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ORIGINAL ARTICLE

# Clinical epidemiological analysis of the mortality rate of liver transplant candidates living in rural areas

Michele Molinari, Paul D. Renfrew, Neil M. Petrie, Sarah De Coutere and Mohamed Abdolell

From the Multi-Organ Transplant Program, Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada

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**Correspondence**
Michele Molinari, QEII HSC, Victoria Building, Room 6-254, 1276 South Park Street, Halifax, NS B3H 2Y9. Tel.: 902-473-7624; fax: 902-473-7639; e-mail: michele.molinari@cdha.nshealth.ca

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## Summary

MELD score has been used to predict 90-day mortality of subjects listed for liver transplantation (OLT). Validation of MELD score for patients on the waiting list in transplant programmes serving rural areas in North America is lacking. A retrospective cohort of patients affected by end-stage liver disease was studied to assess the mortality rate within 90 days after being listed at our transplant centre. Secondary aims were to identify differences between predicted and observed 90-days mortality using MELD and MELDNa scores at the time of listing. Among 126 patients included in this study, waiting list mortality was 35.0%. Ninety-day mortality was 21.1%, which was significantly greater than the mortality estimated by the MELD (9.1%, 95% CI: 6.6–11.5) and MELDNa (9.3%, 95%CI: 6.0–12.5). Despite this underestimation, AUC for MELD and MELDNa was 0.80 and 0.78 respectively. In our study, independent predictors of waiting list mortality were age, diagnosis of cholestatic disease and residence over 500 km from our transplant centre. MELD and MELDNa underestimated the 90-day mortality in patients with liver failure living in rural areas. Validation of these models should be performed in other transplant centres serving patients with limited access to specialized services.

## Introduction

Liver transplantation (OLT) is the standard of care for patients with end-stage hepatic failure. Over the last decades, the number of available liver grafts has not been able to match the requirements and the number of patients dying on the wait-list from end-stage liver disease (ESLD) has increased [1,2]. Data collected from November 1999 to December 2001 by the Organ Procurement and Transplantation Network in the United States (OPTN) have shown that the mortality rate within 90 days after being listed for a cadaveric OLT was 12% [1]. Burak *et al.* from the university of Alberta, Canada, reported similar results with a mortality rate at 90 days of 10% [2]. Mortality rate of patients waiting for OLT mainly depends on three variables: i) the severity of their liver disease, ii) the rate of organ donation and iii) the criteria used for organ allocation. In 2002, the Model for End-Stage Liver Disease (MELD) was introduced in the United States as a reproducible and objective method to assess the severity of hepatic dysfunction and it has been used to stratify patient's disease severity and to allocate liver grafts [3]. The main advantage of using the MELD score is the fact that it is objective and allows the allocation of organs on the base of medical necessity. Some reports indicate that waiting list mortality has been considerably reduced by the implementation of MELD-based allocation criteria [4–7]. Although MELD system has proven effective in predicting short-term mortality in patients with ESLD living in the USA and Europe, it has not been validated in patients with ESLD living in rural areas.

Our transplant program services the Atlantic Provinces of Canada (Nova Scotia, Prince Edward Island, New Brunswick, Newfoundland and Labrador) a large geographical area of 539 594 $km^2$ with a total population of 2 337 600 inhabitants. This makes our transplant centre relatively unique. When compared with other Canadian Provinces, our patients live in rural areas more frequently

(42–55% vs. 15–30%) [8–10], have lower yearly household income (CAN$ 40 000 vs. 42 000), lower education levels and higher unemployment rates (range 9.1–14.7% vs. 4.3–9.1% respectively) [8]. The geography and the socio-economic characteristics of our population make travelling to our transplant centre for routine medical care more challenging.

In addition, the number of physicians per capita is significantly lower in our provinces than in the rest of the country with an average ratio of 1 physician per 207–292 individuals versus 1 physician per 168–207 individuals in other parts of Canada [8].

Based on our clinical experience, we postulated that the mortality for patients awaiting OLT in Atlantic Canada exceeds that of previous published studies.

## Methods

### Aims of this study

To test the hypothesis that patients awaiting for OLT in Atlantic Canada might have increased mortality in comparison with previous published data, a retrospective study of a cohort of patients listed for a cadaveric OLT at our centre was performed with the main aim of assessing the overall mortality rate and the 90-day mortality rate while waiting for a cadaveric graft. Secondary objectives included studying covariates such as demographic characteristics, aetiology of end-stage liver disease and MELD and MELDNa score as possible predictors for the 90-day mortality rate in our population.

### Ethical approval

Ethical approval for this study was granted by the Capital Health Research Ethics Board prior to its initiation.

### Inclusion and exclusion criteria

All adult patients referred and listed for cadaveric OLT at our centre were included. Patients who were younger than 18, whose indication for OLT was acute liver failure or who had undergone a previous solid organ transplant were excluded. Patients lost to follow-up or with incomplete data despite our efforts to obtain data from patients' families or family physicians were excluded.

### Data collection

Data were retrospectively gathered, by medical record review, on all adult patients who satisfied the inclusion criteria and who were wait-listed for their first OLT over a 5 year period: from January 1st, 2004 until December 31st, 2008. Basic socio-demographic variables including gender, age at time of listing and location of residence were obtained. The geographical distance between each patient's home address and our transplant centre was calculated by using software freely available on the internet that estimated the shortest driving route between the two locations [11]. The primary indication for OLT and concomitant causes of liver disease were recorded. Date of waiting list placement and laboratory values closest to this time of listing were collected for calculation of Model for End-Stage Liver Disease (MELD) and the recently derived sodium augmented modification (MELDNa) [3,4]. The follow-up period lasted until June 30th, 2009 to ensure a minimum of 6-month period of observation while on the wait list for OLT. Outcome status was defined as death or removal from wait list due to being deemed too sick to undergo OLT (failure outcome), transplantation or survival on wait list at the end of observation period (the later two being censored outcomes for the survival analysis). For cases of wait-list mortality, the cause of death was obtained when possible. Using the wait-listing laboratory values the MELD (UNOS modification) and MELDNa scores were retrospectively calculated [3,4]. The predicted probability of 90-day wait-list mortality was calculated from the MELD and MELDNa scores utilizing formulae provided by investigators at the Mayo Clinic in Rochester Minnesota (Personal communication, Joanne Benson, Statistical Programmer/Analyst, Division of Biomedical Statistics and Informatics, Mayo Clinic Rochester Minnesota, April 28, 2009).

### Statistical analysis

Categorical variables were summarized as proportions and compared using nonparametric chi square ($\chi^2$) testing. For continuous variables, the median and range values were used as measures of central location and variation respectively. Continuous variables were compared using the nonparametric, Wilcoxon rank-sum test. Model estimates for incidence of 90-day wait-list mortality were compared with the observed incidence utilizing a one-sample t-test. A five percent level of significance was used for tests of comparison. Nonparametric receiver operating characteristic (ROC) analysis was used to evaluate MELD and MELDNa models discrimination. MELD models calibration was assessed using quantile-of-risk analysis. The Kaplan–Meier method was used to assess the survival of the study population from the date of listing for OLT to the date of censoring or death. Patients who dropped-out from the list of suitable candidates for cadaveric liver OLT were censored when removed from the waiting list because their medical condition improved or were considered too ill to undergo OLT. To evaluate variables associated with survival, univariate and multivariate Cox

proportional hazard models were used [12]. Variables found on univariate analysis to have *P*-value of less than 0.10 were submitted to multivariate analysis. Variables with *P*-values of less than or equal to 0.05 on multivariate analyses were considered to be independently associated with the occurrence of waiting list mortality. Intercooled Stata 9.2 (StataCorp, College Station, Texas) was used for all statistical analyses.

## Results

Within the study period, after excluding patients with acute liver failure, 126 individuals were placed on the waiting list for first OLT. Three patients were lost to follow-up while on the waiting list and excluded from the final analysis (Fig. 1). Final analysis was therefore based on a cohort of 123 patients.

Baseline characteristics of the cohort are summarized in Table 1. Seventy-five of the 123 wait-list patients (61%) were male. The median age of the cohort was 56 years (range 18–68). Table 2 summarizes the primary pathological indications for OLT of the entire cohort of patients. The leading primary indication for OLT was alcohol-related cirrhosis (18.0%). The most prevalent cause of chronic liver disease was viral hepatitis C infection (HCV) that was the primary indication for OLT in 15.5% of patients. One quarter of the cohort had cholestatic liver disease defined as patients affected by primary sclerosing cholangitis (PSC) or primary biliary cirrhosis (PBC) while hepatocellular carcinoma was the primary indication in 13.8%. Median MELD and MELDNa scores at the time of wait-listing were 14 (range 7–38) and 17 (range 7–38) respectively. The average MELD and MELD-Na scores at the time of listing were significantly greater for individuals who died or became too ill to undergo OLT compared with those transplanted (median 17 vs. 13, $P = 0.004$ and 21 vs. 15, $P < 0.001$ respectively). For the 77 patients who underwent OLT, the median waiting time was 148 days (range 1–1145 days).

**Table 1.** Summary of the characteristics of the study population (Total no. 123 patients).

| Variable | Value | Withdrawal or death on wait-list | Transplanted or waiting | *P*-value |
|---|---|---|---|---|
| Male gender | 61.0% | 62.8% | 60.0% | 0.762 |
| Median age at listing (range) | 56 years (18–68) | 58 years (18–67) | 55 years (19–68) | 0.054 |
| Median distance to transplant centre (range) | 317 km (3–1526) | 362 km (5–1486) | 311 km (3–1526) | 0.319 |
| Primary indications for liver transplantation (OLT) | | | | |
| Alcoholic cirrhosis | 17.9% | 32.6% | 10.0% | <0.001 |
| HCV | 15.5% | 14.0% | 16.3% | |
| HCC | 13.8% | 4.7% | 18.8% | |
| PSC | 13.8% | 4.7% | 18.8% | |
| PBC | 11.4% | 7.0% | 13.8% | |
| Median listing scores (range) | | | | |
| MELD | 14 (7 to 38) | 17 (7 to 38) | 13 (7 to 32) | 0.004 |
| MELDNa | 17 (7 to 38) | 21 (8 to 38) | 15 (7 to 32) | <0.001 |

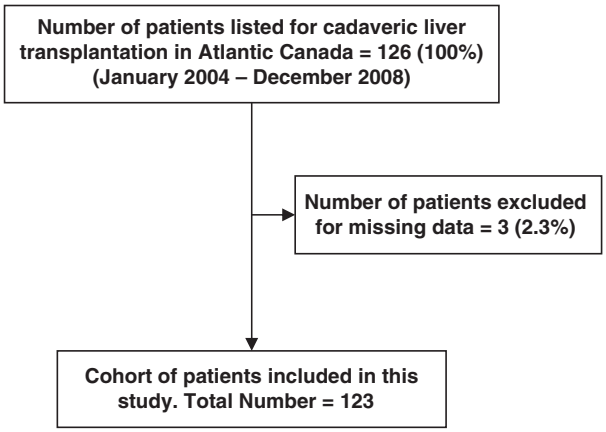


**Figure 1** Flow diagram representing the number of patients listed for cadaveric liver transplantation (OLT) in Atlantic Canada over the period of 5 years (January 2004 – December 2008). The initial cohort of subjects included in this study was 126. Among them, 3 (2.3%) were excluded from the final analysis as they did not have data on their outcomes.

**Table 2.** Summary of the primary indication for liver transplantation (OLT) in this study (Total no. 123 patients).

| Primary indication for cadaveric liver transplantation (OLT) | N. (%) |
|---|---|
| Alcohol-related cirrhosis | 22 (17.4%) |
| HCV (Viral C Hepatitis) | 19 (15.5%) |
| HCC (Hepatocellular Carcinoma) | 17 (13.8%) |
| PSC (Primary Sclerosing Cholangitis) | 17 (13.8%) |
| PBC (Primary Biliary Cirrhosis) | 14 (11.4%) |
| Cryptogenic Cirrhosis | 14 (11.4%) |
| AIH (Autoimmune Hepatitis) | 5 |
| NASH (Non Alcoholic Steato-Hepatitis) | 3 |
| HBV (Viral B Hepatitis) | 2 |
| Polycystic liver disease | 2 |
| Budd Chiari, Wilson's, alpha-1 antitrypsin deficiency, congenital hepatic fibrosis, secondary biliary cirrhosis | 1 each |
| Others | 3 |

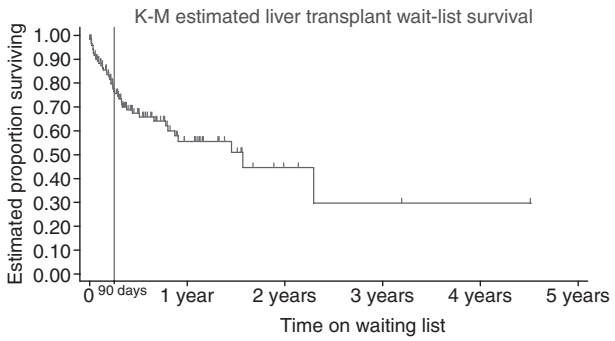


**Figure 2** Kaplan–Meier curve representing the overall survival of the cohort of patients waiting for cadaveric liver transplantation (OLT) in Atlantic Canada. At 90-days, 21% of the cohort experienced death or dropped out from the list for irreversible deterioration of their medical condition.

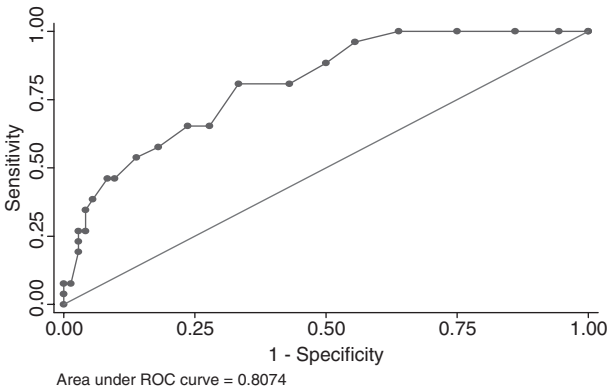


**Figure 3** Receiver Operating Characteristic (ROC) curve for MELD score as instrument used to predict 90-day mortality of patients waiting for cadaveric liver transplantation (OLT) in Atlantic Canada.

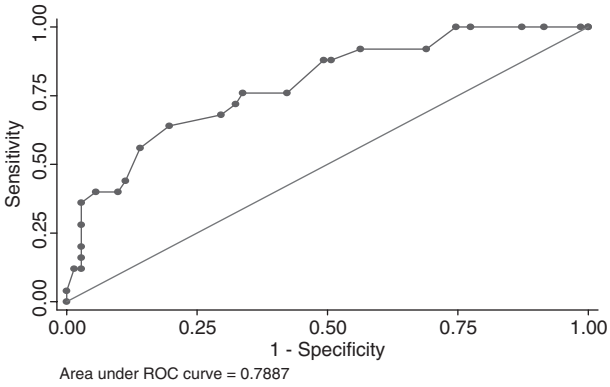


**Figure 4** Receiver Operating Characteristic curve (ROC) for MELDNa score as instrument to predict 90-day mortality of patients waiting for cadaveric liver transplantation (OLT) in Atlantic Canada.

### Wait-list mortality

Of the 123 patients included in this analysis, 43 (35.0%) died or became too ill to undergo OLT while on the waiting list, 77 were transplanted or were still awaiting transplantation ($n = 3$) at the end of the follow-up period. All but six of the wait-list failures were resulting from progression or complications of liver disease (four cardiovascular events and two unknown). Of the wait-list deaths or withdrawals, one quarter occurred within 22 days of listing and the median time to death or drop-out was 79 days. Figure 2 shows the Kaplan–Meier overall survival of the study population and within the 90-day interval while waiting for OLT.

The observed 90-day wait-list mortality rate was 21.1%: 26 of 123 suitable patients died, 23 were transplanted and 74 were still active on the waiting list at 3 months after being listed. The mortality rate observed in our cohort was significantly greater than the estimated probability of 90-day wait-list mortality estimated by using both the MELD and MELDNa scores. In fact, the estimated MELD score mortality risk at 90 days for our cohort was 9.1% vs. the observed 21.1% (95% CI: 6.6–11.5, $P < 0.001$) and when using MELDNa scores the estimated mortality risk at 90 days was 9.3% vs. the observed 21.1% (95% CI: 6.0–12.5, $P < 0.001$). To explore the differences between predicted and observed mortality, discrimination and calibration for MELD and MELDNa were tested. The area under the Receiver Operating Characteristic (ROC) curves for the MELD and MELDNa were 0.80 (95% CI = 0.71–0.90) and 0.79 (95% CI = 0.69–0.89) respectively (Figs 3 and 4). There was no statistical difference between the two Area Under the Curve (AUC) obtained by using the MELD and the MELDNa. These values reflected an acceptable discriminative performance as an AUC equal or less than 0.5 is considered of no discriminative value, while AUC between 0.7 and 0.8 is acceptable and AUC greater than 0.8 has very high clinical predictive value [13]. Figs 5 and 6 represent the results of the model calibration assessment by quartile-of-risk analysis. This analysis disclosed that MELD progressively under-estimated waiting list mortality in patients with scores 11 and higher (Fig. 5). The difference between observed and estimated 90-day mortality for these respective MELD score quartiles were as follows: 14.4% for MELD scores 11–14; 26.4% for MELD scores 15–18; and 34.4% for MELD scores 19–40. A similar deficiency in calibration was found for the MELDNa (Fig. 6), with differences between observed and estimated 90-day mortality of: 7.5% for MELDNa scores 6–12; 11.6% for MELDNa scores 13–17; 26.8% for MELDNa scores 18–22; and 23.4% for MELDNa scores 23–40. As a result of the small number of events in the lower MELD and MELDNa quartiles statistical comparison could not be carried out.

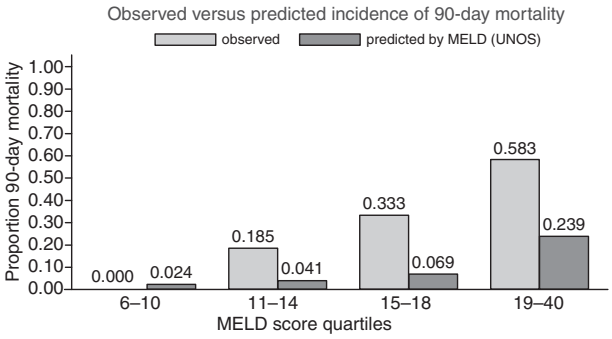


**Figure 5** Quartile-of-risk analysis for the MELD score in predicting 90-day mortality rate of patients waiting for cadaveric liver transplantation (OLT) in Atlantic Canada. Predicted and observed 90-day mortality was calculated for all patients using the MELD score at the time of listing.

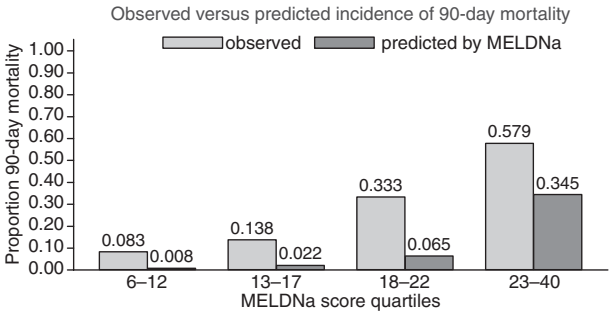


**Figure 6** Quartile-of-risk analysis for the MELDNa score in predicting 90-day mortality rate of patients waiting for cadaveric liver transplantation (OLT) in Atlantic Canada. Predicted and observed 90-day mortality was calculated for all patients using the MELDNa score at the time of listing.

**Table 3.** Univariable analysis of risk factors predicting overall wait-list mortality in patients affected by end-stage liver disease listed for cadaveric liver transplantation (OLT) in Atlantic Canada.

| Variables | Hazard Ratio (95% CI) | *P*-value |
|---|---|---|
| MELD (UNOS) score at wait-listing | 1.12 (1.07–1.17) | <0.001 |
| MELDNa score at wait-listing | 1.12 (1.07–1.18) | <0.001 |
| Gender | 1.19 (0.64–2.22) | 0.576 |
| Age at wait-listing | 1.04 (1.00–1.08) | 0.029 |
| Residence over 500 km from transplant centre | 1.90 (0.98–3.69) | 0.05 |
| Primary indication for liver transplantation | | |
| Alcohol-related cirrhosis | 3.45 (1.79–6.67) | <0.001 |
| Cholestatic liver disease | 0.29 (0.12–0.75) | 0.010 |
| HCV | 0.53 (0.23–1.19) | 0.122 |
| HCC | 0.41 (0.10–1.72) | 0.225 |

**Table 4.** Multivariable analysis of risk factors predicting overall wait-list mortality in patients affected by end-stage liver disease listed for cadaveric liver transplantation (OLT) in Atlantic Canada.

| Variable | Hazard Ratio (95% CI) | *P*-value |
|---|---|---|
| MELD (UNOS) | 1.10 (1.05–1.15) | <0.001 |
| Age at wait-listing | 1.05 (1.01–1.10) | 0.025 |
| Indication: cholestaticliver disease | 0.33 (0.12–0.88) | 0.027 |
| Residence over 500 km from transplant centre | 2.10 (1.05–4.20) | 0.036 |
| MELDNa | 1.13 (1.08–1.18) | <0.001 |
| Age at wait-listing | 1.05 (1.01–1.09) | 0.027 |

### Risk factors for wait-list mortality

Variables analysed using Cox regression were gender, age at wait-listing placement, distance of residence from the transplant centre and listing MELD and MELDNa scores. Additionally, several aetiological categories were evaluated as independent variables in the regression analysis (alcohol-related cirrhosis, cholestatic liver disease, HCV and hepatocellular carcinoma (HCC)). Results of the univariate analysis are summarized in Table 3. Age at wait-listing, residence greater than 500 km from transplant centre, alcohol-related cirrhosis and cholestatic liver disease were included in multivariate analysis along with MELD or MELDNa scores. In conjunction with the MELD score, noncholestatic liver disease, age at wait-listing and residence over 500 km from the transplant centre were found to be independent risk factors for wait-list mortality (Table 4). For multivariate analysis of risk factors assessed in relationship with MELDNa score, only age at wait-listing was found to be an additional independent predictor of mortality (Table 4).

## Discussion

In this retrospective cohort study, we found that patients with end-stage liver disease waiting for OLT in rural areas have a significantly higher mortality rate than previously observed by other transplant centres in North America and Europe [3–5,10,14]. In comparison with published data, patients listed for a cadaveric OLT in our centre had two to three times greater chance of dying while waiting than those listed in other Provinces during the same period [5]. Additionally, we observed that the incidence of mortality was more than twice the value predicted by the MELD and MELDNa scores, suggesting that determinants of wait-list mortality in our population do

not appear to be adequately reflected by these models. MELD was initially created to predict survival after elective creation of trans-jugular intra-hepatic porto-systemic shunts (TIPS) [15] and it was then validated to predict 90-day mortality in patients with end-stage liver disease in selected populations [3–6]. A more recent variation of the MELD score that includes the level of serum sodium measured in patients with end-stage liver disease (MELD-Na) seems to have even a better performance profile for patients with abnormal serum sodium levels in a large population of candidates for primary OLT registered with the OPTN in the United States [4]. Although MELD score has been validated in several studies performed by groups in Europe [16], Asia [17,18], Central [19] and South America [20] and in the Unites States [21,22], validation of the predictive performance of MELD for patients living in rural areas is lacking. The higher mortality rate in patients with end-stage liver disease living in Atlantic Canada is particularly concerning given that the waiting time for transplantation at our centre was not significantly different from that of other Canadian and US centres using similar allocation systems based on levels of severity of liver disease [23–25]. Of the patients who underwent OLT, one quarter was transplanted within 90 days of listing, half within 5 months and three quarters within 11 months. During the study period, approximately 90% of the deceased donor allografts offered were utilized and therefore it seems implausible that failure to provide timely transplantation accounts for the high wait-list mortality in our population.

To explain these inferior wait-list survival results, we sought to identify demographic and disease-related predictors of mortality in our patient population.

Older age has been previously found to be associated with mortality in individuals with end-stage liver disease in several studies [16,26]. In this cohort, age at the time of waiting list placement was confirmed as an independent predictor for waiting list mortality as each 10 year increase in age was associated with a 58–66% relative increase in the hazard ratio (MELDNa and MELD respectively). Although direct comparisons cannot be made, the listing age of our cohort did not seem to be dissimilar from the cohort studied by Wiesner *et al.* (mean 50.7 years) or by Kim *et al.* (median 53 years). Therefore, inferior outcomes observed in this study were not resulting from difference in the age makeup between these groups [3,4].

Cholestatic liver disease such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) was found to be a favourable independent determinant of survival while awaiting OLT. Individuals with PBC or PSC benefited from a relative 67% reduction in the hazard of dying while on the wait-list compared with individuals with other indications independently from other characteristics including their blood groups. Individuals with cholestatic liver disease made up a significantly greater proportion of patients in this cohort (25.2%) in comparison with populations studied by Weisner *et al.* (2.9%) or Kim *et al.* (8%) [3,4]. Contrary to the results of the multivariate Cox proportional analysis that suggested a protective effect of cholestatic disease, the greater prevalence of individuals with PBC and PSC in our cohort did not result in a diminished waiting list mortality rate [3,4]. In our study, alcohol-related cirrhosis was the most common primary indication for transplantation and appeared to be a poor prognostic factor for wait-list mortality in the univariable analysis but failed to be significant when adjusted in regression analysis. Relative to the previously mentioned large American cohorts, the prevalence of HCV in our cohort was less than that observed by Weisner *et al.* (24% vs. 36%) and Kim *et al.* (24% vs. 40%) [3,4]. Although, on univariate analysis, HCV showed a trend towards lower wait-list mortality, it was not statistically significant and it seems implausible that it had an impact on the significantly higher wait-list mortality seen in this series.

Distance from our transplant centre, the only institution in Atlantic Canada where patients with liver failure are referred for evaluation for OLT, was included in this analysis as a proxy for access to specialized health services for patients affected by end-stage liver disease. In fact, our hospital is the only institution in Atlantic Canada where patients with liver failure are referred for evaluation for OLT. When analysed in conjunction with values of MELD scores in multivariate analysis, it was found that individuals who resided over 500 km from the transplant centre had a 2.1 hazard ratio of death while waiting for OLT. This association was independent of disease severity, as measured by MELD score and patient age at time of wait-list placement. We suspect that this may be one of the main factors accounting for the higher incidence of wait-list mortality in this cohort as 22% of patients lived in areas distant more than 500 km from our centre and they represented 30% of the subjects who died on the waiting list.

When compared with the geography of the United States, our catchment area in Atlantic Canada would rank as the third largest state after Texas for land surface, and only 36th after Nevada for number of inhabitants. Approximately 46% of the population of these four provinces live in a rural setting and often they need to travel by air as they live in quite remote areas quickly accessible only by air or by boat [6]. During the study period, this area was relatively under serviced, with, at most, only three hepatologists serving the entire region. We hypothesize that greater distance to transplant centre may have

reflected diminished access to general medical care and above all to specialty and subspecialty physicians. On the same theme, the observation that one quarter of the waiting list failures occurred within 22 days of placement suggests that a significant number of patients were referred late in their disease process. Although in some cases it was hard to determine, progression or complication of liver disease was the primary cause of their death in 86% of cases. More timely or more expert management of these patients with end-stage liver disease may have improved survival. Overall these observations lead us to speculate that diminished access to specialized medical care may have played an important role in the inferior wait-list survival experienced by this cohort.

It has been stated by the developers of the MELD and MELDNa that the degree to which the estimated mortality approximates the observed may vary depending on the population to which the model is applied [27]. The results of this study highlight this point as the 90-day mortality estimates generated by the MELD and MELDNa significantly underestimated the observed mortality in our population. Despite this failure of calibration, the MELD and MELDNa were both significant independent predictors of wait-list mortality with a respective 10% and 5% relative increase in the hazard ration with each one point increase in their score. One explanation for this variability in calibration between populations is most likely resulting from the presence of confounding factors, such as age distribution, patterns of disease aetiology, or, as suggested by this study, health services logistics, that are not accounted for by the MELD and MELDNa models. Conceivably, as a consequence of this variability in calibration, a patient with a given MELD score residing in a large urban centre may not have the same mortality risk as a patient with the same score residing in a rural area.

Differences in calibration must be borne in mind when organ allocation policies are put in place. In fact, regions in which the disease severity index used for prioritization of graft allocation underestimates the mortality risks, they will be disadvantaged if required to use a common disease severity index such as MELD or MELDNa for allocation and sharing of cadaveric grafts. In this scenario, OLT candidates residing in a region where the disease severity index underperforms would suffer the double affront of having their mortality risk understated with the consequence of having local cadaveric organs potentially allocated to recipients living in other regions.

There are several limitations to our study as it is a retrospective cohort with a relative small group of patients. We are aware that patients' selection, sampling and measurement bias could not be completely excluded even if extreme attention was paid to minimize those risks by assessing the quality of the data entered by two independent individuals. On the other hand, one of the strengths of this study is that the risk of censoring bias resulting from the number of individuals excluded from the final statistical analysis for missing data or because lost at follow-up was very low as we were able to capture most of the patients referred to our centre by using a prospective computerized database.

In summary, the mortality for individuals awaiting OLT in Atlantic Canada is significantly greater than previously observed from North American cohort studies and it is significantly underestimated by MELD and MELDNa models. Our study confirmed that advanced age at the time of listing for OLT was a risk factor for mortality while cholestatic disease was somewhat protective. To our knowledge, this is the only study that has assessed the effect that selected socio-economic and geographical factors could have on the mortality risk of patients with end-stage liver disease waiting for cadaveric OLT. In vision of the fact that in rural areas the mortality rate predicted by MELD and MELDNa might be significantly inferior to the observed mortality, further research is warranted to assess the most important factors that could be responsible for regional variations of the predictive performance of MELD and MELDNa scores. As MELD and MELDNa are currently used in many countries besides the United States for organ allocation, validation of their performances for different populations is of utmost importance. Our study suggests that healthcare access and patients' socio-economic characteristics might play a significant role on wait-list mortality besides liver disease severity. Multicentric and prospective studies are necessary to validate these findings.

## Authorship

MM: Designed the study, edited the paper. PDR: Designed the study, performed statistical analysis, edited the paper. NMP: collected the data. SDC: collected the data and obtained the ethics review board approval for the study. MA: supervised the statistical analysis and the quality of the data.

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