Improving survival prediction models for liver transplantation candidates

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Citation
Goudsmit, B. F. J. (2022, June 29). *Improving survival prediction models for liver transplantation candidates*. Retrieved from https://hdl.handle.net/1887/3421016

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3421016

Note: To cite this publication please use the final published version (if applicable).

Part IV: Summary, general discussion, and future perspectives

“Zodat het dan net lijkt alsof u vanaf het begin al de meest verantwoorde gedachten had over uw variabelen (u weet wel, die dingen waar u achteraf altijd zo’n spijt van had), en over uw hypothesen (u weet wel, die dingen die u dan achteraf verzon om het nog ergens op te laten lijken).”

— Arno Goudsmit

Chapter 7

Summary

The persistent scarcity of donor liver grafts necessitates prioritization of patients based on expected future survival without transplantation. The goal of this thesis was to improve survival prediction models for patients on the LT waiting list. Through advancements in prediction models, liver grafts can be allocated in the best way possible.

In **Chapter 2**, the MELD-Na score (devised in the UNOS region) was validated for the Eurotransplant region. We investigated the relationship between serum sodium levels, MELD scores, and 90-day mortality. Hyponatremia of <135, <130, and <125 mmol/L was found in respectively 28.5%, 8.8%, and 2.6% of the patients. We found that between 140 and 125 mmol/L, the risk of 90-day death increased threefold (HR 2.9; 95% CI 2.30-3.53; p<0.001). Every point decrease in serum sodium levels increased 90-day mortality by 8% (HR 0.92; 95% CI 0.90-0.94; p<0.001). Concordance statistics of MELD and MELD-Na were 0.832 and 0.847, respectively. Predictions based on MELD-Na were also more accurate than MELD. Comparing the possible impact of using MELD-Na instead of MELD for allocation on the waiting list, we found that approximately 20% of patients would receive a significantly higher predicted risk of death with MELD-Na and therefore a better chance for timely LT.

In **Chapter 3**, the 20-year-old UNOS MELD score was refitted to the Eurotransplant population. We assessed the relation of each MELD(-Na) parameter to 90-day mortality. Based on the data, the lower and upper parameter bounds and coefficients with the best fit were established. Specifically: creatinine 0.7- 2.5 mg/dL, bilirubin 0.3- 27 mg/dL, INR 0.1- 2.6, and sodium 120- 139 mmol/L. The resulting reMELD(-Na) significantly improved fit, discrimination, and calibration compared to MELD(-Na). Compared to MELD, reMELD-Na could have prioritized patients with on average 1.6 times higher 90-day mortality, thus better effectuating the sickest-first principle.

In **Chapter 4**, we developed and validated joint models for the Eurotransplant (MELD-JM) and UNOS (MELDNa-JM) regions. Repeated MELD(-Na) measurements were modeled flexibly over time and joined with Cox proportional hazards models. It was found that both MELD(-Na) value and its rate of change were strongly associated with waiting list mortality. The JMs significantly improved AUCs and Brier scores for waiting list survival prediction in both regions. MELD(Na)-JM possibly could have prioritized patients with three to five times higher 90-day waiting list mortality than MELD(-Na).

In **Chapter 5**, we constructed and validated the ACLF-JM for patients with ACLF on the waiting list. For the ACLF-JM, repeated MELD-Na scores were corrected for CLIF-C OF scores at baseline, age, sex, life-support dependency, presence of bacterial peritonitis, and presence of cirrhosis. ACLF-JM performance was compared to a landmark MELD-Na Cox model. ACLF grade 1 to 3 was present in respectively 16.4%, 10.4%, and 6.2% of the patients. ACLF-JM performance, measured through AUCs and prediction errors, was significantly better than landmark MELD-Na. The ACLF-JM identified patients with lower MELD-Na scores but four times higher 90-day mortality.

In **Chapter 6**, we studied the survival benefit that LT caused, by comparing 5-year survival with and without LT between patients with and without HCC in the US. HCC patients had lower waiting list survival than non-HCC patients. Most HCC patients were transplanted below MELD(-Na) 14 and most non-HCC patients above MELD(-Na) 26. Liver function (MELD(-Na), albumin) was the main predictor of 5-year benefit. Therefore, during five years, most HCC patients gained 0.12 to 1.96 years from LT, whereas most non-HCC patients gained 2.48 to 3.45 years. Thus, on an individual level, transplanting patients with HCC resulted in survival benefit. However, on a population level, benefit was indirectly wasted, as non-HCC patients were likely to gain more survival due to decreased liver function.