

Development of a Mechanism-Based Joint Model Describing Latent Immune Function Dynamics and Multivariate Immune-Related Outcomes After Lung Transplantation

Wouter Ahmed¹, Edmund J. Gore², Coretta C. van Leer-Buter², Michel M.R.F. Struys^{1,3}, Pieter J. Colin¹, Douglas J. Eleveld¹, Jeroen V. Koomen^{1,4}

1. Department of Anesthesiology, University Medical Center Groningen, University of Groningen, The Netherlands. 2. Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, University of Groningen, The Netherlands. 3. Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium. 4. Medicines Evaluation Board (CBG-MEB), The Netherlands

Background & aim

Management of the immune response after lung transplantation (LTx) relies on therapeutic drug monitoring (TDM) of tacrolimus. While tacrolimus effectively suppresses immune activity, its whole blood concentrations correlate poorly with immunosuppressive status¹. Consequently, immune-related events like graft rejection and infection remain common². To improve the post-LTx outlook, supplementing tacrolimus TDM with an accurate marker of immune-status seems promising^{1,3}. However, most immune-markers reflect only a specific component of the immune system (e.g., T-cell subsets) and therefore fail to capture the complexity of the immune response to a transplanted organ. This project aims to quantify the dynamics of immune function as a whole, by modelling multiple immune-related outcomes simultaneously.

Data & model development

88 LTx patients from the University Medical Center Groningen were included in the study. Collected variables considered in model development were torque teno virus (TTV) load, the forced expiratory volume (FEV) and the (repeated) occurrence of acute rejection, infection or death. Model development was guided by biological knowledge of the interaction between immune function and the outcomes: ‘High’ immune function results in low TTV loads, a decreased risk of infection and a higher occurrence of rejection. FEV decreases and risk of death increases when immune function is either ‘high’ or ‘low’. All models were developed in Monolix2024R1 and judged based on BICc, goodness of fit and convergence assessments.

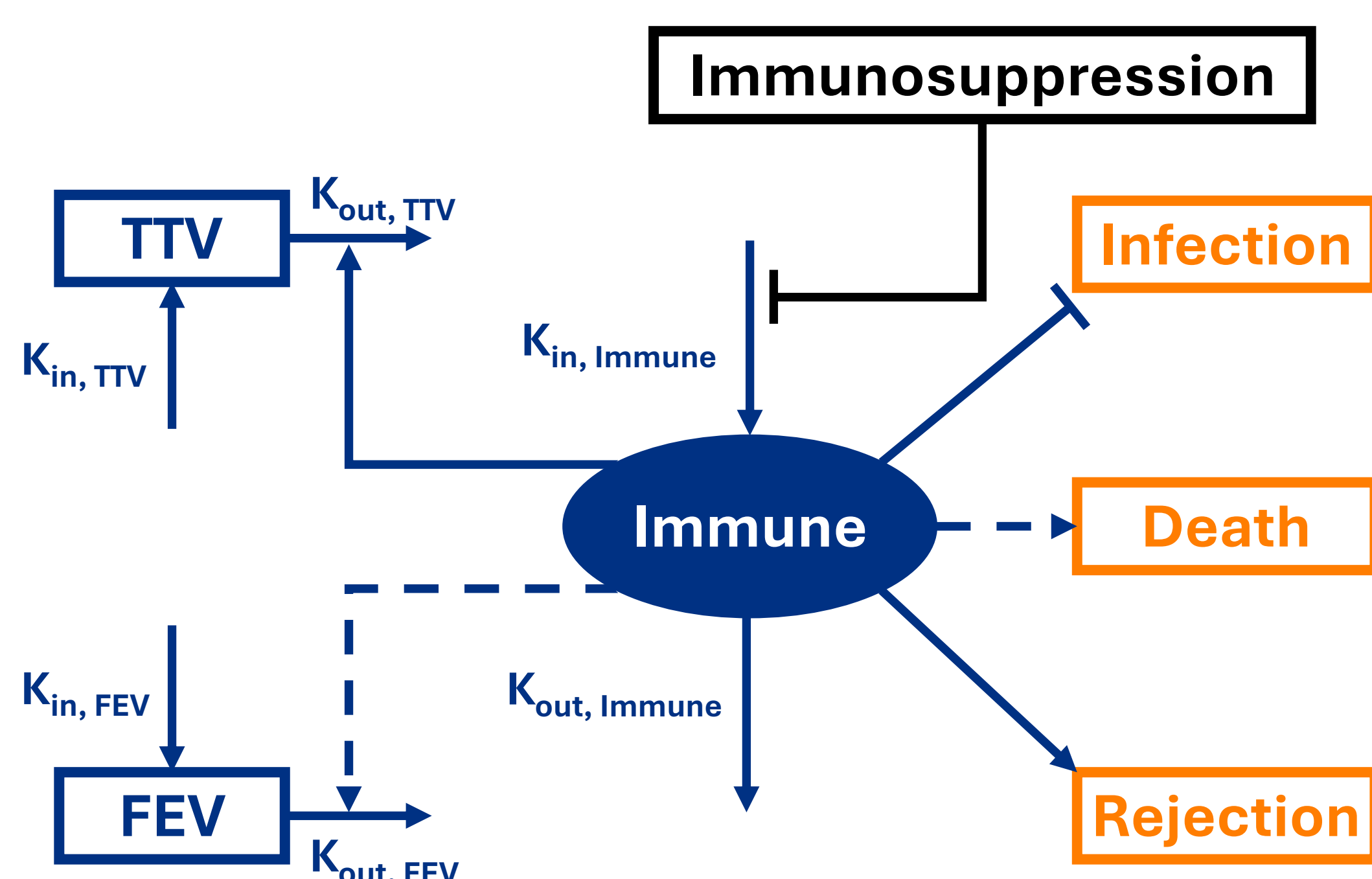


Fig 1. Schematic of *a priori* understanding of the biological system. Arrows pointing from one variable to other variables/rate constants represent stimulatory (solid arrow), inhibitory (solid arrow with flat arrowhead) and bidirectional (dashed arrow) interactions.

A model for immune function

For the model of immune dynamics, it was assumed that patients exhibit no notable therapy-induced impairment of immune status at baseline (i.e., the time of LTx). In addition, we assumed that predicted tacrolimus plasma concentrations⁴ fully account for changes in immune function, as doses of other immunosuppressives remain mostly stable throughout follow-up. Lastly, we required that the model structure was sufficiently flexible to capture expected immune dynamics after LTx: A sharp decrease right after the LTx procedure due to the initiation of immunosuppression, followed by a slower increase over time as tacrolimus maintenance doses are lowered. Under these assumptions, the immune function model can be expressed as:

$$\frac{d\text{Immune}}{dt} = K_{in, \text{Immune}} \times \left(1 - \left(\frac{I_{max} \times C_{tacrolimus}}{I_{50} + C_{tacrolimus}} \right) \right) - K_{out, \text{Immune}}$$

With: $\text{Immune}(0) = 1$, & $K_{in, \text{Immune}} = K_{out, \text{Immune}}$

Current model for the observed outcomes

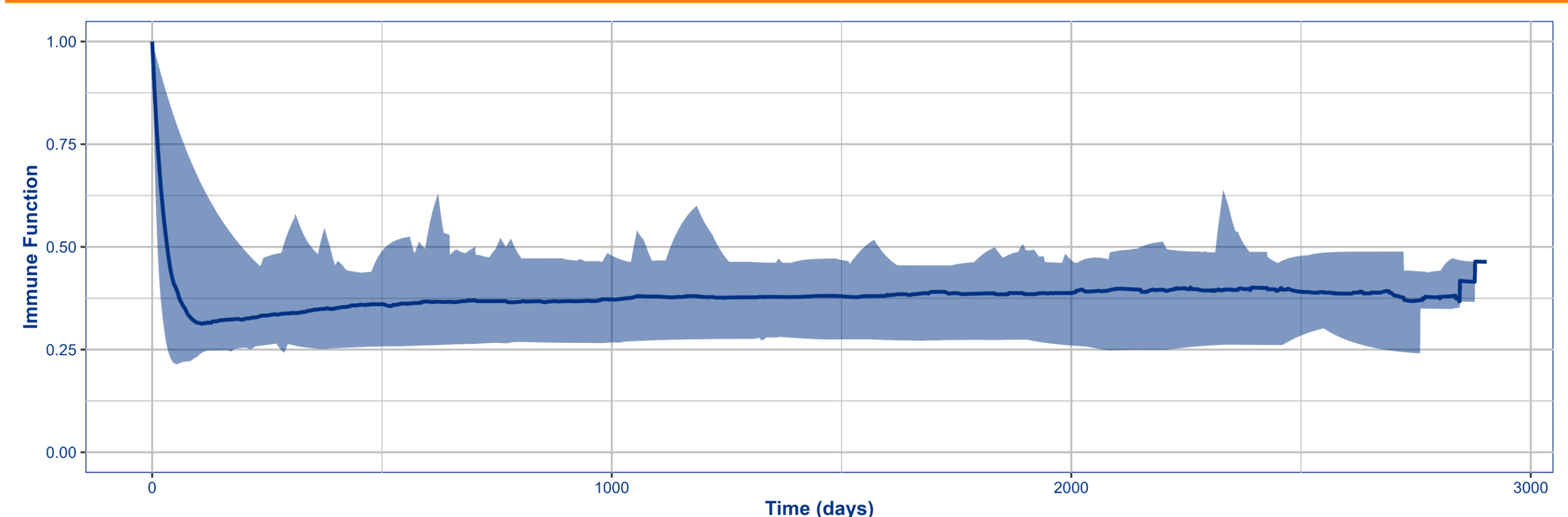


Fig 2. Median and range of predicted immune function dynamics in the study population based on empirical bayes estimates from the current model for the observed outcomes.

TTV and FEV were described using turnover models with immune-driven elimination. To ensure successful convergence, both $K_{out, TTV}$ and $K_{out, FEV}$ had to be fixed to an arbitrary value of 1 ($\Delta BICc$ of -16.53). Event outcomes were described using parametric time-to-event models. No effect could be estimated between immune function and the hazard of infection. The complete model is given by the following equations:

$$\frac{dTTV}{dt} = K_{in, TTV} - K_{out, TTV} \times TTV \times \text{Immune}$$

$$\frac{dFEV}{dt} = K_{in, FEV} - K_{out, FEV} \times FEV \times \left(1 - \frac{1}{1 + \exp(-\delta \times (\text{Immune} - \theta))} \right) \times \frac{1}{1 + \exp(\delta \times (\text{Immune} - \theta))}$$

$$\lambda(t)_{rejection} = \lambda_{0, rejection} \times \exp(\beta_{rejection} \times \text{Immune})$$

$$\lambda(t)_{death} = \lambda_{0, death} \times \exp(\beta_{death} \times |\text{Immune} - \theta|)$$

The current model captures the general trend in the TTV data, but underpredicts the initial peak and overpredicts final decline. For FEV, lung function early after LTx is overpredicted. Fit for acute rejection is unsatisfactory and death is predicted with reasonable accuracy.

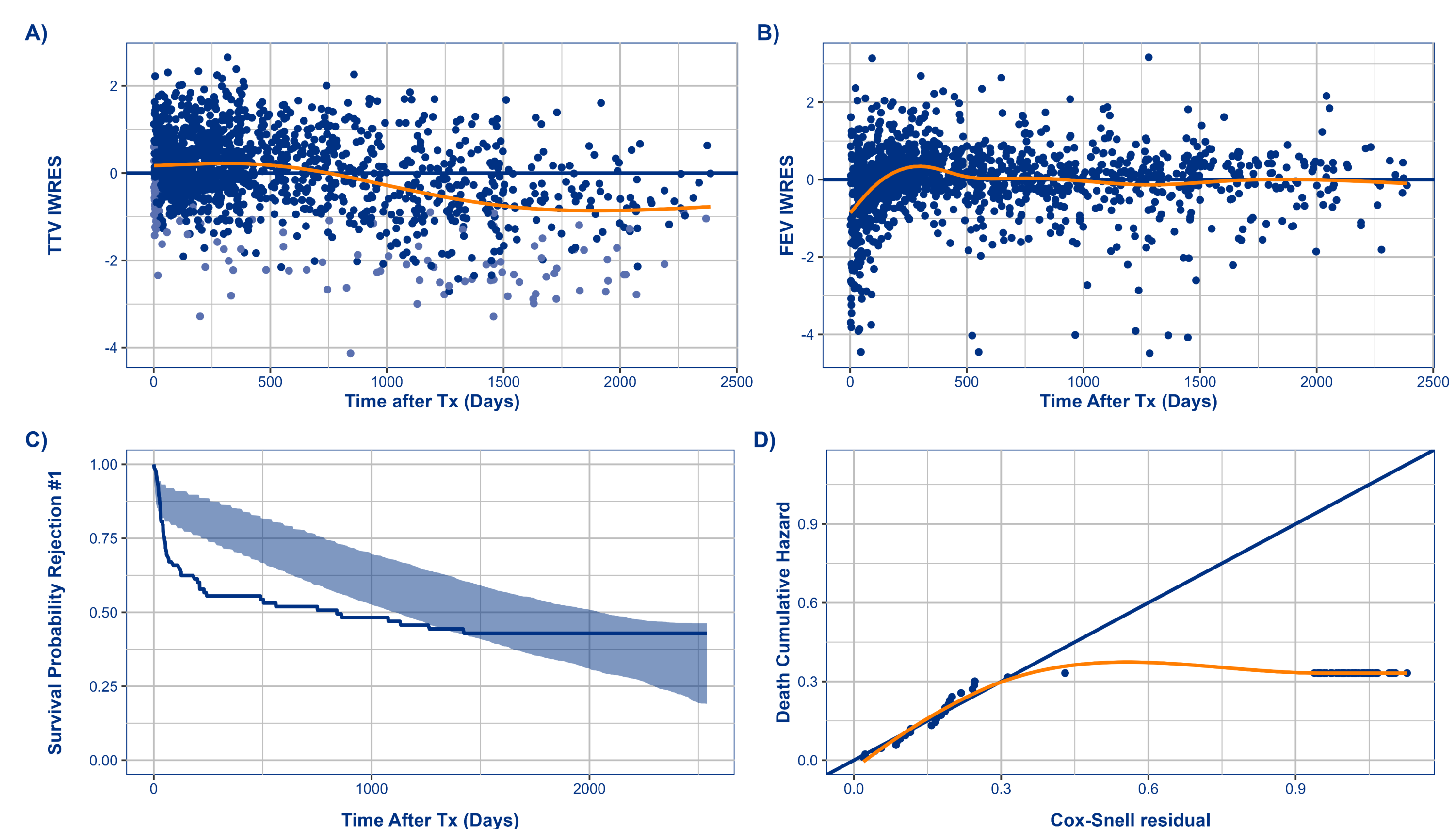


Fig 3. Goodness of fit plots for the different outcomes. A) TTV individual weighted residuals versus time. B) FEV individual weighted residuals versus time. C) Conditional Kaplan-Meier visual predictive check for the first acute rejection event. D) Death Nelson-Aalen Cumulative Hazard versus modified Cox-Snell Residuals.

Next steps & conclusions

We developed a model that describes multiple immune-related outcomes after LTx by linking them through a latent variable. Throughout model development, achieving successful convergence has been very difficult to realize. Consequently, the $K_{out, TTV}$ and $K_{out, FEV}$ parameters had to be fixed to an arbitrary value in the current model. Even then, accuracy of parameter estimation remains suboptimal. To enhance the interpretability of parameter values and prevent the use of artificial constraints, informing the K_{out} from known initial conditions may be considered. In addition, we plan to explore viral dynamic models as they allow for fixing parameters based on literature values. Lastly, future model development will also focus on the improvement of practical identifiability through alternative immune function and outcome models.



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