Improving survival prediction models for liver transplantation candidates

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Chapter 9

Future perspectives

Simulation

Throughout this thesis, several methods were applied to estimate new model impact on the LT waiting list. We used reclassification tables, new-to-old score differences, or estimated changes in waiting list priority. These methods were used because reviewers and policymakers requested evidence of possible model impact on current waiting list outcomes. Although understandable, it is difficult and likely impossible to reliably estimate the impact of a new model on the allocation system. The best way to evaluate the effects of a new model is to implement it. The next best option is evaluation through simulation. For the Eurotransplant region, a simulation program is currently missing. An important future direction of research could therefore be the construction of what could be called the Simulation of the Eurotransplant Liver Allocation System (SELAS). SELAS would improve both Eurotransplant allocation research and policy. It would also help Eurotransplant regain its leading role in organ allocation and development. Realization of SELAS seems feasible given the existing collaboration between Eurotransplant International Foundation and the Technical University Eindhoven, as the latter has considerable experience with simulation models. The longstanding cooperation between Eurotransplant and the Leiden University Medical Center would then ensure integration of allocation, statistical methodology, and clinical knowledge.

In the U.S.A., a liver simulation program is available, that is the Liver Simulated Allocation Model (LSAM). LSAM lets users change existing allocation rules and simulate the effects in historical US data. Indeed, US allocation research is often complemented by simulation evidence. Still, simulated results should be interpreted with care. Evaluation of LSAM showed that although trends were adequately estimated, exact numbers of waiting list deaths and transplants were over- and underestimated, respectively.[68] Also, simulation

performance was significantly worse for pediatric patients,[69] which indicates that simulations might be unreliable for yet undefined subgroups.

Even simulation programs have limitations. Therefore, researchers should rely on their methodology and clinical experience. Consider for example the refit coefficients in **Chapter 3**. We presented significant improvements in fit, discrimination, and accuracy. Although these metrics are important evidence, improvement was most intu-itively shown through visual representation of new and old coefficients Figure 3.3. These clearly showed that reMELD(-Na) better represents the Eurotransplant population and therefore will likely better predict risk in future LT candidates. Simulation of evidence therefore has a role in the path of implementation, but sound methods and reasoning should be considered most important.

New model implementation

Possibilities are investigated to alleviate the shortage of available donor organs, such as more liberal donor criteria, living donation, machine perfusion, organoids, and xenotransplantation. Whatever improvements might be made, survival prediction will remain paramount to decide which patient should be treated. For example, with machine perfusion techniques, a larger number of liver grafts will likely become available and will be preserved longer outside the donor. This could imply more widespread allocation of organs to find the best match with the recipient. Also, with more time available, more complex calculations could be done to estimate outcomes of possible donor-recipient combinations. These calculations could be based on causal inference models, JMs, or ideally a combination of both.

For now, the shortage of donor organs persists. As mentioned, currently the principle of urgency is used for liver allocation, by prioritiz-

ing the sickest patients first. Eurotransplant has maintained this basis since 2006. In this thesis, we showed that significant improvements in survival prediction are possible. Understandably, reasons beyond clinical relevance and statistical significance determine model implementation. Because of (inter)national interests within Eurotransplant, changes in allocation are not easily implemented. Still, in our view, refit MELD (reMELD) would be relatively easy to implement, as no changes in the data structure of Eurotransplant would be required. We therefore urge Eurotransplant policy makers to consider that the refit models were a significantly better fit to the current Eurotransplant population, that ranking patients from most to least ill (discrimination) was significantly improved, and that refit model mortality risk estimates were more accurate. Implementation of (refit) MELD-Na would also not be very difficult, since sodium is a readily available laboratory measurement, that is almost always assessed in combination with creatinine. Again, the significant prediction improvements should form sufficient rationale for further allocation improvements.

Other additions to MELD could also be considered, such as serum albumin, von Willebrand factor and C-reactive protein.[18,20,70] A problem is that these variables are not collected within Eurotransplant. Several aspects of MELD, that are not evidence based, can however be improved without changing existing data registries.[19] Arguably one of the most important and counter-intuitive aspects is MELD's upper bound of 40, which means that patients with MELD>40 receive a score of 40. Therefore, allocation stops considering disease severity in the sickest patients. Already in the first validation study of MELD, MELD's relation to 90-day risk of death was plotted and showed an increasing waiting list mortality above MELD 40.[7] Recent evaluation confirmed this finding, without increased post-transplant mortality for recipients with MELD>40.[71] It therefore makes clinical sense to remove the upper border of MELD in order to improve allocation for the sickest patients. Other suggestions to improve MELD were men-

tioned previously in this thesis, like removing arbitrary lower and upper bounds and using survival probabilities as primary metric.

The implementation of JMs for allocation would require more effort. Eurotransplant would need to ensure that longitudinal data of each listed patient is available every time a liver graft is offered. However, if using one measurement per patient is possible, it should also be possible to use multiple, as these longitudinal data are stored by Eurotransplant. The computation of JM survival predictions would require notably more time than calculating MELD, as simulations are done for each patient. However, we believe that the advantages of correctly specified JMs are convincing. Also, although the JMs were trained in large patient cohorts, their practical application for the Eurotransplant waiting list would mean calculating survival for several hundred patients, which is done within minutes. Considering previous and current data for each patient on the waiting list would be a major improvement.

From urgency to benefit

Deciding how to allocate scarce medical interventions is relevant, as the recent COVID pandemic has shown for vaccines and ICU beds. The COVID pandemic also showed that with increasing resource scarcity, a shift in allocation principle could be warranted, that is from a 'first come first served' to a benefit-based approach.[72]

In the field of LT, organ demand persistently exceeds supply, which argues against sickest-first allocation.[67] This is because prioritizing the sickest ignores currently less ill patients that might gain more from treatment or who could be worse off in the future as disease progresses. Therefore, sickest-first allocation can only be just if the scarcity is temporary, which is not the case. This does evoke questions on how to handle high-urgency patients, as these patients are the pinnacle of urgency-based allocation and receive priority

over other patients that have higher waiting list mortality.[31,49,73] Another extreme of urgency are multi-organ transplants. These possibly save only one life, whereas each of the organs could have saved a patient. Saving more lives is arguably more just. Finally, re-transplantations would require similar reconsideration of urgency and benefit,[73] as the highest priority is given to patients who might gain little and, perhaps more importantly, the liver is then denied to another recipient. Although benefit will not resolve all allocation issues, it is an inherently more just and therefore a better principle than urgency alone.[67]

We devised methods that predict survival benefit from LT. This opens the possibility for the change from urgency- to benefit-based allocation. It is however important to recognize that US data were used for the calculation of benefit. These US data encompass more LT candidate variables, that allow better estimation of future waiting list survival. Currently, Eurotransplant registers fewer LT candidate variables. It is easy to see that this will cause delay in allocation development, especially compared to other regions. This is arguably already the case, as the Eurotransplant liver allocation was last majorly revised in 2006. During this period, survival prediction models in US liver graft allocation were investigated and significantly improved. In our view, Eurotransplant should strive for a data registry structured much like UNOS, which allows researchers easy access to anonymized data. This in turn generates evidence upon which policy can be based. In our view, Eurotransplant should also provide a central platform where professionals and patients can gain insight in allocation policy and evidence. Transparency created through inter-active statistics and accessible prediction models would greatly improve Eurotransplant's scientific basis and would perhaps place more trust in the organization. Most importantly, patients deserve to know their estimated prognosis of waiting for or accepting an organ.

To this end, in this thesis, we provided several prediction models in interactive online applications. The aim was to increase insight for both clinicians and patients.

Another possible solution for the advancement of liver allocation, despite the missing data across Eurotransplant, could be detailed national allocation based on more detailed hospital data. This allocation could be either benefit- or urgency-based, as long as one model is used to calculate future waiting list survival, preferably corrected for dependent censoring. Most organs are allocated nationally, that is 83.4% of MELD-allocated liver grafts in Belgium, Germany, and The Netherlands (*data not published*), which also ignores possibly sicker recipients abroad. Therefore, it seems feasible to abandon the sickest-first principle and to implement benefit-based allocation on a national level. This way, each country would be responsible for the method and accuracy of its survival prediction and subsequent allocation. International organ exchange would then be based on Eurotransplant standards.

Conclusion

In conclusion, this thesis investigated survival prediction models in the setting of LT, where organ scarcity and allocation necessitates continuous development of such methods. Statistically significant and clinically relevant advancements were demonstrated that could improve liver allocation through better survival prediction for patients on the waiting list.

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