The Mathematics of Liver Transplantation

Eduardo Massad

School of Medicine
The University of São Paulo

edmassad@usp.br

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Liver failure occurs when large parts of the liver become damaged beyond repair and the liver is no longer able to function

The most common causes of chronic liver failure (where the liver fails over months to years) include:

- Hepatitis B
- Hepatitis C
- Long term alcohol consumption
- Cirrhosis
- Hemochromatosis (an inherited disorder that causes the body to absorb and store too much iron)
- Malnutrition

The causes of acute liver failure, when the liver fails rapidly, however, are often different. These include:

- Acetaminophen (Tylenol) overdose.
- Viruses including hepatitis A, B, and C (especially in children).
- Reactions to certain prescription and herbal medications.
- Aflatoxin (*Aspergillus flavus*).
- Ingestion of poisonous wild mushrooms.

The Model of Enstage Liver Disease or MELD score.

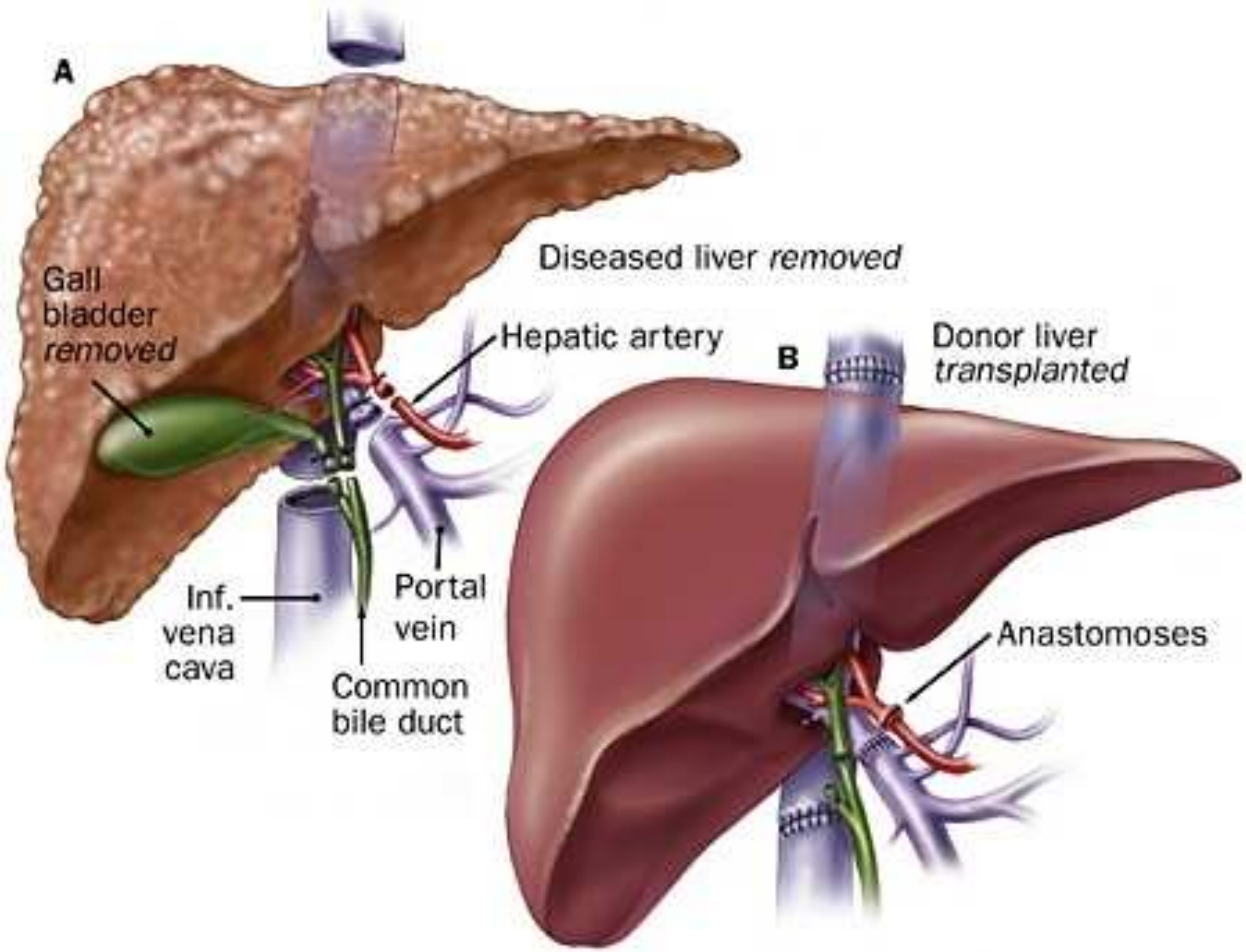
The Model for End-Stage Liver Disease (MELD) score has been in use since February 2002. It is used to measure a patient's risk of dying from chronic liver failure over a 90 day period from the day it was measured. It is used to determine the order and urgency of patients waiting for a liver transplant. The "MELD score" is a number scale. The range is from 6 (less ill) to 40 (gravely ill). The number is calculated using the following laboratory tests:

- **Total Bilirubin**: a measure of how well the liver clears certain body wastes.
- **INR** (International Normalized Ratio or previously known as the prothrombin time): a measures the liver's ability to make blood clotting factors.
- **Creatinine:** a measure of kidney function. Severe liver failure often results in kidney failure.

In general:

If the MELD score is greater than 10 patients are evaluated for a liver transplant. However, even if placed on the liver transplant list, patients are not actively called in for a liver transplant until their MELD score is 15 or greater. As the MELD score increases, patients are progressively sicker and more debilitated.

Liver transplantation or **hepatic transplantation** is the replacement of a diseased liver with a healthy liver from another person (allograft). The most commonly used technique is **orthotopic transplantation,** in which the native liver is removed and replaced by the donor organ in the same anatomic location as the original liver. Liver transplantation is a viable treatment option for end-stage liver disease and acute liver failure.


A
Gall bladder *removed*
Diseased liver *removed*
Hepatic artery
Inf. vena cava
Portal vein
Common bile duct
B
Donor liver *transplanted*
Anastomoses

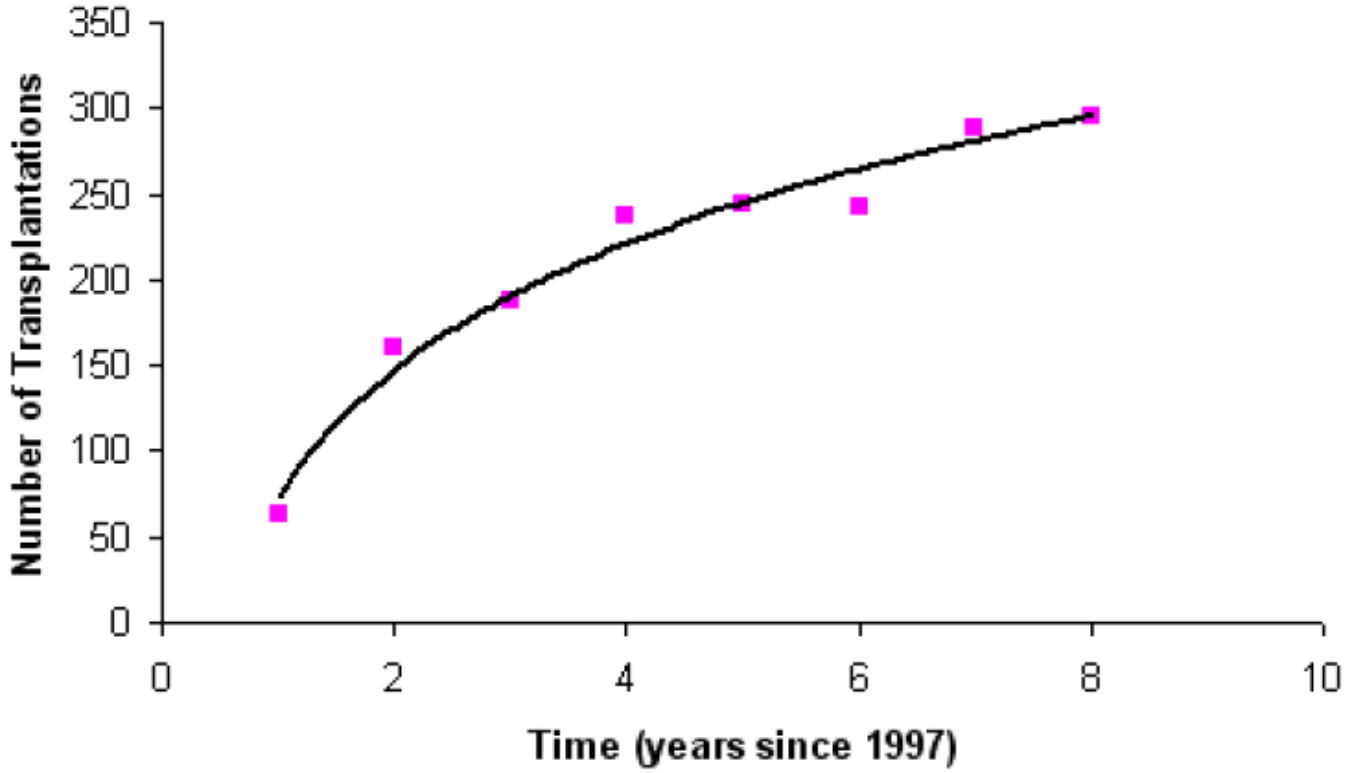
Waiting list dynamics in the state of Sao Paulo, Brazil

The aim of this study is to demonstrate the performance of our state liver transplantation program and analyze when the number of liver transplantation will meet the demand of our waiting list.

The data related to the actual number of liver transplantation, *Tr*, the incidence of new patients in the list, *I*, and the number of patients who died in the waiting list, *D*, in the State of São Paulo since 1997 as:

Year	*Tr*	*I*	*D*
1997	63		
1998	160	553	321
1999	188	923	414
2000	238	1074	548
2001	244	1248	604
2002	242	1486	725
2003	289	1564	723
2004	295	1500	671

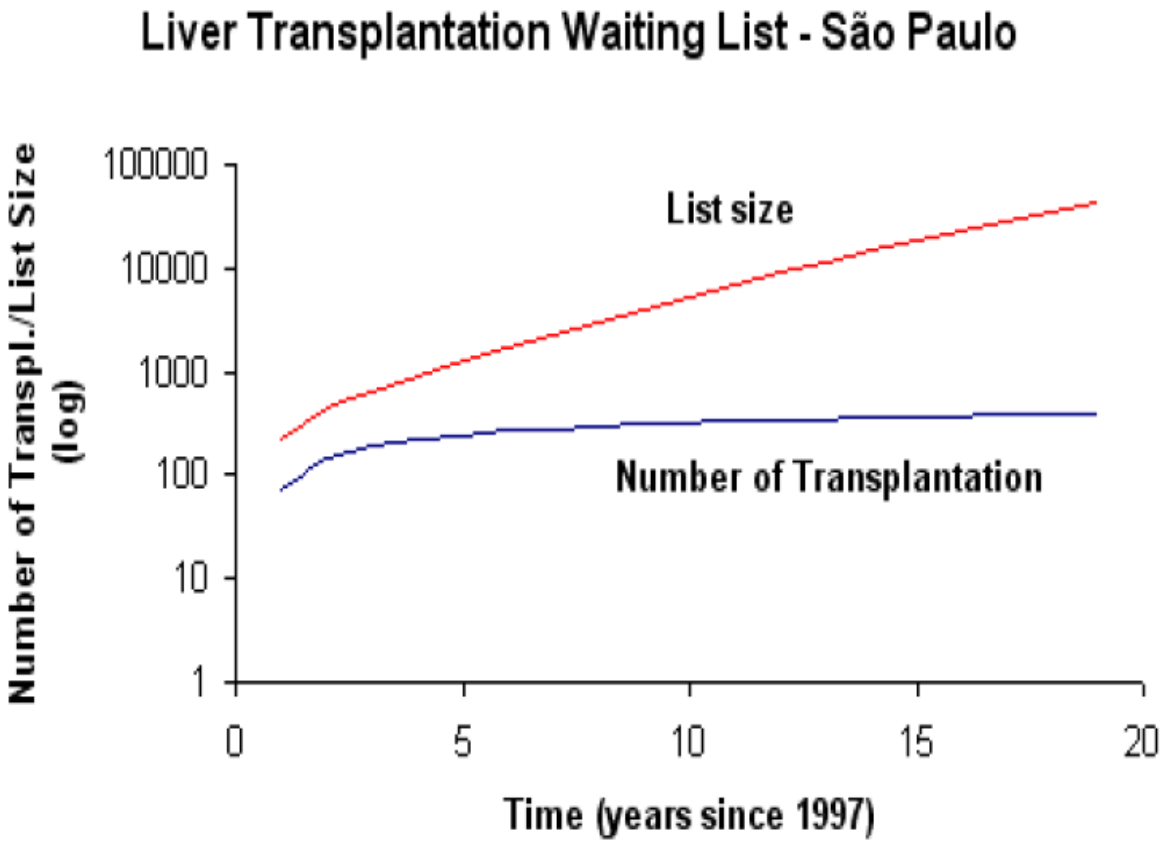
$$Tr = 107.07\ln(year) + 72.943$$



We next projected the size of the waiting list, *L*, by taking into account the incidence of new patients per year, *I*, the number of transplantations carried out in that year, *Tr*, and the number of patients that died in the waiting list, *D*. The dynamics of the waiting list is given by the difference equation:

$$L_{t+1} = L_t + I_t - D_t - Tr_t$$

that is, the list size at time *t+1* is equal to the size of the list at the time *t*, plus the new patients getting into the list at time *t*, minus those patients who died in the waiting list at time *t*, and minus those patients who received a graft at time *t*. The variables *I*, and *D*, from 2004 onward were projected by fitting an equation by maximum likelihood, in the same way that we did for *Tr*.


Liver Transplantation Waiting List - São Paulo
Number of Transpl./List Size (log)
100000
10000
1000
100
10
1
0
5
10
15
20
List size
Number of Transplantation
Time (years since 1997)

The potential impact of using ABO-compatible living donor liver transplantation (LDLT) on the liver transplantation program and waiting list in the state of Sao Paulo, Brazil.

The aim of this work was to analyze through a mathematical equation, the potential impact of using ABO-compatible LDLT on both our liver transplantation program and waiting list in the state of Sao Paulo.

we calculated the probability that a giving receptor has a compatible parent. For this we need first the frequency distribution of each blood type in the population of the State of Sao Paulo. We calculated the frequency distribution of each blood group alleles by applying the Hardy-Weinberg equation for 3 alleles, that is:

$$(p+q+r)^2 = p^2 + q^2 + r^2 + 2pq + 2pr + 2qr$$

Blood Group	Prevalence in the Population	Probability of having a compatible parent	Probability of having at least one compatible sibling
O	0.5067	0.154	0.350
A	0.3217	0.169	0.122
B	0.1345	0.059	0.052
AB	0.0371	0.029	0.029

Blood Group (phenotype)		A	B	AB	O
Genotype	Complete Representation	IAIA or IAIO	IBIB or IBIO	IAIB	IOIO
	Simplified Representation	AA or AO	BB or BO	AB	OO

	A	B	O
A	AA=A	AB	OA=A
B	AB	BB=B	OB=B
O	OA=A	OB=B	OO=O

Let us denote:
p = frequency of A
q = frequency of B
r= frequency of O.

Thus

$$1 = p + q + r$$

and the Hardy-Weinberg Theorem in this case will be

$$1 = (p + q + r)^2 = (p + q + r)\ (p + q + r) = p^2 + pq + pr + qp + q^2 + qr + rp + rq + r^2 =$$

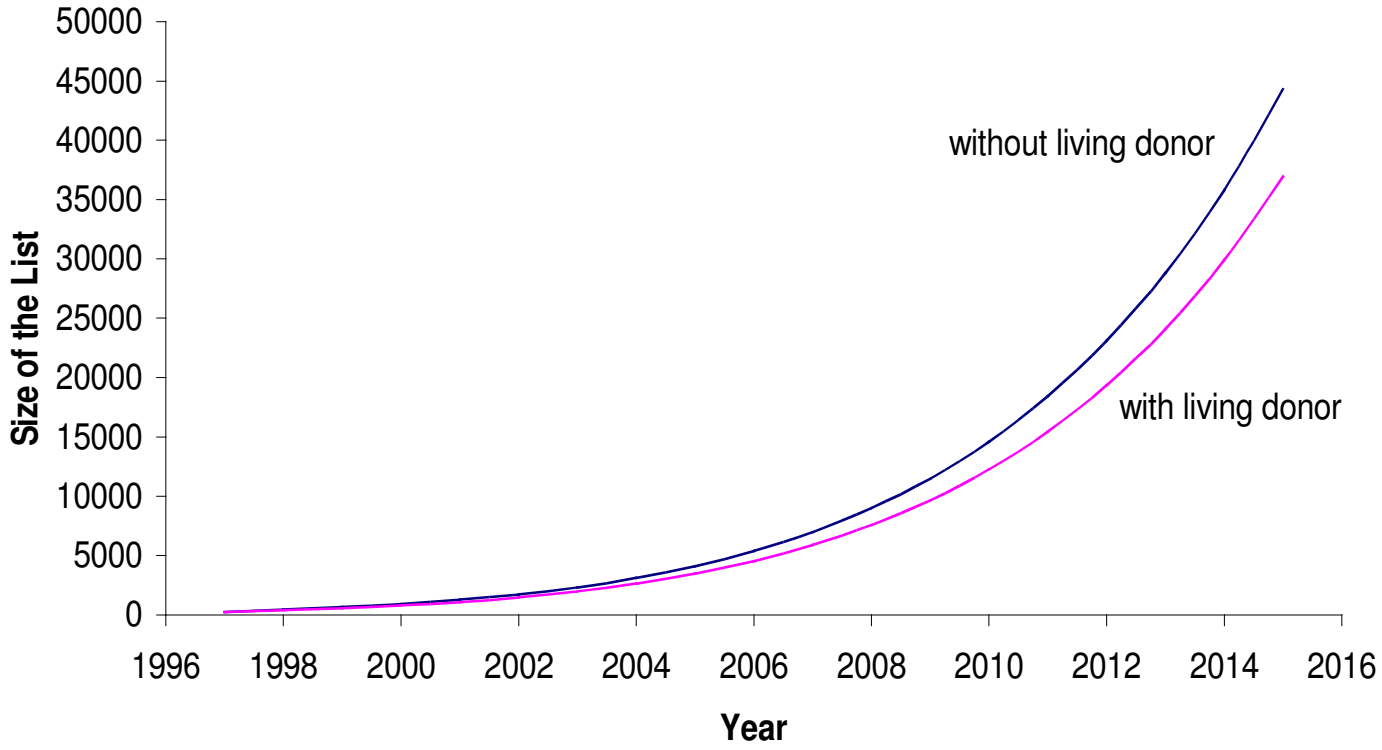
$$p^2 + q^2 + r^2 + 2pq + 2pr + 2qr = 1$$

Blood Type	*O*	*A*	*B*	*AB*
Frequency	*r*	*p+2pr*	*q+2qr*	*2pq*

Now, assuming that on average 25% of list is comprised by children, who should receive a liver from a parent and 75% is comprised by adults, who should receive a liver from a brother or sister, we can calculate the impact of LDLT in the waiting list by writing:

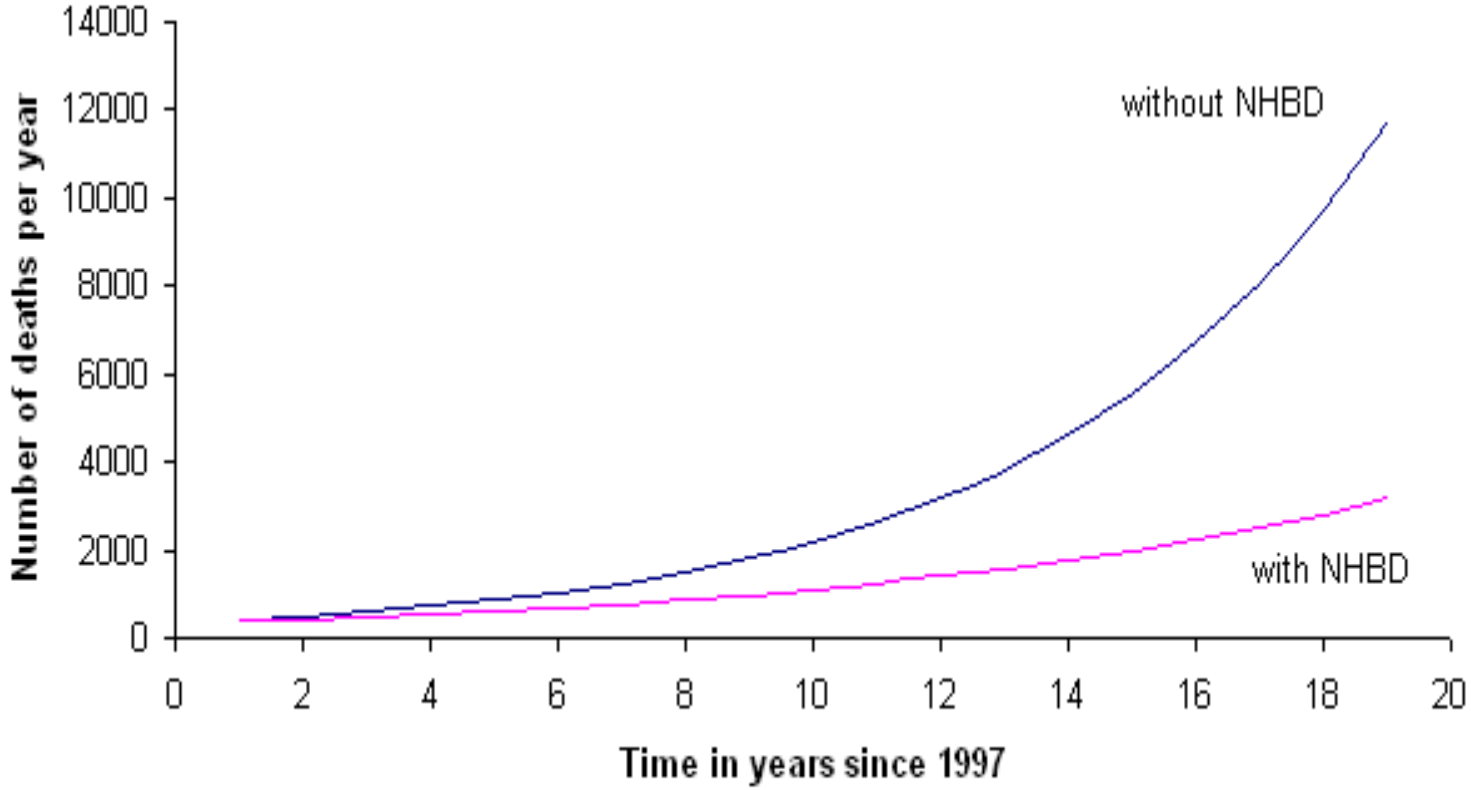
$$L_{t+1} = L_t + I_t - D_t - Tr_t -$$
$$[(0.5076 \times 0.154) + (0.3217 \times 0.169) + (0.1345 \times 0.059) + (0.0371 \times 0.029)]0.25L_t -$$
$$[(0.5076 \times 0.350) + (0.3217 \times 0.122) + (0.1345 \times 0.052) + (0.0371 \times 0.029)]0.75L_t$$

with *L0* = 218, the size of the list in 1997


50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
Size of the List
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year
without living donor
with living donor

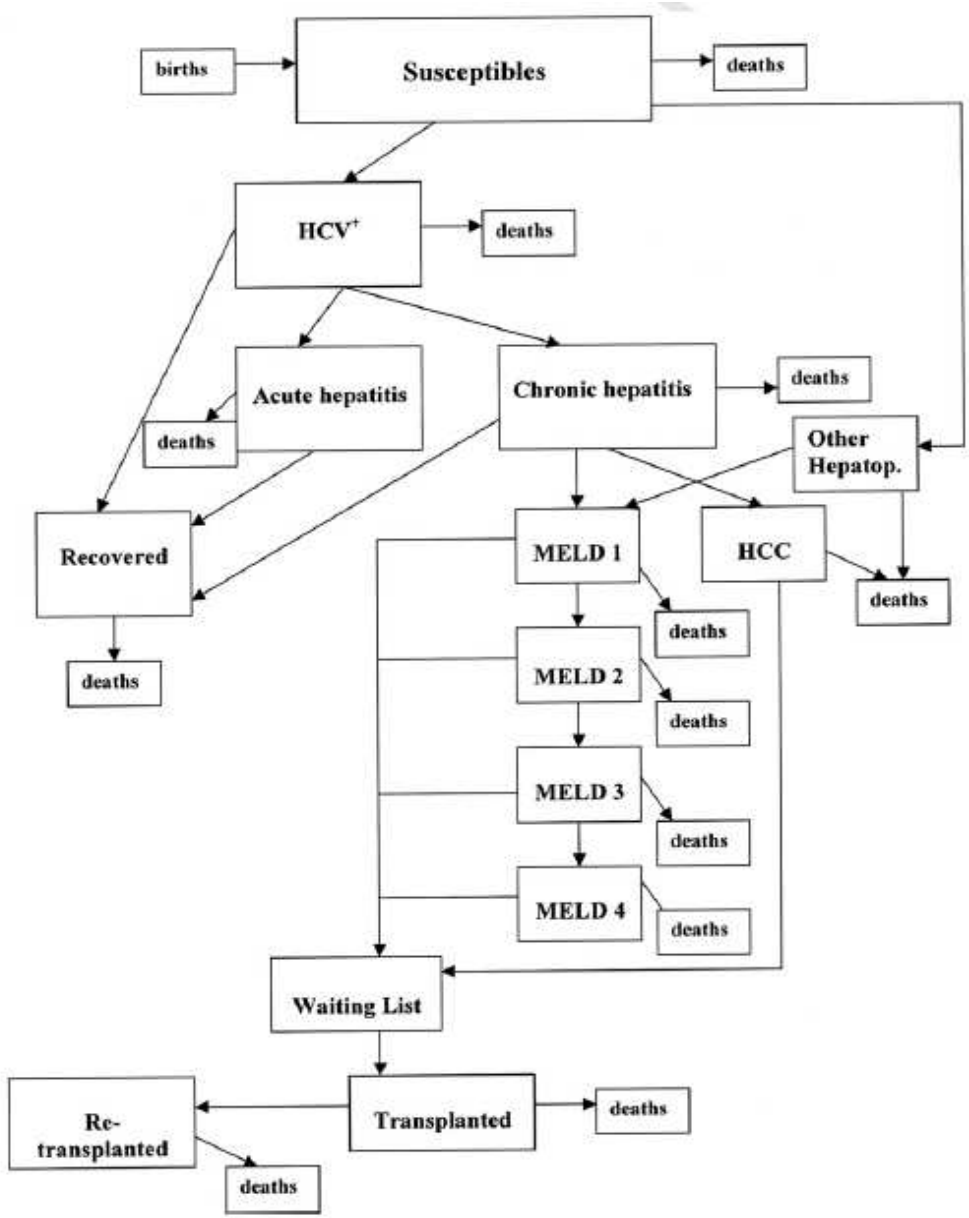
The Potential Impact of Non-Heart Beating Donors on the Liver-Transplantation Waiting List of São Paulo, Brazil

We applied a mathematical model to analyse the potential impact of using Non-Heart Beating Donors policy on the liver transplantation waiting list in the State of São Paulo, Brazil. The model shows that, assuming only 10%, 480 additional liver transplantations. This additional transplantations figure when applied in the model results in a relative reduction of 37% in the size of the waiting list and a projected number of averted deaths of about 41,500 in 20 years.

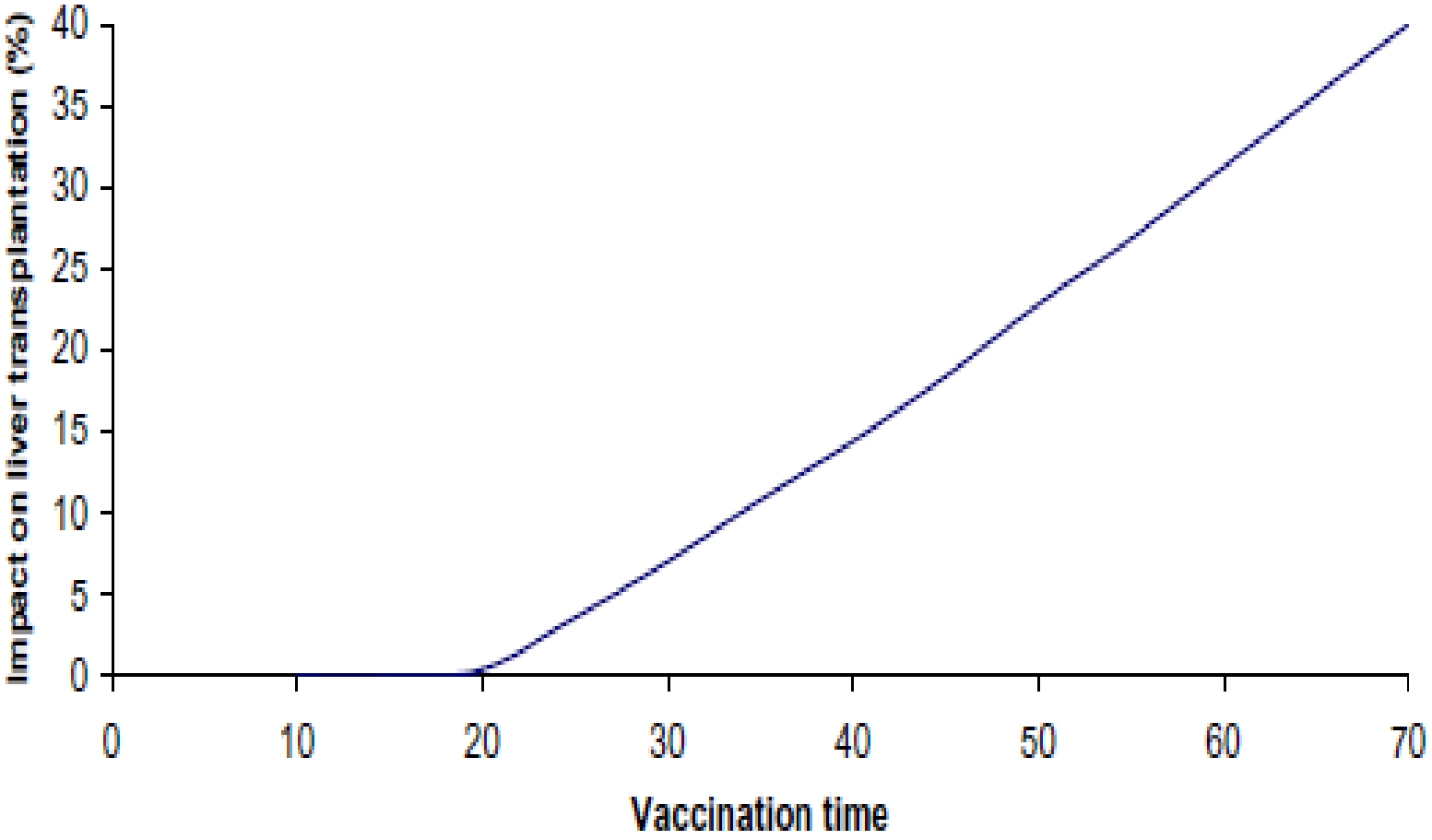

14000
12000
10000
8000
6000
4000
2000
0
Number of deaths per year
without NHBD
with NHBD
0
2
4
6
8
10
12
14
16
18
20
Time in years since 1997

Theoretical impact of an anti-HCV vaccine on the annual number of liver transplantation

The development of an effective vaccine for hepatitis C is of paramount importance, given the global disease burden and its public health impact. We simulated a theoretical vaccine with 98% efficacy and coverage of 95% of the susceptible population, an achievable program. The simulated period of vaccination varied from 0 to 70 years and we calculated, through a mathematical model, the reduction in the number of liver transplantations carried out each year.


births
Susceptibles
deaths
HCV+
deaths
Acute hepatitis
deaths
Chronic hepatitis
deaths
Other Hepatop.
Recovered
deaths
MELD 1
deaths
HCC
deaths
MELD 2
deaths
MELD 3
deaths
MELD 4
deaths
Waiting List
Re-transplanted
deaths
Transplanted
deaths

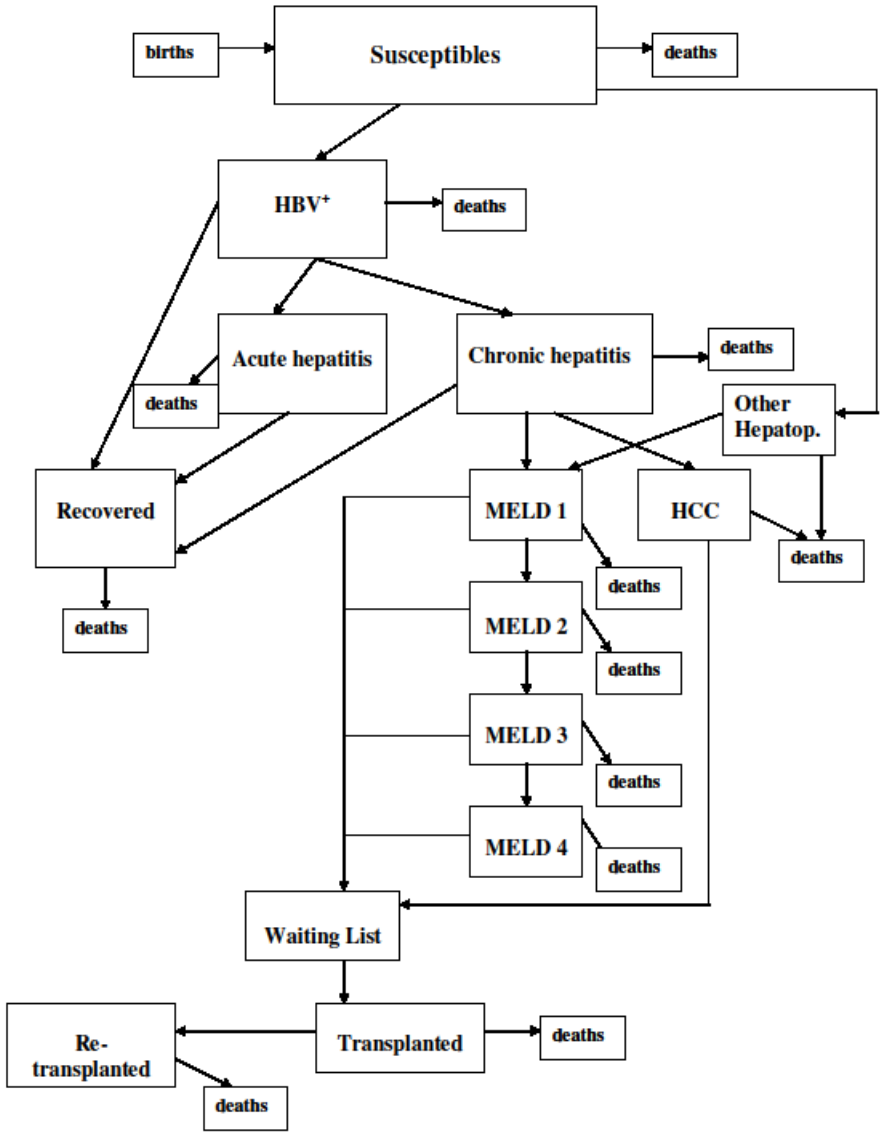
$$\frac{dS_1(t)}{dt} = \Lambda - u\beta_1 HCV(t)\frac{S_1(t)}{N} - u\beta_2 Ac(t)\frac{S_1(t)}{N} - u\beta_3 T_A(t)\frac{S_1(t)}{N}$$
$$- u\beta_4 Chr(t)\frac{S_1(t)}{N} - (\mu + \omega + \xi)S_1(t)$$
$$\frac{dS_2(t)}{N} = \xi S_1(t) - \beta_1 HCV(t)\frac{S_2(t)}{N} - \beta_2 Ac(t)\frac{S_2(t)}{N} - \beta_3 T_A(t)\frac{S_2(t)}{N}$$
$$- \beta_4 Chr(t)\frac{S_2(t)}{N} - (\mu + \omega)S_2(t)$$
$$\frac{dHCV(t)}{dt} = \beta_1 HCV(t)\frac{(S_1(t) + S_2(t))}{N} + \beta_2 Ac(t)\frac{(S_1(t) + S_2(t))}{N}$$
$$+ \beta_3 T_A(t)\frac{(S_1(t) + S_2(t))}{N} + \beta_4 Chr(t)\frac{(S_1(t) + S_2(t))}{N} - (\gamma_1 + \sigma_1 + \sigma_2 + \mu)HCV(t)$$
$$\frac{dAc(t)}{dt} = \sigma_1 HCV(t) - (\delta_1 + \gamma_2 + \alpha_1 + \mu)Ac(t)$$
$$\frac{dR(t)}{dt} = \gamma_1 HCV(t) + \gamma_2 Ac(t) + \gamma_4 Chr(t) - \mu R(t)$$
$$\frac{dChr(t)}{dt} = \delta_1 Ac(t) + \sigma_2 HCV(t) - (\delta_2 + \theta + \alpha_2 + \gamma_3)Chr(t)$$
$$\frac{dMELD_1(t)}{dt} = \delta_2(Chr(t) + Oth(t)) - (\varphi_1 + \varepsilon_1 + \alpha_3 + \mu)NT_C M_1(t)$$
$$\frac{dMELD_2(t)}{dt} = \varepsilon_1 NT_C M_1(t) - (\varphi_2 + \varepsilon_2 + \alpha_4 + \mu)NT_C M_2(t)$$
$$\frac{dMELD_3(t)}{dt} = \varepsilon_2 NT_C M_2(t) - (\varphi_3 + \varepsilon_3 + \alpha_5 + \mu)NT_C M_3(t)$$
$$\frac{dMELD_4(t)}{dt} = \varepsilon_3 NT_C M_3(t) - (\varphi_4 + \alpha_6 + \mu)NT_C M_4(t)$$
$$\frac{dHCC(t)}{dt} = \theta Chr(t) - (\varphi_5 + \alpha_7 + \mu)HCC(t)$$
$$\frac{dWL(t)}{dt} = \sum_{i,j=1}^{4} \varphi_i NT_C M_j(t) + \varphi_5 Chr(t) - (\tau_1 + \alpha_8 + \mu)WL(t)$$
$$\frac{dTx_1(t)}{dt} = \tau_1 WL(t) - (\varphi_6 + \alpha_9 + \mu)Tx_1(t)$$
$$\frac{dWLTx(t)}{dt} = \varphi_6 Tx_1(t) - (\tau_2 + \alpha_{10} + \mu)WLTx(t)$$
$$\frac{dTx_2(t)}{dt} = \tau_2 WLTx(t) - (\alpha_{11} + \mu)Tx_2(t)$$
$$\frac{dOth(t)}{dt} = \omega\big(S_1(t) + S_2(t)\big) - (\delta_2 + \alpha_{12} + \mu)Oth(t)$$


Impact on liver transplantation (%)
40
35
30
25
20
15
10
5
0
0
10
20
30
40
50
60
70
Vaccination time

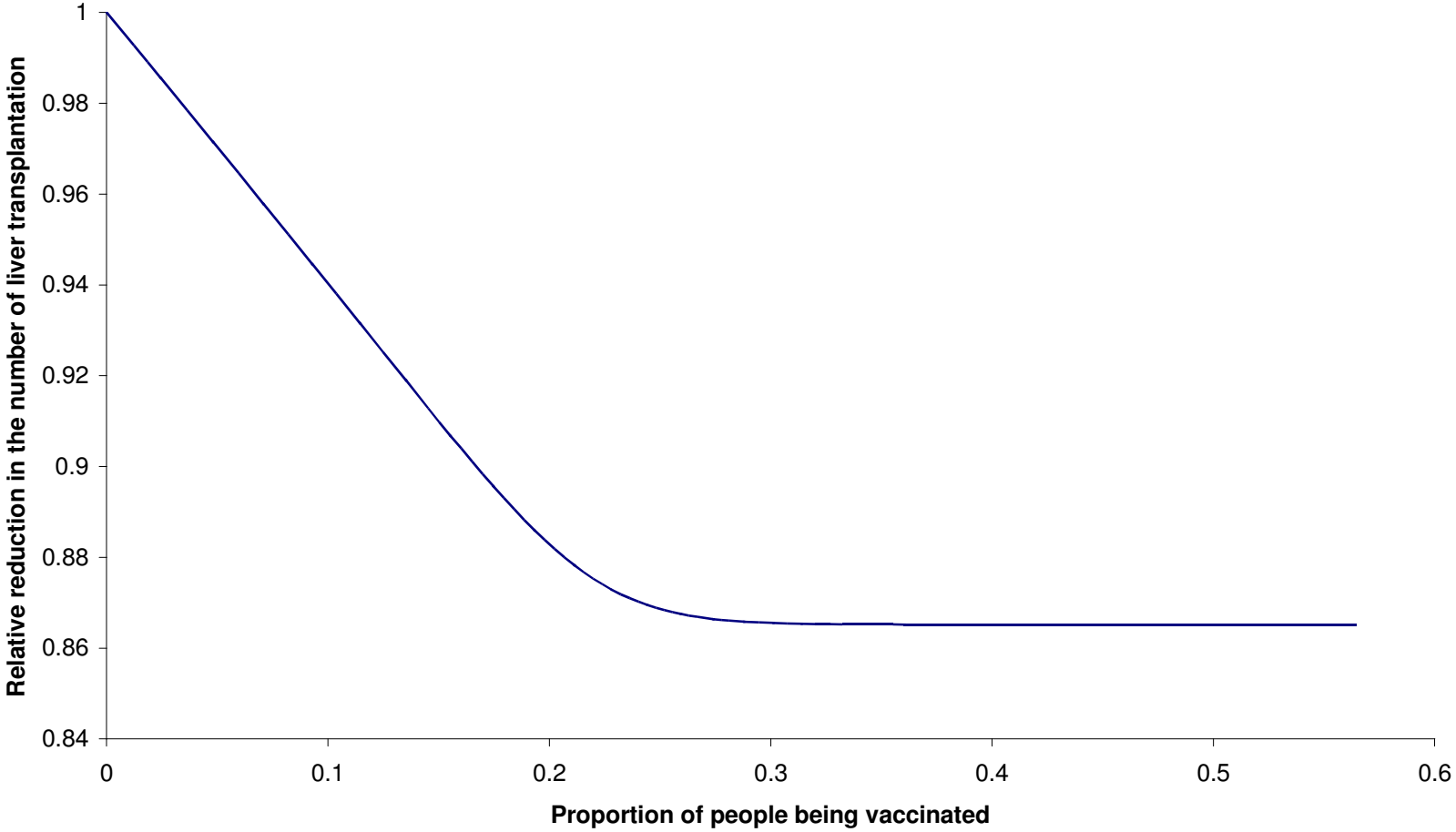
The program is entirely inefficient until 20 years of vaccination and its impact rises linearly with time, reaching a maximum of 40% reduction. The model assumes that approximately 50% of all the liver transplantation carried out in our population are due to HCV infection. Therefore, the maximum reduction in the number of transplantation attained after 70 years is 10% less of the theoretical optimum. This is due to the 2% of primary vaccination failure plus the 5% in the coverage failure, which leaves a small proportion of susceptible individuals who will catch the infection and evolve to liver failure.

Does anti-HBV vaccine make any difference in long-term number of liver transplantation ?

In the absence of any previous study comparing population treated and non-treated with respect to the number of liver failure due to HBV we have decided to apply a model previously proposed to study the projected impact of vaccination against hepatitis C on liver transplantation to the case of hepatitis B as a cause of liver transplantation.


births
Susceptibles
deaths
HBV+
deaths
Acute hepatitis
deaths
Chronic hepatitis
deaths
Other Hepatop.
Recovered
deaths
MELD 1
deaths
HCC
deaths
MELD 2
deaths
MELD 3
deaths
MELD 4
deaths
Waiting List
Re-transplanted
deaths
Transplanted
deaths

$$\frac{dS_1(t)}{dt} = \Lambda - u\beta_1 HBV(t)\frac{S_1(t)}{N} - u\beta_2 Ac(t)\frac{S_1(t)}{N} - u\beta_3 T_A(t)\frac{S_1(t)}{N}$$
$$- u\beta_4 Chr(t)\frac{S_1(t)}{N} - (\mu + \omega + \xi)S_1(t)$$
$$\frac{dS_2(t)}{N} = \xi S_1(t) - \beta_1 HBV(t)\frac{S_2(t)}{N} - \beta_2 Ac(t)\frac{S_2(t)}{N} - \beta_3 T_A(t)\frac{S_2(t)}{N}$$
$$- \beta_4 Chr(t)\frac{S_2(t)}{N} - (\mu + \omega)S_2(t)$$
$$\frac{dHBV(t)}{dt} = \beta_1 HBV(t)\frac{(S_1(t) + S_2(t))}{N} + \beta_2 Ac(t)\frac{(S_1(t) + S_2(t))}{N}$$
$$+ \beta_3 T_A(t)\frac{(S_1(t) + S_2(t))}{N} + \beta_4 Chr(t)\frac{(S_1(t) + S_2(t))}{N} - (\gamma_1 + \sigma_1 + \sigma_2 + \mu)HBV(t)$$
$$\frac{dAc(t)}{dt} = \sigma_1 HBV(t) - (\delta_1 + \gamma_2 + \alpha_1 + \mu)Ac(t)$$
$$\frac{dR(t)}{dt} = \gamma_1 HBV(t) + \gamma_2 Ac(t) + \gamma_4 Chr(t) - \mu R(t)$$
$$\frac{dChr(t)}{dt} = \delta_1 Ac(t) + \sigma_2 HBV(t) - (\delta_2 + \theta + \alpha_2 + \gamma_3)Chr(t)$$
$$\frac{dMELD_1(t)}{dt} = \delta_2(Chr(t) + Oth(t)) - (\varphi_1 + \varepsilon_1 + \alpha_3 + \mu)NT_C M_1(t)$$
$$\frac{dMELD_2(t)}{dt} = \varepsilon_1 NT_C M_1(t) - (\varphi_2 + \varepsilon_2 + \alpha_4 + \mu)NT_C M_2(t)$$
$$\frac{dMELD_3(t)}{dt} = \varepsilon_2 NT_C M_2(t) - (\varphi_3 + \varepsilon_3 + \alpha_5 + \mu)NT_C M_3(t)$$
$$\frac{dMELD_4(t)}{dt} = \varepsilon_3 NT_C M_3(t) - (\varphi_4 + \alpha_6 + \mu)NT_C M_4(t)$$
$$\frac{dHCC(t)}{dt} = \theta Chr(t) - (\varphi_5 + \alpha_7 + \mu)HCC(t)$$
$$\frac{dWL(t)}{dt} = \sum_{i,j=1}^{4} \varphi_i NT_C M_j(t) + \varphi_5 Chr(t) - (\tau_1 + \alpha_8 + \mu)WL(t)$$
$$\frac{dTx_1(t)}{dt} = \tau_1 WL(t) - (\varphi_6 + \alpha_9 + \mu)Tx_1(t)$$
$$\frac{dWLTx(t)}{dt} = \varphi_6 Tx_1(t) - (\tau_2 + \alpha_{10} + \mu)WLTx(t)$$
$$\frac{dTx_2(t)}{dt} = \tau_2 WLTx(t) - (\alpha_{11} + \mu)Tx_2(t)$$
$$\frac{dOth(t)}{dt} = \omega\big(S_1(t) + S_2(t)\big) - (\delta_2 + \alpha_{12} + \mu)Oth(t)$$


Relative reduction in the number of liver transplantation
1
0.98
0.96
0.94
0.92
0.9
0.88
0.86
0.84
0
0.1
0.2
0.3
0.4
0.5
0.6
Proportion of people being vaccinated

Our analysis suggests that increasing the vaccination coverage against HBV in the State of São Paulo would have a relatively low impact on the number of liver transplantation. In addition, this impact would take several decades to materialize due to the long incubation period of liver failure due to HBV.

A Model for Optimizing the Indications of Liver Transplantation in Patients with Hepatocellular Carcinoma in the state of Sao Paulo, Brazil

The Milan Criteria, MC, is defined by the presence of a single nodule up to 5 cm, up to three nodules none larger than 3 cm, with no evidence of extrahepatic spread or macrovascular invasion. The Brazilian law allows patients only within MC to be evaluated and considered for LT. This police implies that some patients with HCC slightly more advanced than those allowed by the current strict selection criteria will be excluded, even though LT for these patients might be associated with acceptable long-term outcomes .

We propose a mathematical approach to study the consequences of relaxing the MC for patients with HCC that do not comply with the current rules for inclusion in the transplantation candidate list. We consider overall 5-years survival rates compatible with the ones reported in the literature. We simulate our model in order to reproduce what is known about the survival of the two groups of patients (those who comply with the strict MC and those who do not) and calculate the best strategy that would minimize the total mortality of the affected population, that is, the total number of people in both group that dies after 5 years of the implementation of the strategy, either by post-transplantation death or by death due to the basic HCC.

The model is based on four assumptions, namely,

1. the mortality rate of non-transplanted, α_{nt} and transplanted, α_t HCC patients are described by the following ad hoc expressions:

$$\alpha_{nt}(s) = \alpha_0(\alpha_1 - e^{-\delta_1 s}) \quad (1)$$

and

$$\alpha_t(s) = \alpha_0 + \delta_2 s \quad (2)$$

where $\delta_i (i = 1,2)$ are the parameters, such that $\delta_1 > \delta_2$ and s is the size of the tumor. In equation (1), when $\alpha_1 = 2$ the above mortality rates coincide for $s = 0$. Since this is necessary, we assume $\alpha_1 = 2$ for the rest of the paper. Note that s is the size of the tumor at the moment patients get into the transplantation program. So, equations (1) and (2) take into account the fact that tumors grow with time and so does the mortality rates. This is included in a a rather cavalier manner in equations (1) and (2) since the functional relationship of tumors growths related mortality with time are not known.

Equations (1) and (2) are illustrated in figure 1, in which it is shown the mortality rates for both the transplanted and non-transplanted HCC patients as a function of the tumor size s at presentation.

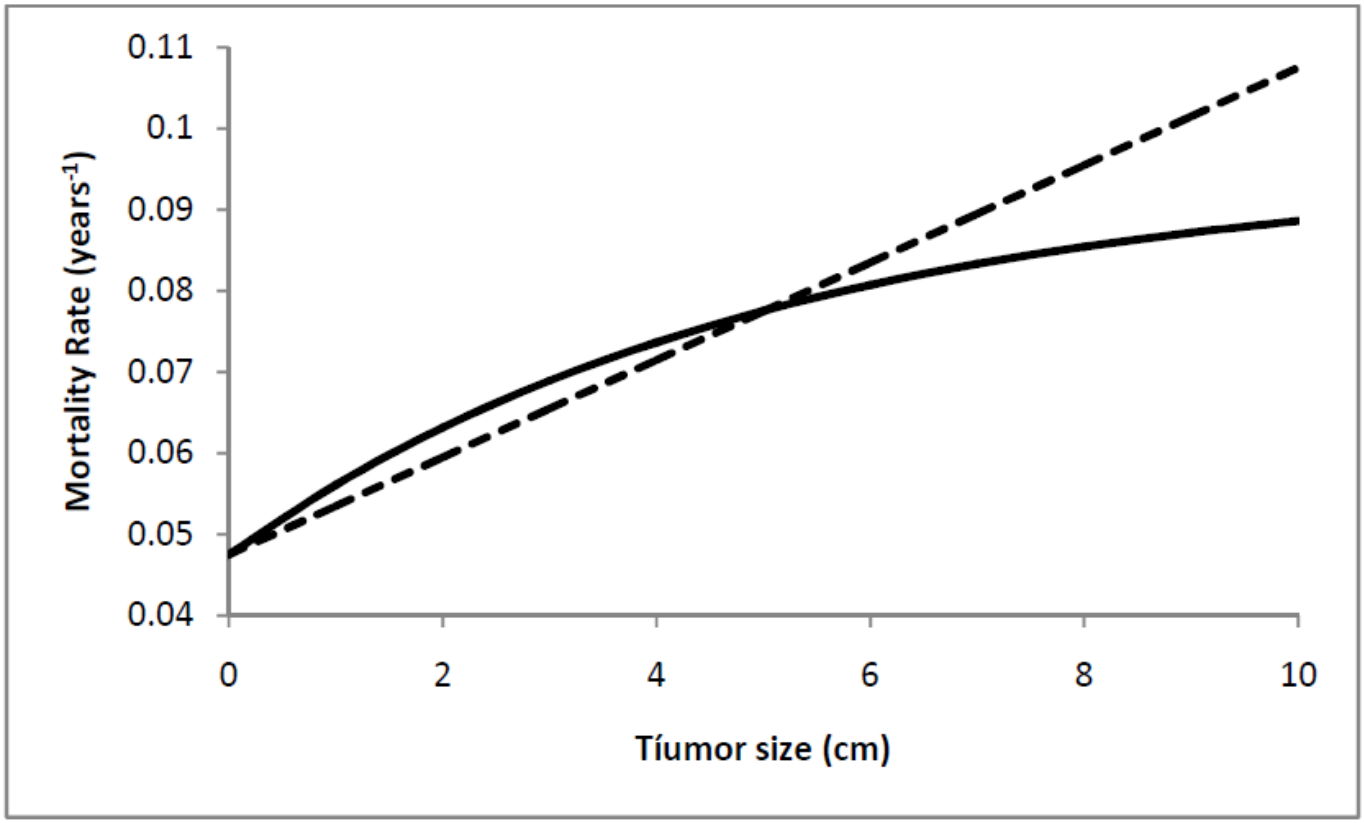


Figure 1.Mortality rates for transplanted (dotted line) and non-transplanted (solid line) HCC patients. Results of the theoretical population analyzed, according to equations (1) and (2) with $\alpha_0 = 0.048$, $\delta_1 = 0.2$ and $\delta_2 = 0.006$.

The probability of surviving after T years for non-transplanted and transplanted patients, $\pi_{nt}(s)$ and $\pi_t(s)$, respectively, as a function of their tumor size, s, at the time individuals are included in the transplantation program, is given by

$$\pi_{nt}(s) = \exp(-\alpha_{nt} T) \tag{3}$$

and

$$\pi_t(s) = \exp(-\alpha_t T) \tag{4}$$

2. the mortality of both transplanted and non-transplanted HCC patients is a monotonically increasing function of tumor size at presentation (tumor size is, therefore, taken as an indication of gravity).

3. the number of available livers to be grafted, F , is limited and always less than the total number of HCC , N ,who have transplantation indication; and finally,

4. the tumor size, s, at the time individuals are included in the transplantation program, is distributed in the HCC population according to an exponential distribution, such that the probability that a given HCC patient has tumor size s is described by the *probability density function (p.d.f.)*:

$$f(s,\lambda) = \lambda e^{-\lambda s} \tag{5}$$

where λ is the *rate parameter* of the distribution. This implies that in a HCC population, many individuals have tumor of small size and a very low number of who present tumors of larger size. Again, this distribution of tumor size is that at the moment the patients get into the transplantation program. The *cumulative distribution function (C.D.F.)* is given by

$$F(s,\lambda) = \int_0^s \lambda e^{\lambda t}\, dt = 1 - e^{-\lambda s} \tag{6}$$

In figure 2 we show the actual distribution of tumor size, fitted to an exponential distribution. The parameter λ in this case is equal to 0.3. As the total number of patients in these samples was 327 patients, this implies in an average size of 3.3 cm and a 95% confidence interval of [2.9; 3.7] [9-11].

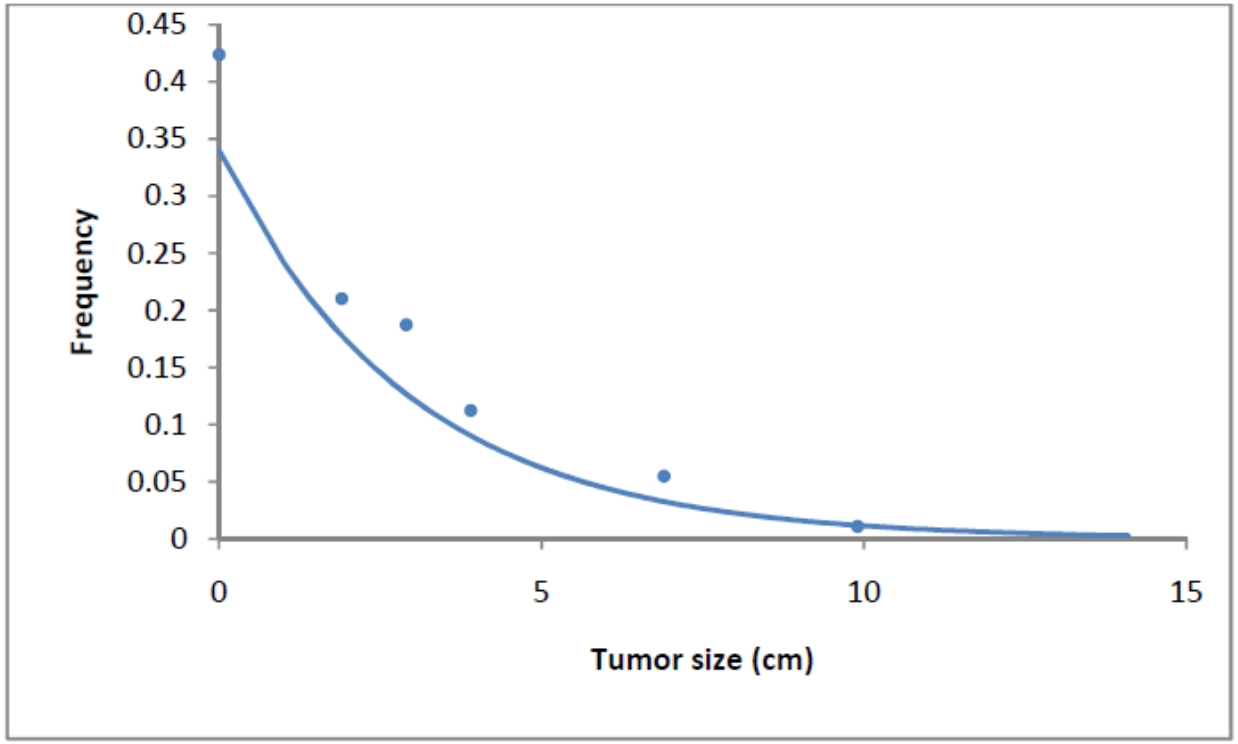


Figure 2. Frequency distribution of tumor size. Dots represent actual values from references [9 - 11] and the line is the exponential fitting to the real data (R^2=0.92). Parameter $\lambda = 0.3$ which implies in an average tumor size of 3.3 cm.

$$M(s_0) = N - \left[F \int_0^{s_0} \lambda e^{-\lambda s} e^{-\alpha_t(s)T} ds + N \int_0^{s_0} \left(1 - \frac{F}{N}\right) \lambda e^{-\lambda s} e^{-\alpha_{ns}(s)T} ds + N \int_{s_0}^{\infty} \lambda e^{-\lambda s} e^{-\alpha_{ns}(s)T} ds \right]$$

We illustrate the above analysis for a simulation of a theoretical population of 1,500 HCC patients with tumor size parameter distribution of λ equal to 0.3. As the total number of patients in the real samples from which data was retrieved was 327 patients, this implied in an average size of 3.3 cm and a 95% confidence interval of [2.9; 3.7] [9-11].. The total number of available livers to be grafted was assumed to be 500. With this, we simulated the total number of deaths in both transplanted and non-transplanted HCC patients after 5 years as a function of the tumor size of transplanted patients. The result is shown in figure 3.

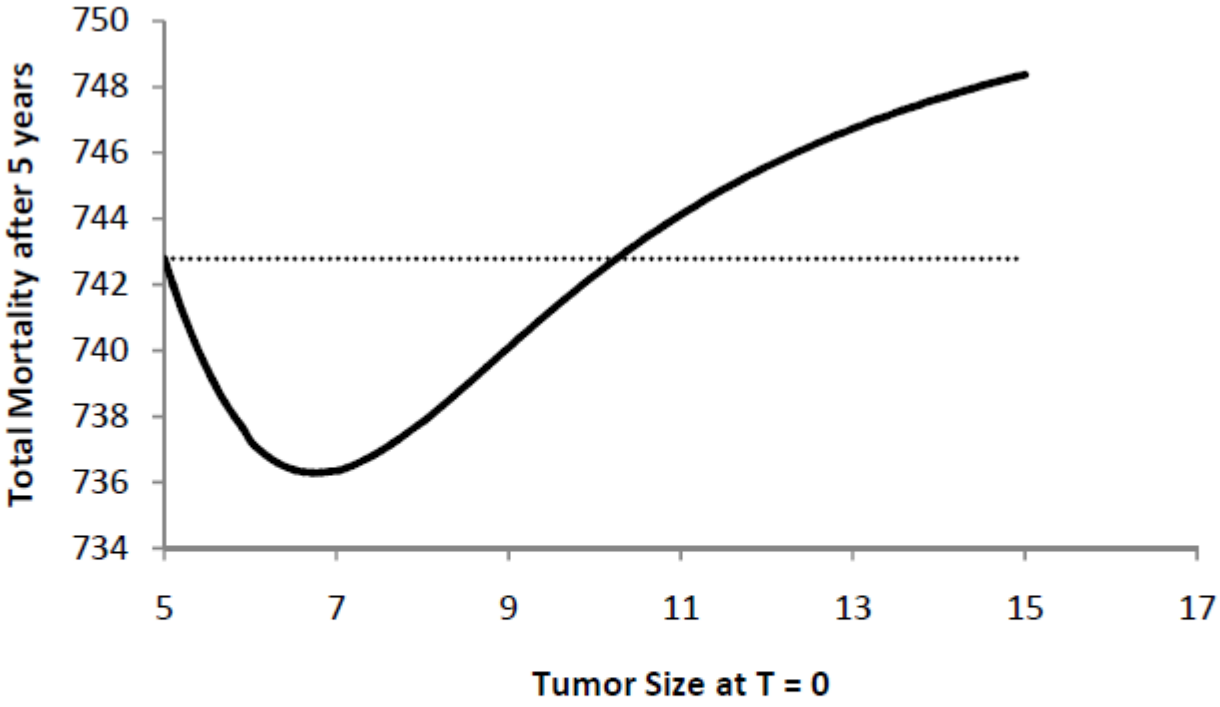


Figure 3.Total mortality after 5 years comprising both transplanted and non-transplanted HCC patients in a 1,500 theoretical population. We show only what happens when individuals with tumor size greater that the strict Milan criteria (5 cm).

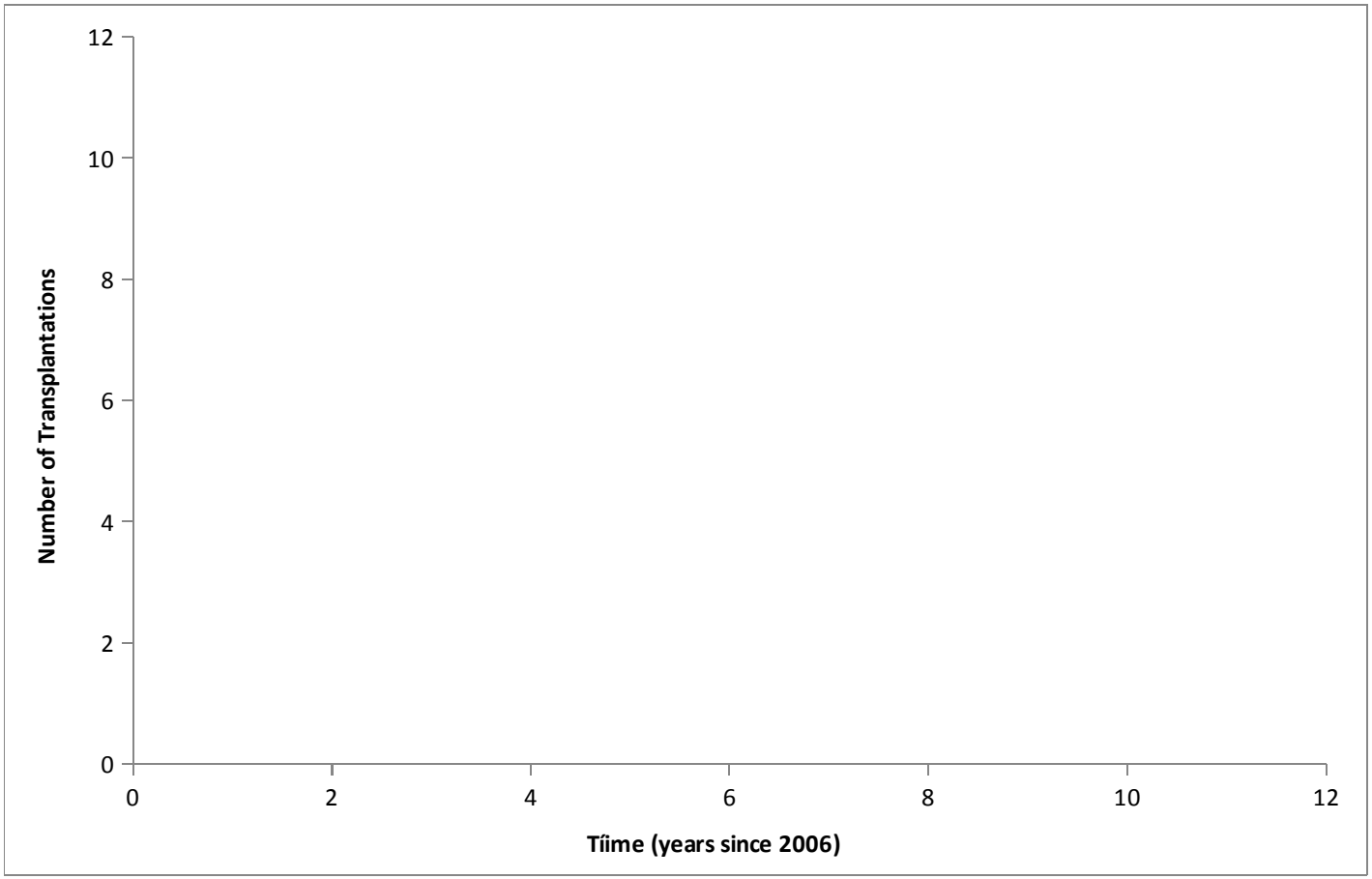
The impact of MELD score on the waiting list dynamics in the state of Sao Paulo, Brazil

The aim of this study is to analyze the impact of the introduction of the MELD score in 2006 in São Paulo, as a criteria for liver transplantation on the waiting list dynamics.

The data related to the actual number of liver transplantation, *Tr*, the incidence of new patients in the list, *I*, and the number of patients who died in the waiting list, *D*, in the State of São Paulo since 2006 is now:

Year	***Tr***	***I***	***D***
2006	349	1566	895
2007	330	1022	734
2008	454	1213	490
2009	609	1287	455
2010	671	1415	403
2011	609	1577	470
2012	501	1488	441

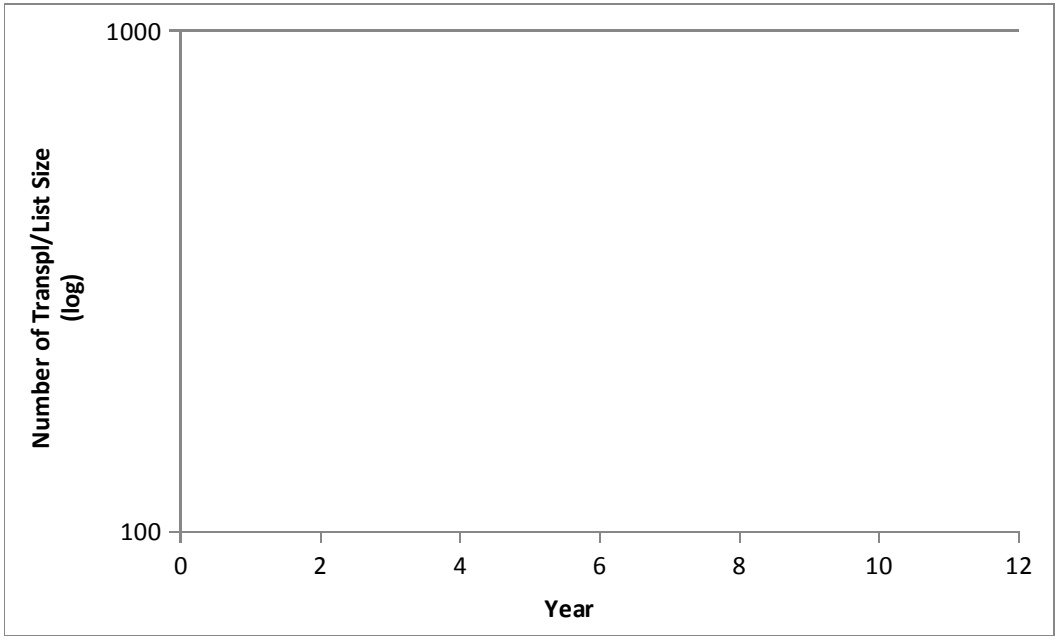
$$Tr = 500\ln(year) + 184.7$$



We next projected the size of the waiting list, *L*, by taking into account the incidence of new patients per year, *I*, the number of transplantations carried out in that year, *Tr*, and the number of patients that died in the waiting list, *D*. The dynamics of the waiting list is given by the difference equation:

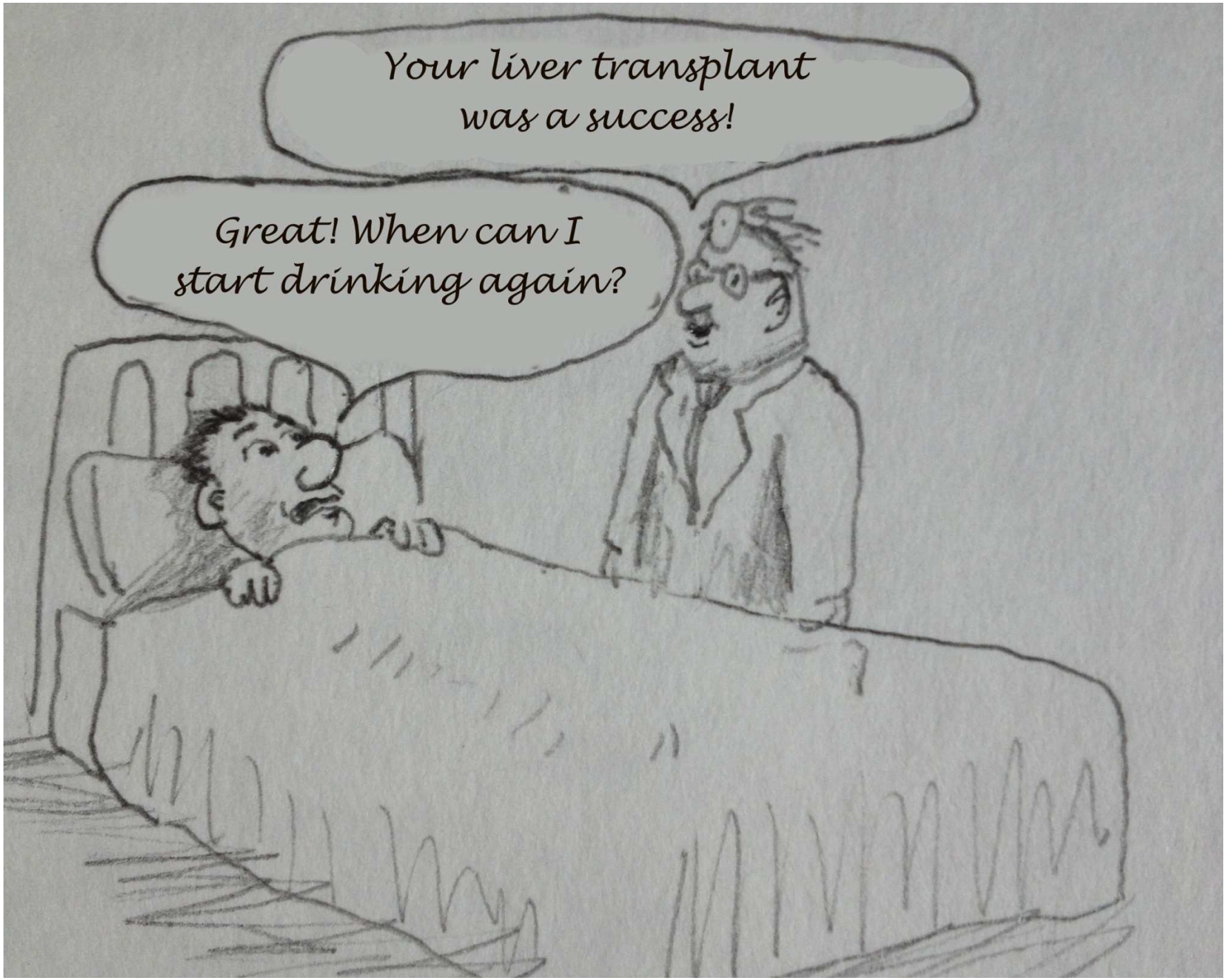
$$L_{t+1} = L_t + I_t - D_t - Tr_t$$

that is, the list size at time *t+1* is equal to the size of the list at the time *t*, plus the new patients getting into the list at time *t*, minus those patients who died in the waiting list at time *t*, and minus those patients who received a graft at time *t*. The variables *I*, and *D*, from 2006 onward were projected by fitting an equation by maximum likelihood, in the same way that we did for *Tr*.


1000
100
Number of Transpl/List Size (log)
0
2
4
6
8
10
12
Year

Collaborators:

- Eleazar Chaib
- Francisco Antonio Bezerra Coutinho
- Luis Fernandez Lopez
- Marcos Amaku
- Marcelo Nascimento Burattini


Your liver transplant was a success!
Great! When can I start drinking again?