High emergency organ allocation rule in lung transplantation: a simulation study

– Appendix –

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1 Parametrization

1.1 Sources of parameters

We developed an agent-based model of lung transplantation waiting queues using *Netlogo*.[1] Patients with end-stage lung diseases were simulated from their first inscription on the waiting list for lung transplantation (LT) to their eventual death, that could occur while on the waiting list or after having received a graft. Most parameters of the model came from actual data from the US[2] and French[3] organ procurement and transplantation networks (OPTN, Table 1).

[1] Sklar E. *NetLogo, a multi-agent simulation environment.* Artif Life. 2007;13(3):303-11.
[2] United Network for Organ Sharing (UNOS), www.unos.org
[3] Agence de la Biomédecine (ABM), www.agence-biomedecine.fr

Table 1: List and sources of the parameters used in the simulations

Event	Method	Values	Source
New patients enlisted on the waiting list	Drawn weekly from a Poisson distribution	335 years^{-1}	ABM
New available organs	Drawn weekly from a Poisson distribution	322 years^{-1} (R96); 268 years^{-1} (R80)	ABM
Initial characteristics of patients on the waiting list (*age at inscription; BMI; diabetes; NYHA; FVC; six-minutes walking distance <150ft; O2 requirement at rest; CMV; serum creatinine; PAP; PCW*)	Drawn from correlated normal and lognormal and logistic distributions fitted on UNOS data	-	UNOS
Evolution of patients' quantitative characteristics over time (*BMI; FVC; O2 at rest; serum creatinine; PAP; PCW*)	Linear mixed models fitted on UNOS data	-	UNOS
Evolution of patients' qualitative characteristics (*NYHA and CMV*)	NYHA switched to class IV in diagnosis groups B, C and D; CMV switched to positive in diagnosis groups C and D three weeks before the estimated date of death	-	ABM
Actual date of death without transplantation	Drawn from a Weibull distribution extrapolating survival predictions from the LAS model in UNOS patients	$\lambda_{WL} = 1200$*; $k_{WL} = 1.2$*	LAS, UNOS
Estimated date of death without transplantation	Drawn from a normal distribution whose mean is the actual date of death and whose standard deviation is the value s	$\sigma_{WL} = 1.5$*	-
Patient enlisted in the high-emergency waiting list	Event occurred a certain period δ before the estimated date of death	$\delta = 3$*	ABM
Post-transplantation survival	Drawn from a Weibull distribution extrapolating survival predictions from the LAS model in UNOS patients	$\lambda_{PT} = 2500$*; $k_{PT} = 1.6$*	LAS, UNOS

ABM: Agence de la Biomédecine (French OPTN); UNOS: United Network for Organ Sharing; BMI: body mass index; NYHA: New York Heart Association; FVC: forced vital capacity; CMV: continuous mechanical ventilation; PAP: pulmonary artery pressure; PCW: pulmonary capillary wedge.
**Parameters whose influence on results was evaluated in sensitivity analysis.*

1.2 Calibration of the initial characteristics of the virtual patients

As stated precedently, the initial characteristics of virtual patients (VP) were based on actual data from 8,315 patients from UNOS database. Selection criteria for patients in the UNOS database were: (1) first registration between May, 2005 and February, 2009; (2) known date for LT; (3) known date of last follow-up; and (4) known vital status at the last follow-up. Additionally, the most extreme outliers were excluded as

they disrupted the modeling process.

The process started with the attribution of the diagnosis group: (A) obstructive lung disease (e.g. emphysema); (B) pulmonary vascular disease (e.g. primary pulmonary hypertension); (C) cystic fibrosis or immunodeficiency disorder; and (D) restrictive lung disease (e.g. idiopathic pulmonary fibrosis). The diagnosis group and the blood type of the VP were sampled at random to match the observed frequencies. Then, quantitative characteristics (i.e. age [years], body mass index [BMI, $kg.m^{-2}$]; pulmonary forced vital capacity [FVC, %]; O_2 at rest [$L.mn^{-1}$]; serum creatinine [$mg.dL^{-1}$]; pulmonary artery pressure [PAP, $mmHg$]; and pulmonary capillary wedge pressure [PCW, $mmHg$]) were sampled using correlated normal (for the age) and lognormal (for the other variables) distributions. For this purpose, the simulation employed means and robust covariance matrices (after Cholesky decomposition) of these variables (plus the LAS score) in UNOS patients within each diagnosis group. The comparisons of the distributions of the quantitative characteristics in UNOS and virtual patients are shown in Fig. 1. Third, each binary characteristics (i.e. diabetes, New York Heart Association [NYHA] class IV, six-minutes walking distance above 150 feet, and continuous mechanical ventilation [CMV]) was sampled according to the individual values of the quantitative characteristics using separated logistic regression models. Overall, this process allowed a reasonable representativity of the VP.

1.3 Calibration of the evolution of the virtual patients' characteristics

As VP's base characteristics were used to compute on-list survival (without graft), post-transplantation survival depended on characteristics at the time of the LT. Hence, for the post-transplantation survival to reflect the aggravation of the VP's state while waiting for an organ, the characteristics needed to evolve with time. The evolution of the quantitative characteristics of VP over time replicated that of UNOS patients in the first 24 weeks following inscription. For this purpose, individual slopes were estimated within each diagnosis group using linear mixed models. The mean evolution of each quantitative characteristics within each diagnosis group is shown in Fig. 2. Changes in qualitative variables were not modelled in the same way since very few changes were observed in UNOS patients. However, in order to reflect the criteria for high-emergency transplantation (HELTx) in France, VP qualifying for HELTx (i.e. three weeks before their estimated date of death) switched to NYHA class IV in diagnosis groups B, C and D, and to CMV in diagnosis groups C and D.

1.4 Calibration of the survival times

Both pre- and post-transplantation survival times were calculated from the VP's characteristics using the equations from the LAS scoring system without and after LT, respectively.[4] We extrapolated the baseline survival functions, which are described only for the first year in the original scoring system, to allow the simulation of long-term survival. The shape (k) and scale (λ) parameters of the Weibull distributions were chosen in order to obtain realistic survival times (Table 2).

Table 2: Pre- and post-transplantation survival (in years) computed from the LAS scoring system according to diagnosis group. Data are reported median [90% central range].

Diagnosis group	Group (A)	Group (B)	Group (C)	Group (D)	Overall
Pre-transplantation	4.2 (0.4; 14.8)	1.6 (0.2; 7.1)	1.7 (0.2; 6.7)	1.3 (0.1; 5.8)	2.0 (0.2; 10.8)
Post-transplantation	6.3 (1.2; 15.2)	4.8 (0.9; 12.4)	6.4 (1.2; 15.6)	5.0 (1.0; 13.0)	5.6 (1.1; 14.2)

(A) obstructive lung disease (e.g. emphysema); (B) pulmonary vascular disease (e.g. primary pulmonary hypertension); (C) cystic fibrosis or immunodeficiency disorder; and (D) restrictive lung disease (e.g. idiopathic pulmonary fibrosis).

[4]UNOS. A guide to calculating the LAS. www.unos.org/wp-content/uploads/unos/lung_allocation_score.pdf

Figure 1: Distribution of quantitative characteristics among UNOS [pink] and virtual patients [blue].

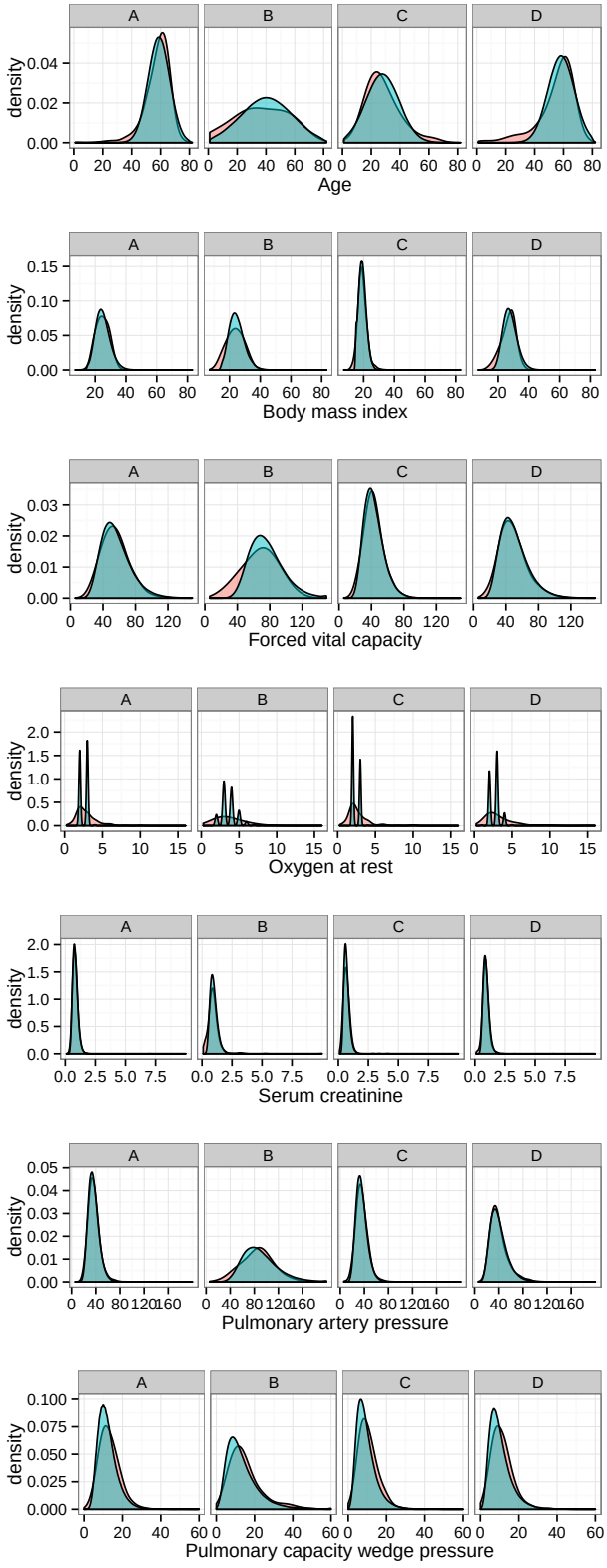
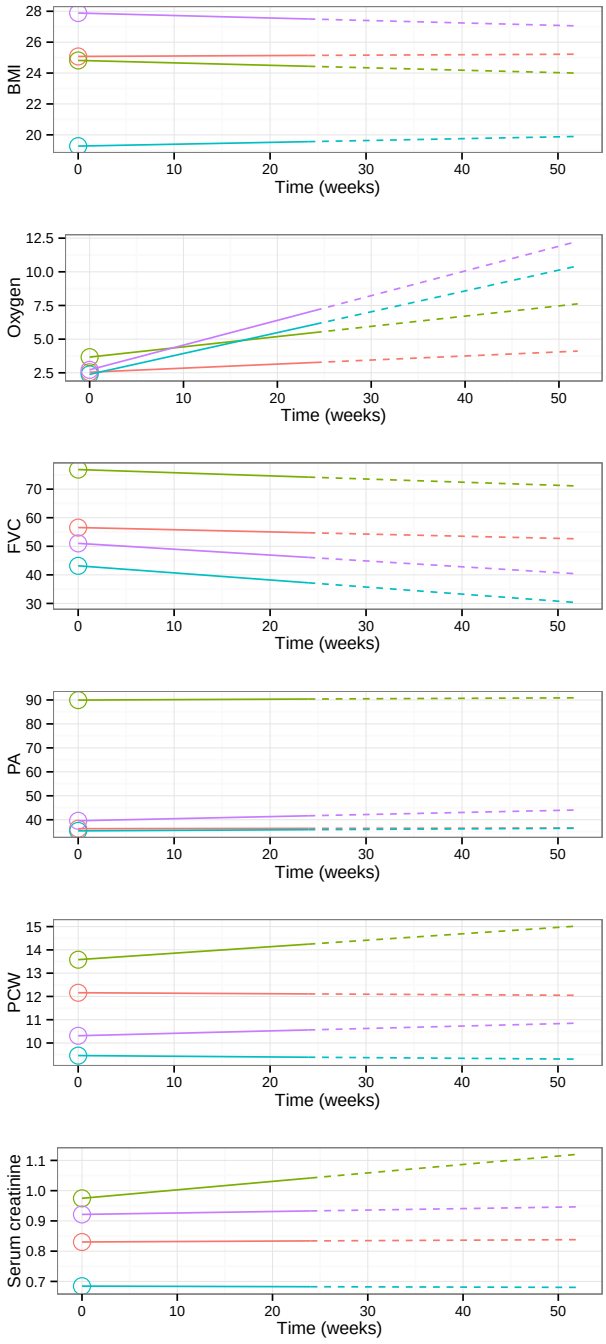


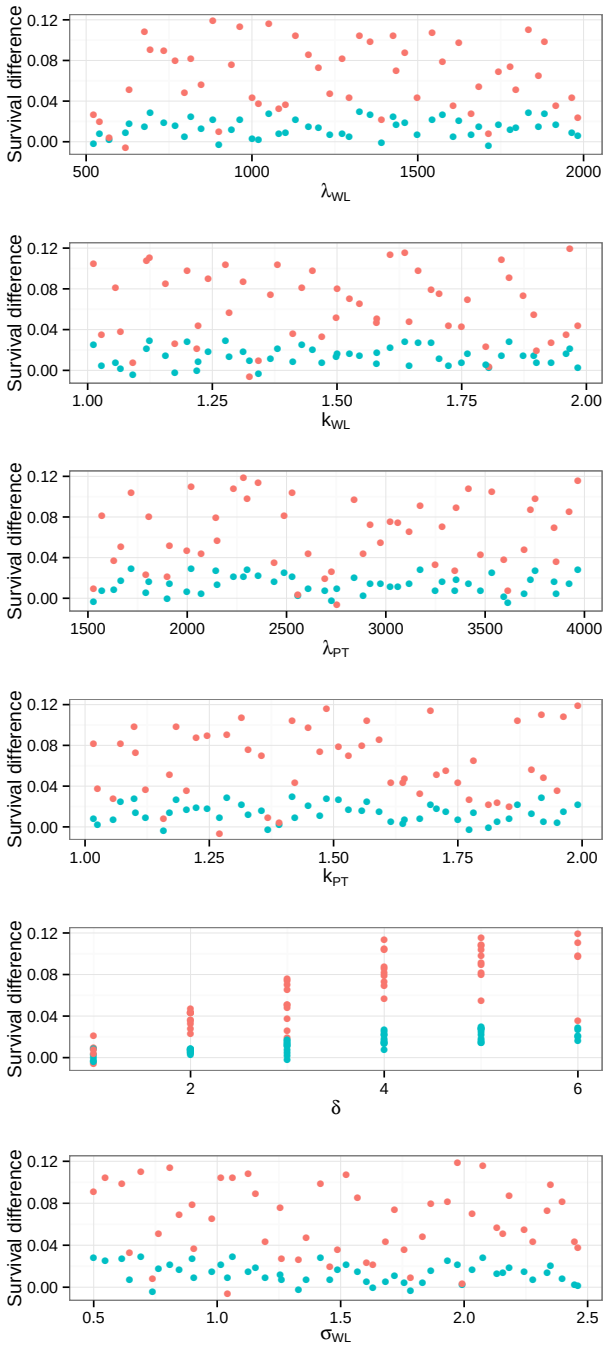
Figure 2: Mean evolution of VP's quantitative characteristics over the first year after inscription as extrapolated from the evolution in UNOS patients in the first 24 weeks, according to the diagnosis group A [red], B [green], C [blue], or D purple)



1.5 Sensitivity analyses

We ckecked the robustness of our choices in parameter values by testing several combinations of parameter values in sensitivity analyses using Latin hypercube sampling (Fig. 3). Survival rate differences one year after inscription were not influenced by the values of the shape (k_{WL}) and scale (λ_{WL}) parameters of the baseline on-list survival, nor by the values of the shape (k_{PT}) and scale (λ_{PT}) parameters of the baseline post-transplantation survival. The values of the parameters driving enlistment in the high-emergency waiting list (i.e. the number of weeks before its *estimated* date of death δ a VP was enlisted and the variance σ_{WL} of the normal distribution around the *actual* date of death this *estimated* date of death was drawn from) had a more notable impact on the outcome: the earlier a VP was enlisted in the high-emergency waiting list, the higher was the probability of undergoing LT and the larger was the difference between the FIFO and HELTx operating rules. However, the direction of the effect of implementing HELTx was always the same, and there was no situation in which early survival was higher under a FIFO rule.

Figure 3: Sensitivity analysis: influence of the variation of parameter values on the survival advantage brought by the implementation of the HELTx allocation rule one year after the first inscription on the waiting list in scenarios R96 [blue] and R80 [red].



2 Additional results

2.1 Waiting list outcome by diagnosis group

The implementation of the HELTx allocation rule led to fewer deaths on the waiting list, except in patients with diagnosis group A (i.e. with obstructive lung disease) in scenario R96 (Table 3). This was achieved at the cost of an overall increase in the time spent on the waiting list.

Table 3: Outcome of virtual patients leaving the waiting list (WL) according to the diagnosis group (A, B, C or D), the operating rule (FIFO or HELTx) and the organ/receiver ratio (R96 or R80). Data are reported as percentage or median and 90% central range across simulations.

Group	Ratio	Rule	Grafted		Dead on WL	
			Proportion	*Time*	*Proportion*	*Time*
A	R96	FIFO	97.6%	1.2 [0; 4.6]	1.5%	1.2 [0; 4.2]
A	R96	HELTx	95.8%	2.1 [0; 6.9]	2.5%	1.8 [0; 6.5]
A	R80	FIFO	88.7%	7.4 [3.7; 11.1]	7.3%	3.9 [0.2; 9]
A	R80	HELTx	77.2%	13.8 [4.8; 22.2]	14.1%	7.4 [0.7; 17.5]
B	R96	FIFO	94.4%	1.2 [0; 4.4]	4.8%	1.2 [0; 4.2]
B	R96	HELTx	95.2%	1.8 [0; 6.5]	3.1%	1.2 [0; 5.8]
B	R80	FIFO	74.7%	7.4 [3.5; 11.1]	21.7%	3.7 [0; 8.5]
B	R80	HELTx	79.4%	11.1 [0.2; 20.8]	13.6%	6.0 [0; 16.6]
C	R96	FIFO	94.9%	1.2 [0; 4.4]	4.2%	1.2 [0; 4.2]
C	R96	HELTx	95.5%	1.8 [0; 6.7]	2.7%	1.2 [0; 5.8]
C	R80	FIFO	76.9%	7.4 [3.5; 11.1]	19.5%	3.7 [0; 8.8]
C	R80	HELTx	80%	11.3 [0.2; 21.0]	12.7%	6.2 [0; 16.4]
D	R96	FIFO	93.3%	1.2 [0; 4.4]	5.9%	1.2 [0; 3.9]
D	R96	HELTx	94.8%	1.8 [0; 6.5]	3.6%	1.2 [0; 5.5]
D	R80	FIFO	70.8%	7.4 [3.5; 10.8]	25.6%	3.7 [0; 8.5]
D	R80	HELTx	77.5%	10.4 [0.2; 20.3]	15.9%	5.8 [0; 16.2]

2.2 The impact of HELTx on waiting list dynamics

Over time, HELTx led to an accumulation of patients on the waiting list, especially in the R80 scenario (Figure 4). This effect was particularly important for patients of group A, as they were more numerous and were excluded from enlistment in the HEWL. This led to increased waiting times in every diagnosis group (Figure 5). Consequently, patients undergoing LT were in more severe condition (Figure 6) which in turn led to lower post-transplantation survival times (Figure 7).

2.3 The impact of HELTx on overall survival

While the implementation of HELTx led to an augmentation of waiting times and a diminution of post-transplantation survival, it also prevented a small number of deaths on the waiting list. When considering overall survival (i.e. from the date of inscription to the date of death whatever the transplantation status, VP being still in the waiting list at the end of the simulation being considered as right-censored), the superiority

of HELTx was clear on the survival rate one year after inscription in each scenario of organ/recipient ratio, except in patients of group A (Figure 8). At early stages of simulation, the implementation of HELTx had no consequence on survival rates at years 5 or 10 (Figure 9). However, as simulation progressed and VP kept accumulating on the waiting list, the overall long-term survival under HELTx decreased and was in the end moderately lower than under FIFO rule.

Figure 4: Evolution of the yearly number of grafts, the yearly number of deaths on the waiting list and the size of the waiting list as simulation progresses with HELTx rule according to the organ/receiver ratio (R96 [left column] or R80 [right column]) and to the diagnosis group [rows], assuming the arrival of 335 new receivers per year.

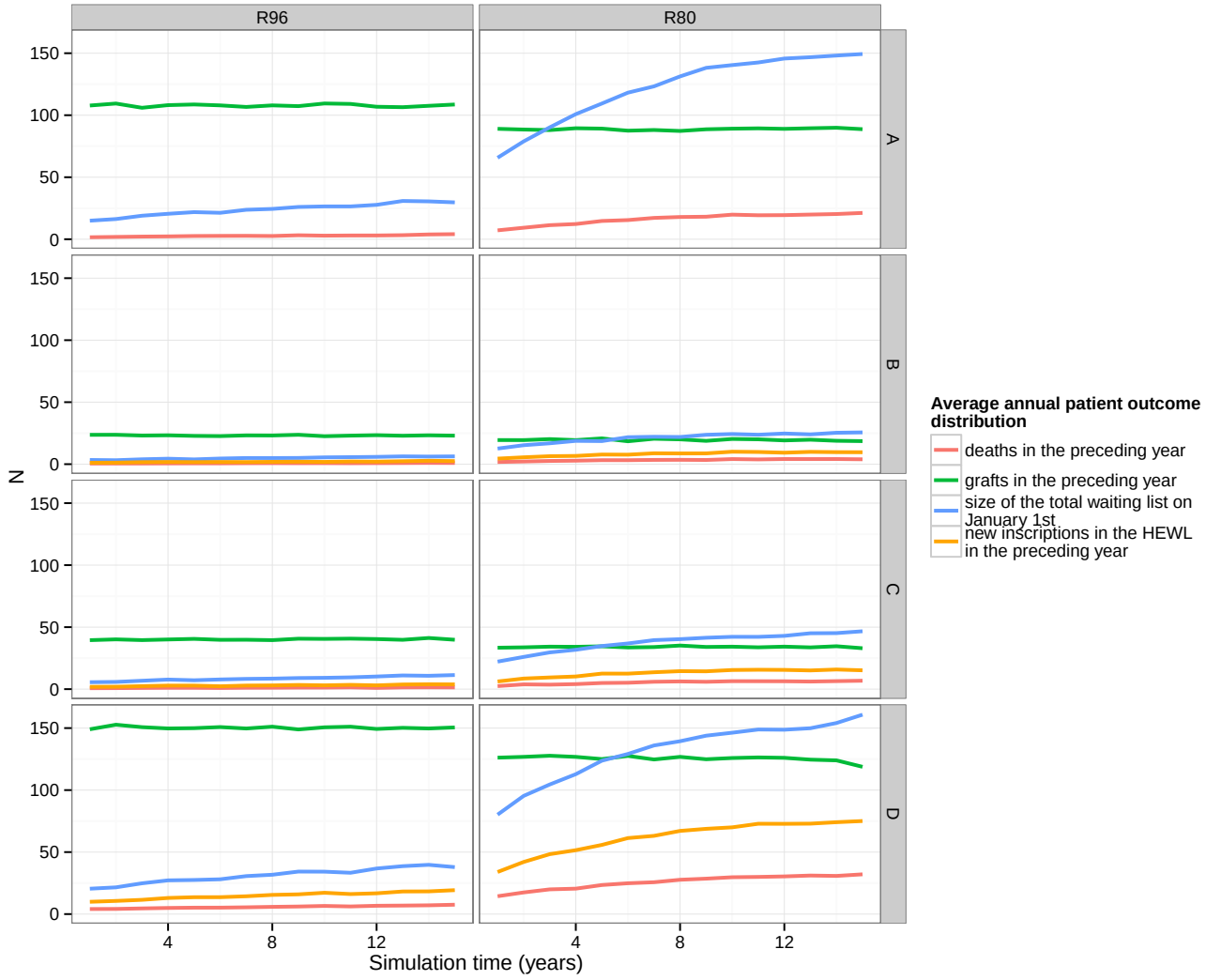


Figure 5: Evolution of the mean waiting time as simulation progressed, according to the diagnosis group, operating rule (FIFO [left column] or HELTx [right column]), the organ/receiver ratio (R96 [top row] or R80 [bottom row]).

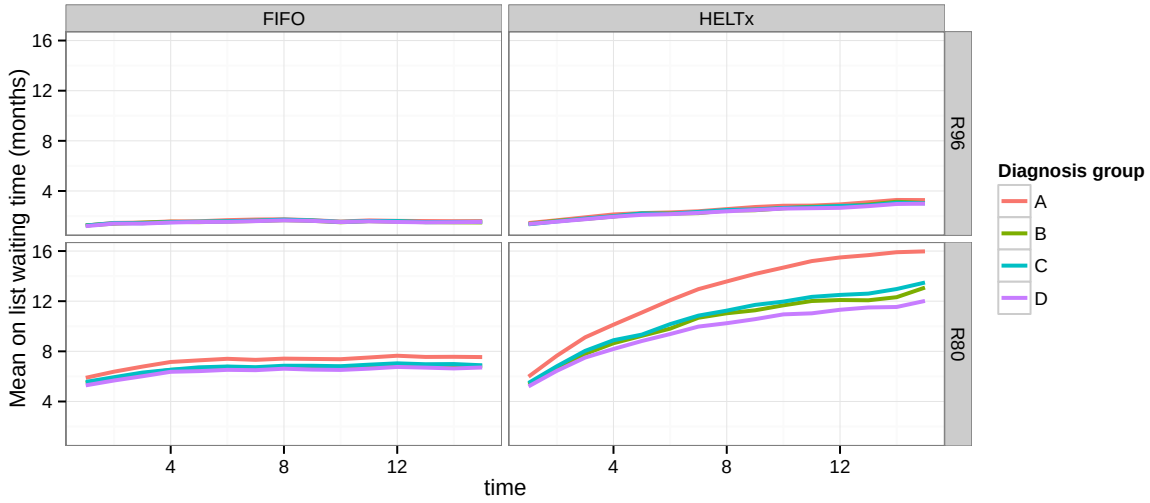


Figure 6: Severity of patients at the time of transplant as reflected by the mean LAS score, according to the diagnosis group, operating rule (FIFO [left column] or HELTx [right column]), the organ/receiver ratio (R96 [top row] or R80 [bottom row]).

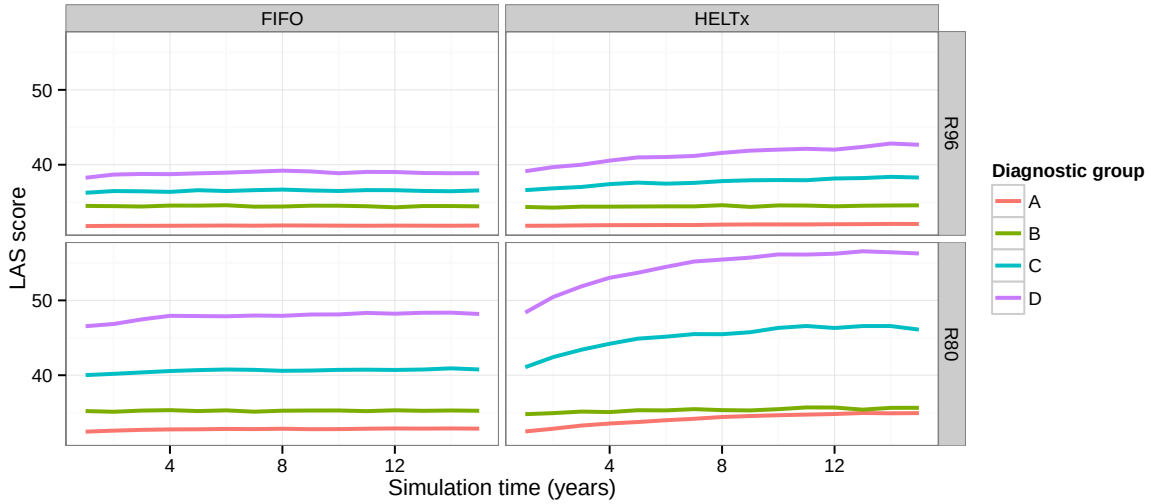


Figure 7: Evolution of the mean post-transplantation survival time as simulation progressed, according to the diagnosis group, operating rule (FIFO [left column] or HELTx [right column]), the organ/receiver ratio (R96 [top row] or R80 [bottom row]).

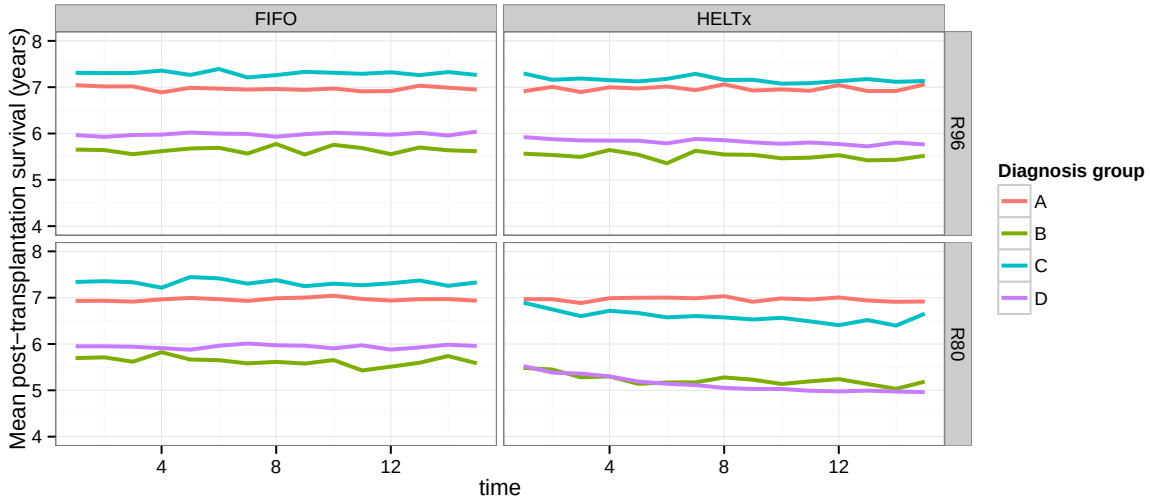


Figure 8: Overall survival rates at years one, five and ten according to the operating rule (FIFO [blue] or HELTx [red]), the organ/receiver ratio (R96 [left column] or R80 [right column]), and the diagnosis group (A, B, C, or D).

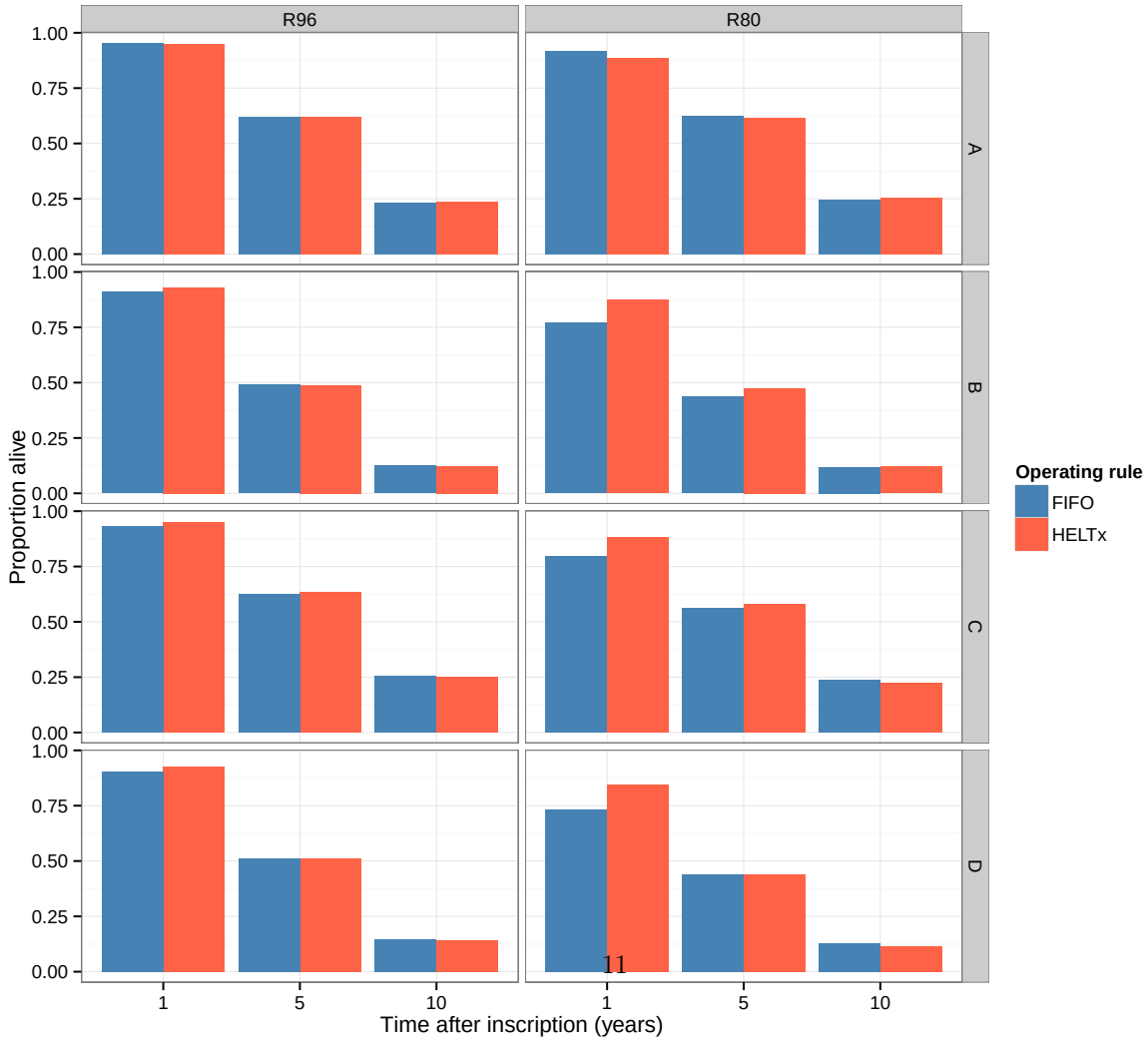


Figure 9: Overall survival rates at years one, five and ten according to the operating rule (FIFO [blue] or HELTx [red]), the organ/receiver ratio (R96 [left column] or R80 [right column]), and the period of inscription during the simulation (early [years 1-5], intermediate [years 6-10] or late [years 11-15]).