survival after transplantation, which was almost the same in the two groups (8.10 and 7.89 years). It arises from the estimated survival without transplantation, which was shorter in

Delta patients (3.41 versus 5.45 years). The values are indicative and do not represent causal effects.

Early and late outcomes did not depend on etiology. These data support liver transplantation as a therapeutic option in Delta cirrhosis.

5. INTEGRATED DIGITAL SYSTEM FOR MONITORING LIVER TRANSPLANT PATIENTS

The chapter presents the TransplantCare digital platform, developed to meet the monitoring needs identified in chapters 3 and 4. The originality of the solution was recognised by Innovator Certificate No. 6463 of 23 April 2026. The platform is at the prototype stage, built as a mobile application for the iOS and Android systems. The prototype was tested internally, with fictitious data, without the participation of patients.

5.1. Clinical context and rationale for the platform

In the post-transplant stage, the national programme has a dual structure, with patients transplanted in the country (n = 78) and in international centres (n = 90). This structure fragments clinical data and hinders standardised follow-up. Deaths are concentrated in the perioperative period, and after discharge follow-up depends on scheduled visits. These findings motivated the development of a bidirectional monitoring platform.

5.2. From risk stratification to the digital tool

The results of chapter 3 took the form of a risk stratification algorithm applicable at the assessment for listing. The algorithm combines the MELD-Na severity category with virological status and assigns the patient to one of three risk categories. For each category a monitoring approach is proposed, which has not yet been evaluated prospectively. The platform calculates, displays and records the score, but does not make prioritisation decisions. The decision remains with the clinical team.

5.3. Functional architecture of the TransplantCare platform

The platform has three user modules, Administrator, Physician and Patient, connected to a central data processing core. The core includes the longitudinal patient database, the automated alert system, the automatic calculation of MELD-Na and DPS for patients on the waiting list, the chronological history of clinical parameters and the secure messaging module between physician and patient.

5.4. Key clinical functionalities

The patient module allows daily recording of blood pressure, heart rate, temperature and weight. Symptoms are reported on a standardised list, with severity graded on a scale from 1 to 5. The system automatically classifies reported events into three severity levels, with differentiated response protocols. Critical alerts are generated by symptoms with a potential for rapid deterioration, such as progressive jaundice, fever above 38.5°C or gastrointestinal bleeding, and trigger immediate notification of the attending physician. The thresholds were set on the basis of the EASL guidelines and the national protocol. Their prospective validation remains a subsequent stage.

5.5. Potential clinical value, stage of development and prospects for implementation

The intended clinical value is the reduction of the interval between the onset of a symptom and medical assessment. The platform is designed so that a critical alert reaches the attending physician in real time, independently of the visit schedule. Patients transplanted in external centres and those transplanted in the country can be followed up with the same tools, which may reduce data fragmentation. The clinical value of the platform requires prospective validation.

GENERAL CONCLUSIONS

1. Patients with HDV cirrhosis had a more severe clinical and biological profile than those with non-Delta viral cirrhosis, characterised by significantly more pronounced hemorrhagic syndrome, thrombocytopenia, leukopenia and hypoalbuminemia. Despite this severity, the MELD-Na score remained similar between groups, which suggests an underestimation of the real risk and the need for additional prognostic stratification tools in patients with Delta coinfection.
2. PAM cluster analysis (n = 290) identified three clinical and biological phenotypes, with relatively preserved liver function (C1), hepatocellular (C2) and portal-hypertensive (C3), with a one-year mortality of 12%, 19% and 27%. Delta coinfection was concentrated in phenotypes C2 and C3 (69% and 76%, versus 20% in C1). The portal-hypertensive phenotype had the highest mortality in the absence of encephalopathy, which indicates a risk insufficiently reflected by the conventional criteria of decompensation.
3. Competing risk analysis showed that, on the waiting list, death exceeds transplantation in the long term (42.6% versus 34.4% at 5 years). Cumulative mortality did not differ significantly between HDV and non-HDV patients (45.9% versus 38.5% at 5 years, Gray's test $p = 0.345$), whereas transplantation was more frequent in HDV patients (43.1% versus 23.3%, $p < 0.001$).
4. The cause-specific Cox model identified HDV infection as an independent predictor of death on the list (csHR = 2.01, 95% CI 1.40–2.89), in addition to MELD-Na, whereas on the Fine-Gray scale the effect on absolute risk did not reach statistical significance (sHR = 1.20, 95% CI 0.89–1.62). Access to transplantation was greater in HDV patients (sHR = 1.89, 95% CI 1.25–2.86). Delta patients thus have an additional risk of death for as long as they remain on the list, not an allocation inequity, which supports the inclusion of Delta etiology in risk stratification.
5. Post-transplant survival was favourable (82.4% at 1 year, 78.5% at 10 years), with no disadvantage for HDV etiology (log-rank $p = 0.974$), which suggests that the risk associated with Delta infection on the waiting list is not found after transplantation. Viral recurrence was absent, and mortality was concentrated in the perioperative period (14 of 22 deaths in the first 30 days).
6. The Delta Prognostic Score (DPS) was derived, which stratifies the risk of death on the list into three categories, with a hazard 3.43 times higher in the high-risk category (95% CI 2.12–5.54) and with the hierarchy maintained in the temporal validation. The prototype of the TransplantCare digital platform for integrated monitoring was developed. Together, they provide a tool for risk stratification and surveillance, aimed at preventing complications in patients with Delta coinfection, whose clinical use requires external validation and prospective evaluation.

PRACTICAL RECOMMENDATIONS

At the level of practical medicine

1. Use of the Delta Prognostic Score (DPS), with an indicative role, as a tool complementary to the MELD-Na score in patients with liver cirrhosis of viral Delta etiology registered on the waiting list. The score does not replace the allocation scores, does not estimate absolute risk and requires external validation.

2. Active screening for HBV/HDV coinfection in all HBsAg-positive patients with liver cirrhosis assessed for inclusion on the waiting list.

3. Intensified monitoring in the first 30 days after transplantation in all patients.

4. Implementation of the TransplantCare digital platform, as a pilot project, in the monitoring of liver transplant patients in the Republic of Moldova.

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

1. Revision of the National Clinical Protocol PCN-347 "Liver transplantation", with assessment of the inclusion of Delta etiology (HBV/HDV) as an element of risk stratification in the prioritisation process, with prior external validation of the proposed score.

2. Development of a prospective registry of patients with liver cirrhosis of viral Delta etiology in the Republic of Moldova, integrated with the Transplant Agency database, allowing standardised longitudinal follow-up and the provision of data comparable with the European registries (ELTR, Eurotransplant).

3. Completion of the national liver transplant registry with the variables required to assess perioperative outcomes, namely cold ischemia time, intraoperative parameters, the functional status of the graft at pre-established intervals and the date of its last assessment. In the present research, the absence of these data prevented the analysis of graft survival as an outcome distinct from patient survival, as well as the assessment of the recognised determinants of early graft dysfunction.

At the level of future scientific research

1. External validation of the Delta Prognostic Score (DPS) in independent populations from European centres with high endemicity of HDV infection, including validation of the dynamic recalculation of the score during the waiting period.

2. Prospective evaluation of the impact of the TransplantCare digital platform on the rate of emergency hospitalisation, adherence to immunosuppressive treatment and the quality of life of post-transplant patients, through a controlled intervention study in a national follow-up cohort.

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INFORMATION ON THE VALORIZATION OF THE RESEARCH RESULTS

SCIENTIFIC WORKS

- **Articles in scientific journals:**

✓ ***articles in journals indexed in WoS, SCOPUS or other databases recognised by ANACEC***

1. Peltec A, **Buga D**, Hotineanu A, et al. Impact of hepatitis delta virus infection on waiting list outcomes: A competing-risks analysis. World Journal of Hepatology. 2026;18(10):124709. ISSN 1948-5182. doi:10.4254/wjh.124709. https://doi.org/10.4254/wjh.124709 (IF Clarivate 3.4, 2025)

✓ ***articles in category B journals***

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- **Abstracts/theses in the proceedings of national and international scientific conferences**

✓ ***International***

10. **Gudima D**, Taran N, Tofan L, Țurcanu A, Hotineanu A, Codreanu I, Peltec A. Liver cirrhosis induced by delta virus in Republic of Moldova: prevalence and mortality on the liver transplant waiting list. *Journal of Gastrointestinal and Liver Diseases*. 2018;27(S2):56. ISSN 1841-8724.
11. **Buga D**, Hotineanu A, Tcaciuc E, Taran N, Peltec A. Liver cirrhosis induced by delta virus: clinical and evolutive peculiarities in patients on the waiting list for liver transplantation in the Republic of Moldova. In: *Perspectives of the Balkan medicine in the post COVID-19 era: The 37th Balkan Medical Week. The 8th Congress on Urology, Dialysis and Kidney Transplant from the Republic of Moldova „New Horizons in Urology”*; 7–9 June 2023; Chișinău. Bucharest: Balkan Medical Union; 2023. p. 143. ISSN 1584-9244 (print); ISSN 2558-815X (online).

✓ ***National***

12. Toacă I, Hotineanu A, Pîrvu V, Peltec A, **Buga D**, et al. Complications of liver transplantation. In: *Congresul consacrat aniversării a 75-a de la fondarea USMF „Nicolae Testemițanu”: 21–23 October 2020: Abstract book*. Chișinău: CEP „Medicina”; 2020. p. 457.

- **Active participation in scientific forums**
- **Participation with presentations at scientific forums:**

✓ ***international***

13. **Buga D**, Hotineanu A, Taran N, Pîrvu V, Babitchi V, Burgoci S, Peltec A. Particularitățile clinice și de urmărire la pacienții cu ciroză hepatică virală după transplant hepatic. *Oral presentation at:* Congresul Național Romtransplant, 12th edition; 15–16 September 2023; Iași, Romania.
14. **Buga D**, Hotineanu A, Peltec A. Ciroza hepatică de etiologie virală delta: particularitățile pacienților aflați pe lista de așteptare transplant hepatic. *Oral presentation at:* The 8th Congress on Urology, Dialysis and Kidney Transplant from the Republic of Moldova with international participation „New Horizons in Urology”; 7–9 June 2023; Chișinău, Republic of Moldova.
15. **Buga D**. Supravegherea pacientului cu transplant hepatic. *Oral presentation at:* 4th Update on Hepatology Course. Boli hepatice rare – tranziția îngrijirii medicale de la copil la adult; 9 December 2023; Chișinău, Republic of Moldova.

✓ ***national***

16. **Gudima D**. Complicațiile cirozei hepatice de etiologie virală delta. *Oral presentation at:* Conferința Științifică anuală consacrată Zilelor Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”; 15–19 September 2018; Chișinău, Republic of Moldova.
17. **Buga D**. Profilul clinic și biologic de risc în ciroza hepatică Delta – instrument pentru prioritizarea pacienților pe lista de așteptare pentru transplant hepatic. *Oral presentation at:* Al VI-lea Congres Național de Gastroenterologie și Hepatologie din Republica Moldova cu participare internațională; 21–22 November 2025; Chișinău, Republic of Moldova.

- **Participation with posters at scientific forums:**

✓ ***international***

18. **Gudima D**, Taran N, Tofan-Scutaru L, Țurcanu A, Hotineanu A, Codreanu I, Peltec A. Liver cirrhosis induced by delta virus in Republic of Moldova: prevalence and mortality on the liver transplant waiting list. *Poster presented at:* Al XXXVIII-lea Congres Național de Gastroenterologie, Hepatologie și Endoscopie Superioară; 24–26 May 2018; Craiova, Romania.
19. **Buga D**, Hotineanu A, Taran N, Peltec A. Liver cirrhosis induced by delta virus: clinical and evolutive peculiarities in patients on the waiting list for liver transplantation in the Republic of Moldova. *Poster presented at:* 11th Update on Hepatology Course; 21–23 March 2024; Bucharest, Romania.
20. **Buga D**, Hotineanu A, Taran N, Peltec A. Clinical and follow-up features in transplanted patients for viral liver cirrhosis. *Poster presented at:* 11th Update on Hepatology Course; 21–23 March 2024; Bucharest, Romania.
21. Peltec A, **Buga D**, Taran N, Hotineanu A. Profile of Liver Transplant Candidates on the National Waiting List in the Republic of Moldova. *Poster presented at:* 4th International Meeting Delta Cure; 9–10 October 2025; Hanover, Germany. Abstract book: Abstract ID 68, Poster ID 40.

- **Innovator certificates**

22. Innovator Certificate No. 6463 of 23.04.2026. “TransplantCare” mobile application, intended for monitoring patients before and after organ transplantation.

ANNOTATION

BUGA DIANA. CLINICAL COURSE OF LIVER CIRRHOSIS OF VIRAL B AND DELTA ETIOLOGY IN THE PRE- AND POST-TRANSPLANT STAGE.
Doctoral thesis in medical sciences, Chișinău, 2026.

Relevance of the research: The Republic of Moldova is a European endemic focus of hepatitis Delta virus infection. Liver cirrhosis of viral Delta etiology is the main indication for liver transplantation in the national programme. The classical prognostic scores do not fully reflect the risk of these patients.

Aim of the research: To establish the clinical, biological, evolutionary and prognostic particularities of liver cirrhosis of viral Delta etiology, with a view to implementing modern strategies for monitoring patients on the liver transplant waiting list and transplant recipients.

Research objectives: 1. To determine the clinical, biological and virological particularities of patients with liver cirrhosis of viral Delta etiology included in the liver transplant programme. 2. To identify the clinical and biological phenotypes of patients with Delta liver cirrhosis by cluster analysis. 3. To assess the course of patients with Delta liver cirrhosis on the waiting list, through the analysis of competing events (death on the list and liver transplantation). 4. To evaluate the prognostic factors on the waiting list using cause-specific Cox and Fine-Gray models and to develop a Delta prognostic score. 5. To assess the early and late outcomes of liver transplantation in patients with Delta liver cirrhosis. 6. To develop strategies for monitoring patients with Delta liver cirrhosis, aimed at preventing and delaying the onset of complications.

Scientific novelty and originality: This is the first systematic analysis of the entire national cohort of 313 liver transplant candidates (2013–2025), carried out within the competing risks framework. Three clinical and biological phenotypes were identified. The Delta Prognostic Score (DPS) was derived and temporally validated, with a concordance index of 0.62 in the entire cohort and 0.65 in the temporal validation.

Main new results: HDV infection was associated with a twofold higher cause-specific hazard of death on the list (csHR = 2.01, 95% CI 1.40–2.89), with no difference in cumulative incidence at five years compared with non-Delta viral cirrhosis (45.9% versus 42.9%). After transplantation, survival was 82.4% at one year and 78.5% at ten years, with no difference associated with Delta coinfection. Of 22 deaths, 14 occurred in the first 30 days. In patients alive at 90 days, ten-year survival was 92.9%. No recurrence of HBV or HDV was recorded under combined prophylaxis.

Theoretical significance of the research: The study shows that the effect of etiology differs on the cause-specific scale and on the subdistribution scale when transplantation, as a competing event, is unevenly distributed between groups.

Applied value of the study: The DPS is a tool for complementary pre-transplant assessment, with an indicative role until external validation. The prototype of the TransplantCare digital platform (Innovator Certificate No. 6463) automatically calculates the risk category and issues alerts when it changes.

Implementation of the scientific results: The research results are implemented in the clinical activity of the "Timofei Moșneaga" Republican Clinical Hospital and in the teaching process of "Nicolae Testemițanu" SUMPh.

Thesis structure: The thesis comprises the introduction, 5 chapters, discussion, general conclusions and practical recommendations, a bibliography of 142 titles and 2 annexes. The main text has 108 pages, 35 tables and 28 figures. The results are reflected in 22 scientific works and materials.

Keywords: hepatitis Delta, liver cirrhosis, liver transplantation, HBV/HDV coinfection, waiting list, MELD score, Delta Prognostic Score, competing risks, clinical phenotypes, post-transplant survival.