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Evolution of HBs anti-bodies titers ans analysis of risk factors for Loss of seroprotection in patients transplanted from solid organs previously vaccinated against hepatitis B

Sophie Lejeune

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UNIVERSITÉ GRENOBLE ALPES

UFR DE MÉDECINE DE GRENOBLE

Année : 2020

**ÉVOLUTION DES TAUX D'ANTICORPS ANTI-HBS ET IDENTIFICATION
DES FACTEURS DE RISQUE DE PERTE DE LA SÉROPROTECTION CHEZ
LES TRANSPLANTÉS D'ORGANES SOLIDES PRÉALABLEMENT
VACCINÉS CONTRE L'HÉPATITE B**

THÈSE

PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

DIPLÔME D'ÉTAT

Sophie LEJEUNE

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ABREVIATIONS

ATG: *Antithymocyte globulins*

AZA: *Azathioprine*

BMI: *Body mass index*

CI: *Confidence interval*

HBcAb: *Anti-hepatitis B virus core antibodies*

HBsAb: *Anti-hepatitis B virus surface antigen antibodies*

HBsAg: *Hepatitis B virus surface antigen*

HBV: *Hepatitis B virus*

IQR: *Inter-quartile range*

IST: *Immunosuppressive therapy*

MMF: *Mycophenolate mofetil*

mTOR: *Mechanistic target of rapamycin*

SOT: *Solid organ transplantation*

RESUME

Introduction : La surveillance annuelle de la persistance de la protection vaccinale contre l'hépatite B est recommandée chez les transplantés d'organes solides (TOS). Sa persistance est toutefois méconnue au sein de cette population.

Méthodes : Nous avons analysé les données de 321 patients transplantés d'organe solide suivis dans notre centre entre 2009 et 2019, négatifs pour l'antigène anti-HBs et l'anticorps anti-HBc et présentant un taux d'anticorps HBs (AChBs) avant la greffe >10 IU/L (témoignant d'une vaccination contre l'hépatite B). Nous avons étudié la persistance des AChBs, et les facteurs associés à la persistance de la séroprotection.

Résultats : Après TOS, au cours du suivi (médiane 104 jours (interquartile range 92-381)) la perte de séroprotection (AChBs <10UI/L) était observée chez 90/321 (28,0%) patients. En analyse univariée, la transplantation hépatique, l'âge de plus de 50 ans lors de la greffe, l'indice de masse corporelle (IMC) de plus de 30 kg/m² lors de la greffe, les taux d'AChBs pré-transplantation inférieurs à 100UI/L, un traitement d'induction par ATG ou tacrolimus ou corticoïdes, et un traitement de maintenance par MMF ou corticoïdes étaient associés à la perte de la séroprotection. En analyse multivariée, l'organe transplanté, le taux d'Ac anti-HBs pré-transplantation et l'IMC étaient associés avec la persistance de la séroprotection : en effet, les transplantations rénale (HR 0,20 [IC95% 0,12; 0,34]), pulmonaire (HR 0,15 [IC95% 0,04; 0,50]) et cardiaque (HR 0,33 [IC95% 0,13; 0,83]) étaient associées à un risque moindre perte de la séroprotection que la transplantation hépatique (p<0,001) ; de même, ce risque était diminué pour les patients avec un taux d'AChBs avant la transplantation d'organes compris entre 100 et 300 UI/L (HR 0,32 [IC95% 0,18-0,60]) ou supérieur à 300 UI/L (HR 0,10 [IC95% 0,05-0,21]) par rapport à des taux inférieurs à 100 UI/L (p<0,001) ; enfin, les patients avec un IMC inférieur à 18 kg/m² présentaient un risque plus élevé de perte de la séroprotection (HR 3,28 [IC95% 1,42-7,61]) que les patients avec un IMC entre 18 et 30 (p=0,01).

Conclusion : Nous avons identifié des facteurs de risque de perte précoce de la protection vaccinale chez les patients vaccinés contre l'hépatite B avant la transplantation d'organe solide. La surveillance post-vaccinale doit être renforcée dans ces populations.

ABSTRACT

EVOLUTION OF HBs ANTI-BODIES TITERS AND ANALYSIS OF RISK FACTORS FOR LOSS OF SEROPROTECTION IN PATIENTS TRANSPLANTED FROM SOLID ORGANS PREVIOUSLY VACCINATED AGAINST HEPATITIS B

Background: Annual monitoring of the persistence of vaccine-induced protection against hepatitis B virus in solid organ transplanted (SOT) is recommended. However, the longevity of this protection is poorly characterized within this population.

Methods: We analysed the data of 321 solid organ transplanted patients, followed up in our centre between 2009 and 2019, negative for anti-HBs antigen and anti-HBc antibody and displayed a pre-transplant anti-HBs antibody (HBsAb) level >10 IU/L (reflecting hepatitis B virus vaccination). We explored the persistence of protective HBsAb titers and the factors associated with the loss of seroprotection (HBsAb <10UI/L).

Results: After SOT, during follow-up (median 104 days (interquartile range 92-381)), loss of seroprotection (HBsAbs <10UI/L) was observed in 90/321 (28.0%) patients. In univariate analysis, liver transplantation, age under 50 years and body mass index (BMI) under 30 kg/m² at time of transplantation, pre-transplantation HBs levels above 100UI/L, induction therapy with antithymocyte globulins, tacrolimus or corticosteroids and maintenance therapy with mycophenolate mofetil or corticosteroids were associated with loss of seroprotection. In multivariate analysis, kidney (HR 0.20 [CI95% 0.12; 0.34]), lung (HR 0.15 [CI95% 0.04; 0.50]) and heart (HR 0.33 [CI95% 0.13; 0.83]) transplantations were associated with delayed loss of seroprotection compared to liver transplantation (p<0.001), similarly, the risk of loss of seroprotection was lower for patients with pre-transplantation HBsAb levels between 100 and 300 IU/L (HR 0.32 [CI95% 0.18-0.60]) or above 300 IU/L (HR 0.10 [CI95% 0.05-0.21]) (p<0.001) compared to levels under 100 IU/L, lastly, patients with BMI under 18 kg/m² had a higher risk of loss of seroprotection (HR 3.28 [CI95% 1.42-7.61]) than patients with a BMI between 18 and 30 (p=0.01).

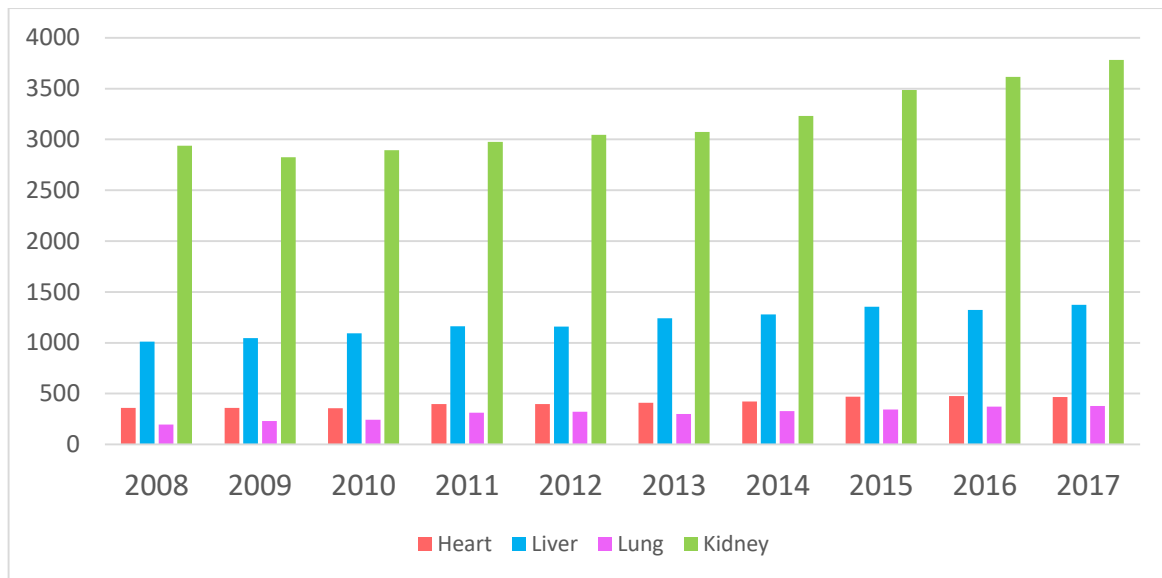
Conclusion: We identified risk factors of early loss of vaccine protection in vaccinated patients against hepatitis B prior to transplantation. Post-vaccination surveillance should be increased in these populations.

INTRODUCTION

- ***Solid-organ transplantation and infections***

In the last two decades, the number of solid-organ transplantation (SOT) has considerably increased with 139,024 solid-organ being transplanted worldwide in 2017. In France in 2017, 6,105 solid-organ transplantations were performed. Kidney transplants are the most frequent, followed by liver transplants then a minority of heart and lung transplants (figure 1). Overall, one-year and five-year post-transplantation survival rates are respectively about 90% and 70% thanks to the improvements of surgical and medical procedures. However, immunosuppressive therapy (IST) exposes SOT recipients to diverse risks, including infectious diseases, which can in addition trigger graft rejection (1). Infection risk in SOT recipients depends on the type of transplantation, the time since transplantation, and the type and intensity of immunosuppressive therapy (IST). Infections during the first month following transplantation are mostly due to bacteria and yeasts; infections developing afterward are tightly linked to IST-induced B and T cell deficiency (2).

Figure 1: Organ transplantation from 2008 to 2017 in France (Agence de Biomédecine)



- **Vaccine prevention**

Prophylaxis against infection relies on various means, including vaccination. Therefore, it is recommended to immunize SOT recipients against various diseases (both before and [for inactivated vaccines] after transplantation), including hepatitis B (HBV), a disease chronically affecting 257 million worldwide (3). Indeed, SOT recipients are at higher risk of Hepatitis B infection both in terms of frequency and gravity. In some countries with a high prevalence of hepatitis B, the incidence of *de novo* hepatitis B infection post-transplantation is higher than in the general population, ranging from 10% to 94% depending on the status of the donor (4,5). To prevent *de novo* HBV infection in liver transplant recipients receiving HBcAb (+) grafts, vaccination against HBV (in combination with lamivudin and/or hepatitis B immunoglobulins if HBsAb <1000 IU/L) is an effective strategy (6). In case of liver transplantation, *de novo* post-transplantation HBV infection is a major source of morbidity and mortality, with a higher risk of progression to chronic infection. It also leads to serious transplants

complications in 60% of the patients with graft loss (30%) or death (20%) (1). HBV vaccination in the general population is safe and effective in preventing HBV infection (7,8).

- ***Vaccine response***

- *General population*

Anti-HBs antibody levels can be routinely assessed with standardized methods; it is currently considered that a HBsAb titer above 10 IU/L is protective against hepatitis B virus infection based on vaccine efficacy studies (9,10). A primary three-dose vaccine series (0, 1, 6 month schedule, 20µg per injection) induces protective antibody concentrations in >90% of healthy children and young adults (11). 5 to 10% of healthy vaccinated subjects are non-responders (HBsAb <10 UI/l) or weak responders (HBsAb <100 UI/l). Older age, male sex, obesity, smoking, and injection into the buttock (instead of the deltoid or anterolateral side of the thigh in children) are risk factors leading to being non-responder (12).

- *Transplanted patients*

Vaccination before and after solid organ transplantation is likely to be less effective because of the underlying disease and the ongoing immunosuppression. Indeed, after a schedule using double doses of vaccination, only 55% to 76% of patients on haemodialysis with a kidney transplantation project and 30% to 50% of patients awaiting liver transplant develop protective anti-HBs titers (13). After transplantation, immunosuppressive therapy (ATG, glucocorticoids, azathioprine, MMF, cyclosporine, tacrolimus, rituximab) reduces B-cell and/or T-cell immune reactions (14) and the response rate to primary vaccination in immunocompromised organ transplant patients appears low. The response rate of primary immunisation in

patients vaccinated after liver transplant is 7-40% (15,16); similarly, poor antibody response rates are described in heart (13%), renal (36%) and lung (54%) transplant recipients (17–19). In a study among liver transplanted patients, renal function, age, regime of immunosuppression and time since transplantation did not modify the vaccine response to primary vaccination; but vaccine dose regimen had an impact (15).

Therefore, in 2014, the French High Council of Public Health recommended that patients with hepatic and renal failure should receive four injections of two doses (0, 1, 2, 6 months interval) of 20µg hepatitis B vaccine. In case of urgent transplantation, in the absence of anti-HBV immunity, it is recommended to vaccinate as early as possible transplant candidates (three injections of one dose in twenty-one days (0, 7, 21 days), followed by a booster twelve months later) (20).

- ***Duration of vaccine protection***

- *General population*

In the general population, among patients who had previously responded to the primary immunization series, fifteen years after 90.5% had anti-HBs antibody concentrations ≥ 10 IU/mL 60.3% ≥ 100 IU/mL (21), and thirty years after 51% still had HBsAb levels ≥ 10 IU/L (22).

- *Transplanted patients*

In addition to the low frequency of post-vaccinal seroconversion, the loss of long-term seroprotection appears to be more frequent in this population. However, data on long-term persistence of HBsAb during the post-transplantation period are limited, and derives from series with either a small number of patients or short-term follow-ups (23). Among kidney transplanted patients, this loss appears to be major during the first year following transplantation; 25% of patients had lost protective HBsAb titers. Protective

titers persisted for 33% of patients with initial post-vaccine HBsAb titers <100 IU/L at twelve month compared to 93% of patients with initial post-vaccine titer \geq 100 IU/L (24). Data on other vaccine-preventable diseases also show that long-term vaccine protection is reduced for solid organ recipients. Indeed, in liver and kidney transplant recipients, a much faster decline in antibodies was observed compared with healthy controls two years after vaccination with two doses of hepatitis A vaccine (25). Among kidney, liver and heart transplant recipients who received the 2009H1N1 influenza vaccine and had an adequate response measured 5 weeks after, only 32,9% maintained detectable antibody titers one year after vaccination, however without comparison to healthy subjects (26). Lastly, in a 2007 study, after 7 or 23-valent pneumococcal polysaccharide vaccine of kidney transplanted patients, among patients with anti-pneumococcal response to at least one serotype (defined as a twofold increase in titer from baseline and an absolute titer \geq 0.35 μ g/mL), the proportion of patients with persistence of their protection three years later was 57.4%; a strong post-vaccinal response was the only predictive factor of the durability of the seroprotection (27). The French High Council of Public Health recommended that transplant recipients should be tested annually for anti-HBs antibody titers. A booster injection is suggested when the titer falls below 10 IU/L (20).

Despite the indisputable contribution of vaccination for the prevention of infections in SOT recipients, few studies have explored the long-term immunogenicity of HBV vaccine in this population. Our study aims to determine the dynamics of HBsAb over time and to identify risk factors associated with the loss of protective HBV antibody levels after SOT in patients immunized before SOT.

METHODS

- ***Patients***

We conducted a retrospective monocentric study. We included in the study patients who had undergone a solid organ transplantation (heart, kidney, liver or lung) at the Grenoble-Alpes university hospital between 2009 and 2019, were over 18 years old at transplantation, and had been successfully vaccinated before receiving the transplant. The date and type of vaccination could not be collected because it was not always mentioned in the clinical records in retrospect. We therefore included patients:

- with a pre-transplantation HBsAb titer ≥ 10 IU/L,
- with serological assessment of HBV status and without HBV infection markers (HBc antibody, HBs antigen),
- and for whom two or more successive HBsAb titer measures had been performed, with at least one before and one after transplantation.

If a patient received a vaccine injection after transplantation, we did not include in the analysis the subsequent titers; moreover, we arbitrarily considered that the patients with an increase of HBsAb >100 UI/L between 2 measures may have received a booster injection, and similarly we did not include this second measure and the following in the analysis.

- ***Outcome analysis***

Data were collected by review of medical records. Patient data (e.g., age, gender, body mass index [BMI] at time of transplantation), details regarding solid organ transplantation (e.g., SOT date, type of transplant) and immunosuppressive therapy during the induction phase and the 6 months maintenance phase were collected. The

primary outcome was the loss of seroprotection, i.e. the decrease of HBsAb titer below 10 UI/L after SOT.

- ***Biological marker***

Serological analyses were performed by Enzyme immunoassay (VIDAS[®], Biomérieux[™]) in serum or ELFA (Enzyme Linked Fluorescent Assay) in plasma. Quantitative analysis of HBsAb titers were performed and qualitative assays for HBcAb and HBsAg.

- ***Ethics***

All patients had approved retrospective use of their medical data in the context of transplantation. This study was approved by the Clinical Research Delegation (DRCI) of Grenoble Alpes University Hospital.

- ***Statistics***

The different variables, demographic and biological, were described through descriptive statistics. The variable to be explained was categorised into two classes: persistence of HBsAb >10UI/L and loss of HBsAb >10UI/L. The others variables studied were categorised as follows: age at the time of SOT (< or ≥50 years), sex (male or female), type of transplant (liver, kidney, lung and heart), BMI (<18, 18–30, and >30 kg/m²) at the time of SOT, and immunosuppressive regimen (by molecules). Monitoring time since transplantation was kept as a continuous variable. We first describe the population characteristics. The comparison between quantitative variables was estimate with non-parametric Wilcoxon test. We than describe the patient characteristics associated with loss of seroprotection during follow-up. Survival distribution function was estimated using the Kaplan-Meier method; nonparametric log-rank test was used to compare the different groups. Patients were censored at the time

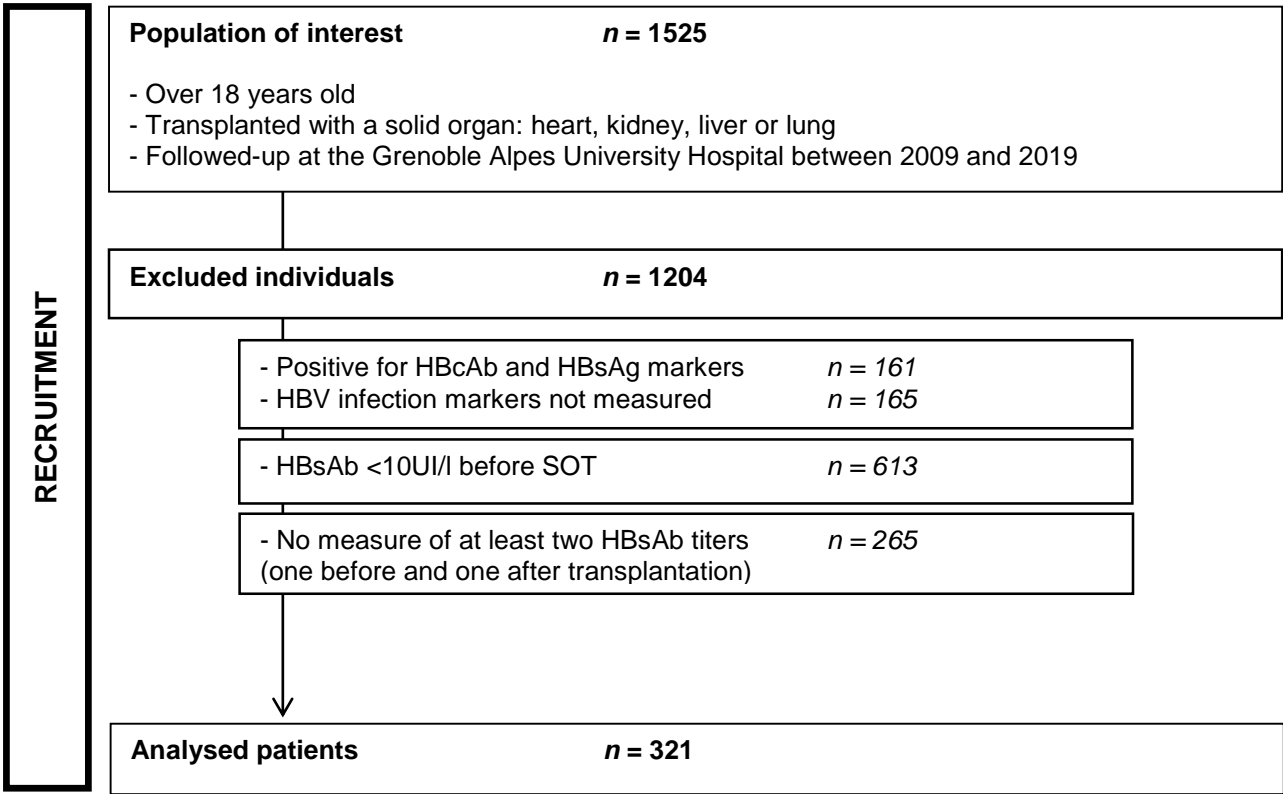
of the last assessment of HBsAb value. Then, a Cox model was elaborated to determine patient characteristics effects on seroprotection loss. The proportional hazards assumption of cox regression was tested with a Schoenfeld test. We relied on the literature and we selected the variables with $p < 20\%$ in the univariate analyses and then used a stepwise method to retain the variables in the final model (as risk factors for loss of seroprotection or confounding factors). We used a Wald test to test the models' coefficients. The risk of the first species α was fixed, by convention, at 5%. All the tests were carried out with bilateral hypotheses. For each of these tests, a value below the alpha risk threshold set at 5% ($p < 0.05$) was considered to be significant. Statistical analyses were carried out using the R software (version 4.0.0)(28).

RESULTS

• **Study population**

1525 transplanted patients received a solid-organ transplantation in our center between 2009 and 2019 (figure 2), among which 161 were positive for HBsAg and/or HBcAb and 165 were not tested, hence excluded. Among the 1199 HBsAg and HBcAb negative patients, 586 patients had HBsAb >10 IU/L before SOT, including 321 patients with HBsAb measured before and after transplantation and who did not receive a booster vaccination during their monitoring period.

Figure 2: Flow chart



HBV: Hepatitis B virus, HBcAb: Hepatitis B core antibody, HBsAg: Hepatitis B surface antigen, HBsAb: Anti-hepatitis B virus surface antigen antibodies, SOT: solid organ transplantation

The population finally included for analysis was not statistically different from the whole solid organ transplant population of the CHU Grenoble-Alpes between 2009 and 2019 regarding the ages and the transplanted organs (table 1).

Table 1: Characteristics of the SOT recipient population of the CHU Grenoble-Alpes and the analysed population

		Total SOT recipient population				Analysed patients			
		n	(%)	Age ^x		n	(%)	Age ^x	
				Median	(IQR)			Median	(IQR)
<i>All</i>		1525	(100)	54,8	(18.8)	321	(100)	52,48	(20.1)
Transplanted organ	Heart	92	(6.0)	50,3	(15.9)	14	(4.3)	41,5	(20.6)
	Liver	354	(23.1)	57,6	(13.1)	97	(30.2)	57,8	(12.9)
	Lung	85	(5.5)	56,3	(16.5)	13	(4.0)	50	(29.6)
	Kidney	1003	(65.4)	53,8	(22.0)	197	(61.4)	51	(21.8)

IQR: inter-quartile range, ^xage at the time of transplantation (years)

- **Characteristics of the patients**

Among the 321 patients, 204 (63.6%) were males and 117 (36.4%) females. Median age at time of SOT was 52 years (interquartile range (IQR 43-63)), 179 (55.8%) patients were older than 50 years (figure 3). Median BMI at time of SOT was 24.07 kg/m² (IQR 21.6-26.93) with 20 (6.2%) patients under 18 kg/m² and 47 above 30 kg/m² (14.6%). Kidney recipients (197, 61.4%) and liver recipients (97, 30.2%) were the most represented transplant recipients (figure 4).

Figure 3: Age distribution in men and women

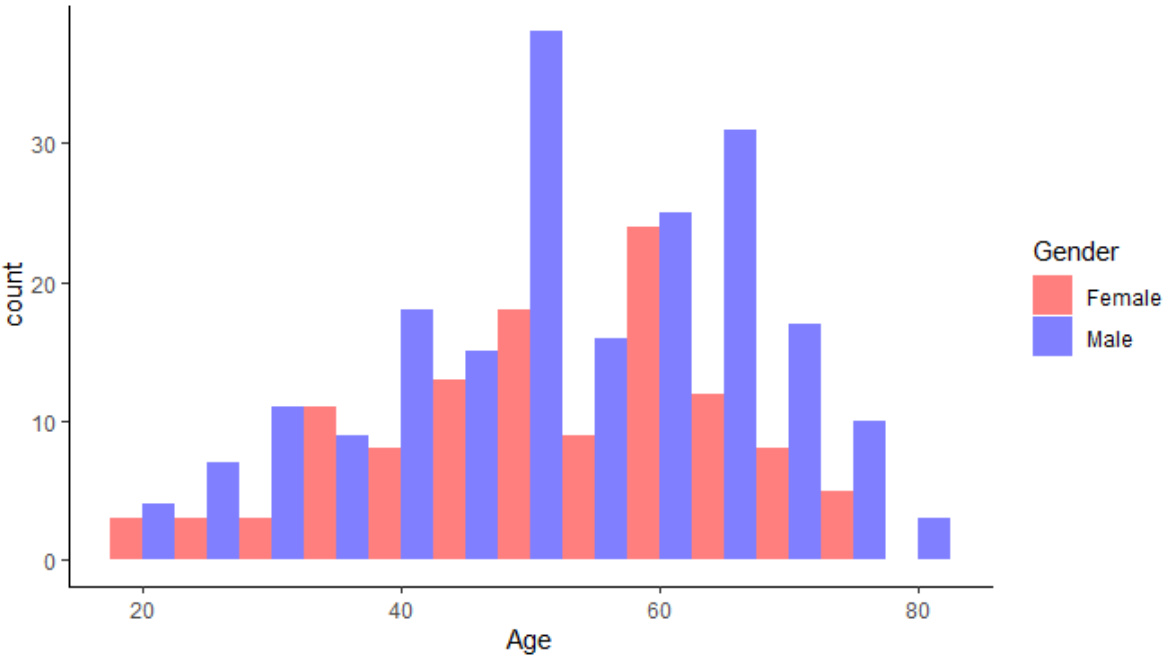
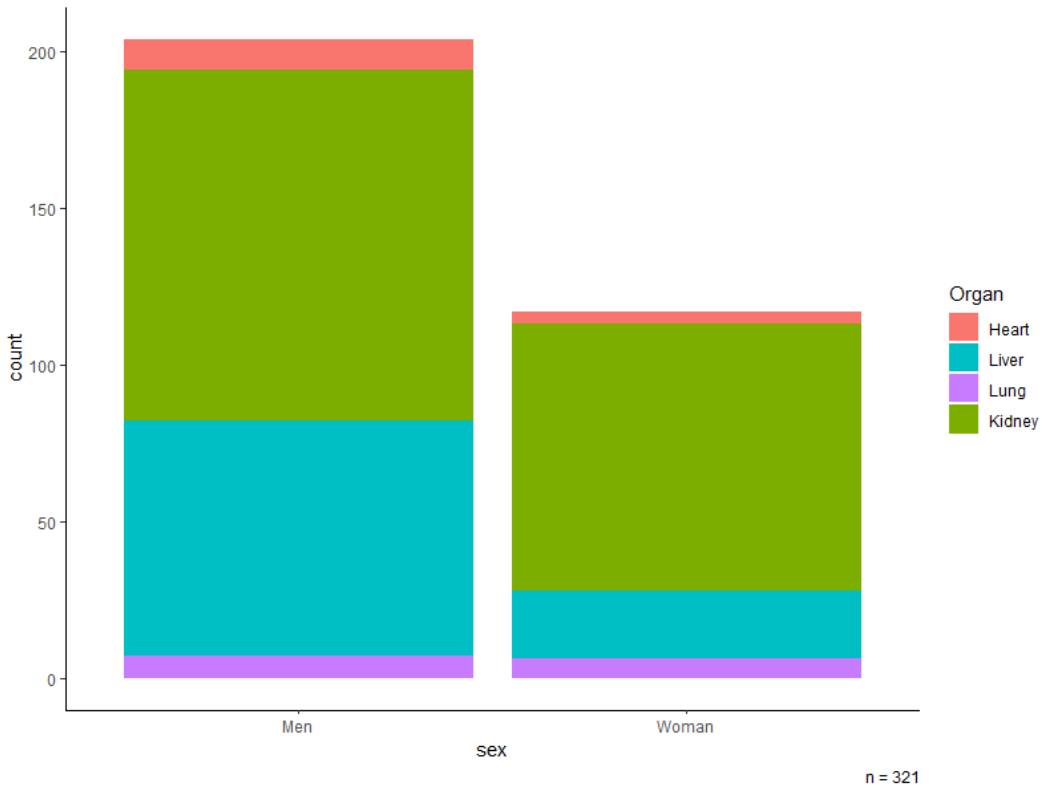


Figure 4: Distribution of the transplanted organs in men and women



n = 321

Characteristic of the patients by transplanted organ are described in table 2. Liver recipients were older than kidney recipients ($p=0.03$), than heart recipients ($p=0.001$), and no significantly than lung recipients ($p=0.1$). In addition, only 25/97 (25.8%) of liver recipients were younger than 50 years old, 99/197 (50.3%) of kidney recipients, 7/13 (53.8%) of lung recipients and 11/14 (78.6%) heart recipients. Liver recipients had a lower BMI than kidney recipients ($p=0.03$), and than lung recipients ($p=0.001$), but no than heart recipients ($p=0.2$). 1/14 (7.2%) of heart recipient patients were under 18 kg/m² at time of SOT, and respectively 2/13 (15.4%) of lung transplanted patients, 5/97 (5.2%) of liver transplanted patients, and 12/197 (6.1%) of kidney transplanted patients.

Table 2: Characteristics of the patients by transplanted organ

n = 321	Kidney n= 197		Liver n= 97		Lung n= 13		Heart n= 14	
Gender, n (%)								
Female	85	(43.1)	22	(22.7)	6	(46.2)	4	(28.6)
Induction IST, n (%)								
ATG	173	(87.8)	0	(0.0)	5	(38.5)	0	(0.0)
basiliximab	22	(11.2)	0	(0.0)	2	(15.4)	0	(0.0)
ciclosporine	0	(0.0)	0	(0.0)	0	(0.0)	13	(92.9)
tacrolimus	192	(97.5)	97	(100.0)	0	(0.0)	1	(7.1)
MMF	174	(88.3)	97	(100.0)	0	(0.0)	12	(85.7)
mTOR	22	(11.2)	0	(0.0)	0	(0.0)	0	(0.0)
corticosteroide	0	(0.0)	97	(100.0)	0	(0.0)	13	(92.9)
Maintenance IST, n (%)								
ciclosporine	3	(1.5)	10	(10.9)	1	(7.7)	2	(14.3)
AZA	2	(1.0)	2	(2.2)	1	(7.7)	0	(0.0)
tacrolimus	190	(98.4)	75	(81.5)	12	(92.3)	12	(85.7)
MMF	155	(80.3)	54	(58.7)	12	(92.3)	13	(92.9)
mTOR	17	(8.8)	12	(13.0)	4	(30.8)	3	(21.4)
corticosteroide	171	(88.6)	5	(5.4)	12	(92.3)	9	(64.3)
Age at SOT, median (IQR)								
	51.98	(41.1-62.9)	57.79	(50.5-63.4)	49.98	(34.2-63.8)	41.46	(29.4-50.1)
HBsAb pre SOT, median (IQR)								
	206.5	(55.0-1000.0)	88.4	(33.8-350.1)	103.8	(27.6-1000.0)	287.1	(44.4-716.5)
BMI, median (IQR)								
	23.96	(21.7-26.4)	24.690	(22.5-28.4)	19.29	(18.3-23.5)	23.41	(19.2-26.7)

SOT: Solid organ transplantation, HBsAb: anti-Hepatitis B surface antigen antibody IST: Immunosuppressive therapy, BMI: body mass index, ATG: antithymocyte globulins, MMF: mycophenolate mofetil, AZA: Azathioprine, mTOR: mechanistic target of rapamycin, IQR: interquartile range

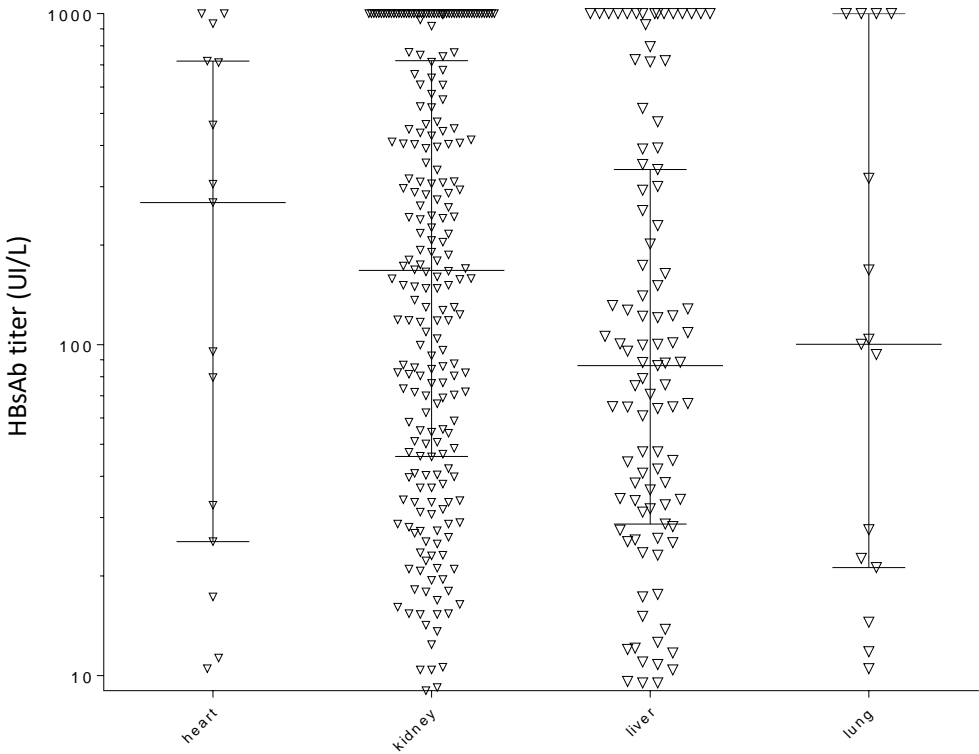
- **HBsAb titers**

- *Pre-transplantation titers*

In the pre-transplantation period, the median level of HBsAb was 151.0 IU/L (IQR 44.7-725.8); 133/321 patients (41.4%) had pre-transplantation titers under 100 IU/L and 122/321 (38.0%) above 300IU/L. Liver transplant recipients had lower pre-transplanted HBsAb with a median of 88.4 IU/L (IQR 33.8-350.1), compared to 206.1 IU/L (IQR 55.0-1000.0) for kidney recipients ($p=0.001$), 287.1 IU/L (IQR 44.4-716.5) for heart recipients (not significant: $p=0.3$), and 103.8 IU/L (IQR 27.6-1000.0) for lung transplanted patients (not significant: $p=0.4$) (table 2 and figure 5).

51/97 (52.6%) of liver transplanted patients had pre-transplantation HBsAb levels lower than 100IU/L and 27/97 (27.8%) over 300IU/L, and respectively 71/197 (36.0%) and 83/197 (42.1%) of kidney transplant recipients, 6/14 (42.8%) and 7/14 (50.0%) of heart transplant recipients, and finally 5/13 (38.5%) of lung transplant recipients had lower than 100IU/L HBsAb and the same proportion over 300IU/L.

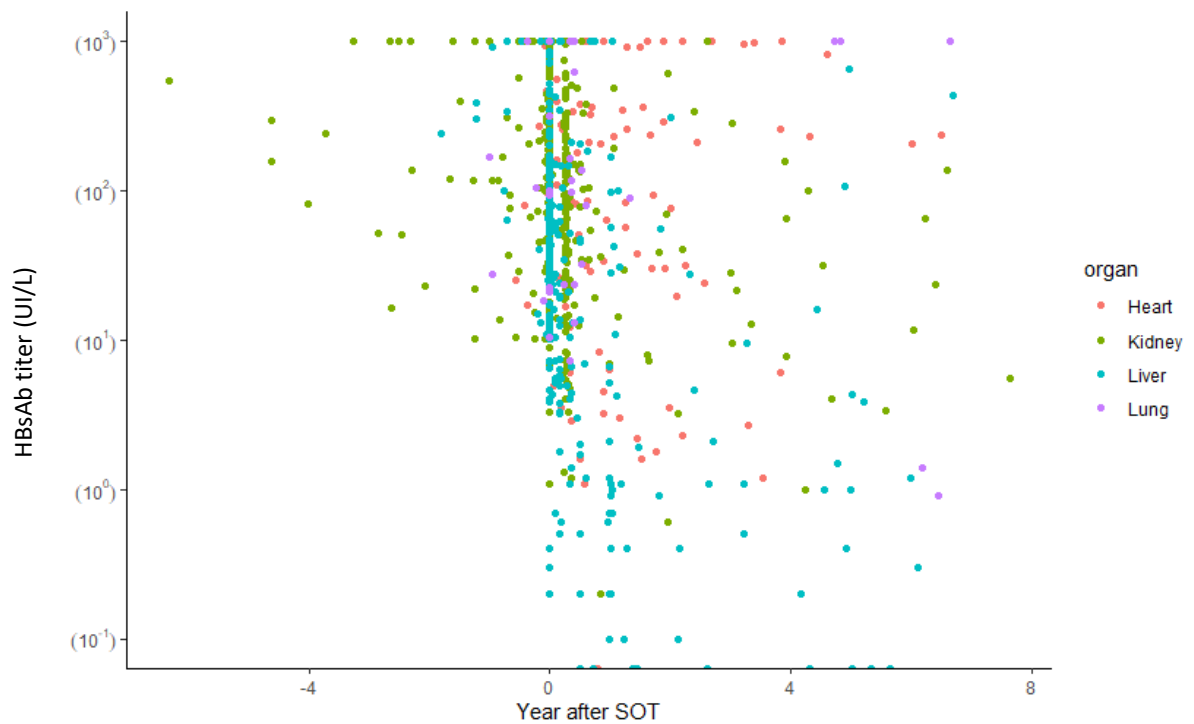
Figure 5: Pre-transplantation HBsAb titer (UI/L) distribution in transplanted organ



○ *Follow-up*

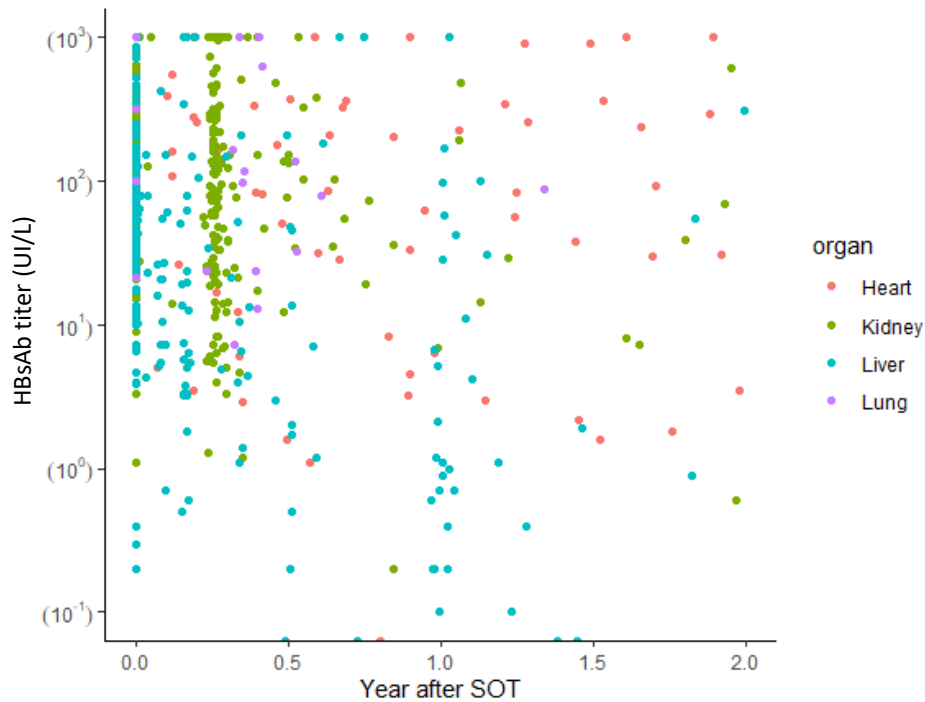
The median time of HBsAb titers monitoring after transplantation was 104 days (IQR 92-381). It was shorter for kidney recipients (97 days, IQR 92-146), compared to 151 days (IQR 130-1725) for lung ($p < 0.001$), 357 days (IQR 57-665) for liver ($p = 0.02$) and 749 days (IQR 499-1201) for heart ($p < 0.001$) (figure 6 and 7).

Figure 6: Analysed of HBsAb value (UI/L) over time



(10 HBsAb values (=0UI/L) are not represented due to the logarithmic ordinate scale), HBsAb: anti-Hepatitis B surface antigen antibody

Figure 7: Analysed of HBsAb value (UI/L): focused on the 2 years post-transplantation follow-up

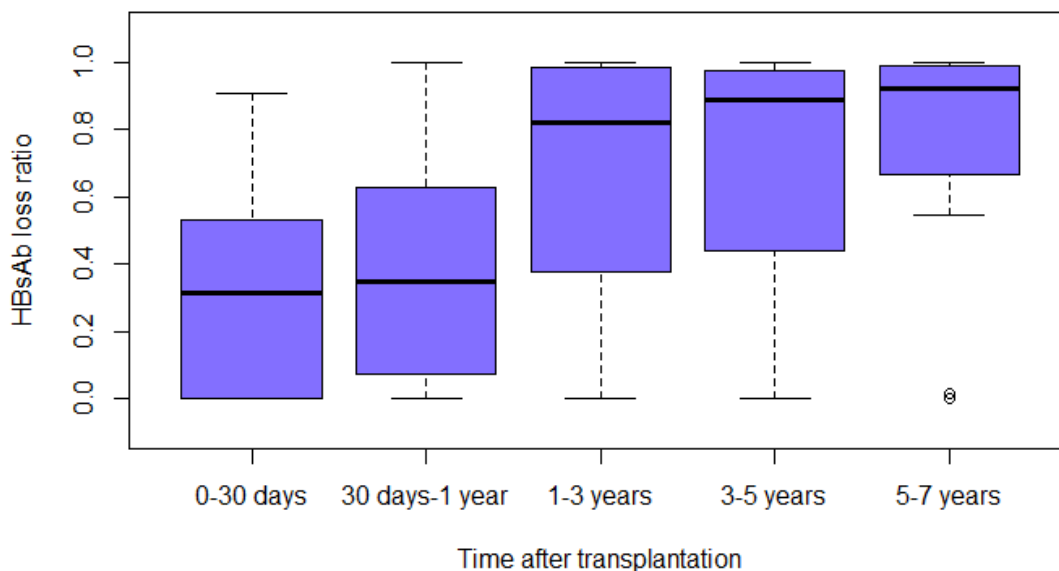


HBsAb: anti-Hepatitis B surface antigen antibody

- *Quantitative loss of HBsAb*

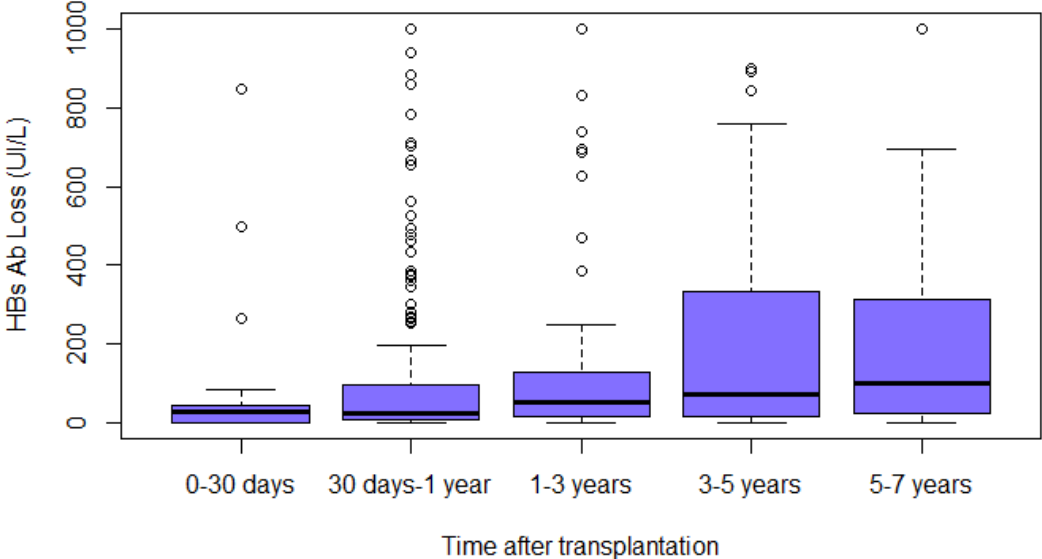
During the first 30 days after SOT, patients had lost in median 31.5% (IQR 0.00-0.52) of their pre-transplantation HBsAb titers, 34.6% (IQR 0.07-0.62) between 30 days and 1 years after SOT and 81% (IQR 0.37-0.98) between 1 and 3 years after SOT (figure 8). In absolute value, compared to pre-transplantation HBsAb, this represents a median loss of 27.1 UI/L (IQR 0.00-41.4) during the first 30 days, 22.6 UI/L (IQR 4.7-96.0) between the 30th day and 1 years post SOT and 49.15 UI/L (IQR 13.55-125.15) between 1 and 3 years (figure 9). Therefore, HBsAb titers decrease was major in the first years post transplantation.

Figure 8: Ratio between HBsAb loss and pre-transplantation HBsAb level according to the time interval since transplantation



HBsAb: anti-Hepatitis B surface antigen antibody

Figure 9: Median HBsAb loss (UI/L) according to time after transplantation



HBsAb: anti-Hepatitis B surface antigen antibody

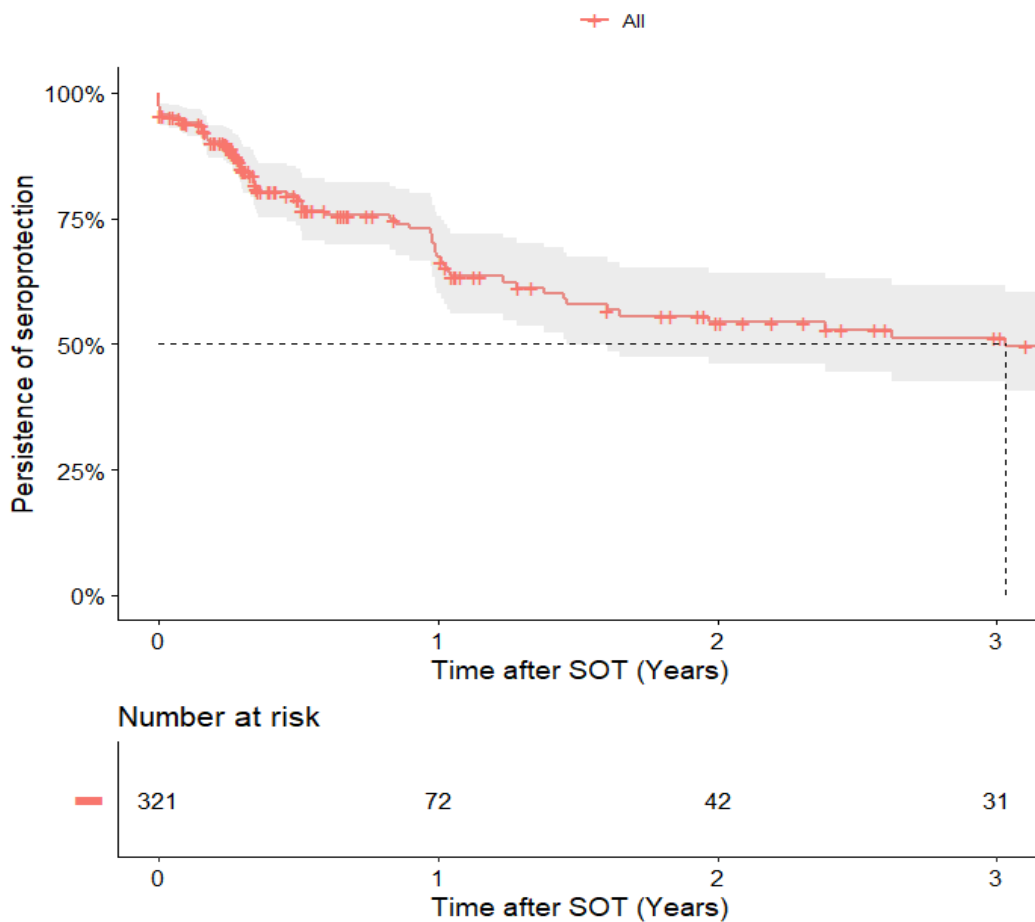
- **Seroprotection loss (HBsAb <10UI/L)**

- *Time to seroprotection loss*

Seroprotection loss (HBsAb <10UI/L) during the post-SOT monitoring time was observed in 231/321 (72%) patients. So there was 28.0% of the patients presenting a loss of protection during the follow up time.

Interval of time between transplantation and loss of seroprotective HBsAb titer was estimated by Kaplan-Meier estimator. Overall, the cumulative probability of maintaining seroprotection 1, 2 and 5 years after the transplantation was respectively: 67.3% (IC 95% 0.601-0.754), 54.3% (IC 95% 0.46-0.642) and 33.3% (IC 95% 0.235-0.47). The median of time of seroprotection persistence was about 3 years (1106 days) (IQR 533-1666) (figure 10).

Figure 10: Probability of maintaining seroprotection over time



- **Risk factors of seroprotection loss after SOT**

- *Univariate analysis*

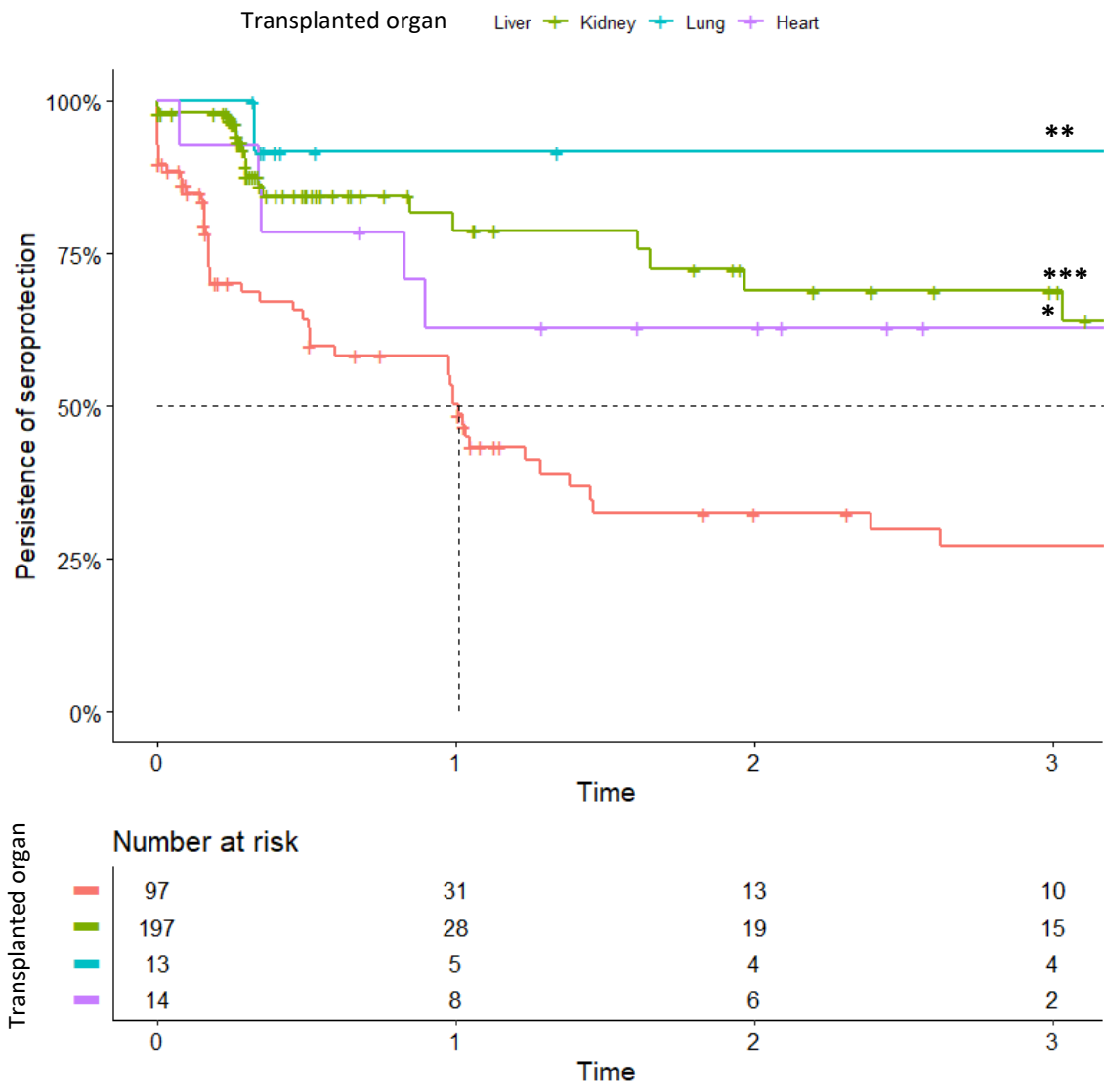
In univariate analysis (table 3) we explored factors associated with seroprotection loss (HBsAb <10UI/L) after transplantation.

- Transplanted organ

Kidney, lung and heart recipients were significantly less at risk of seroprotection loss compared to livers recipients with a hazard ratio (HR) of 0.26 [CI95% 0.16; 0.42] ($p<0.001$) for kidney recipients, 0.18 [CI95% 0.06; 0.60] ($p<0.001$) for lung recipients, and 0.33 [CI95% 0.13; 0.85] ($p<0.001$) for heart recipients.

The median duration of seroprotection was also significantly shorter in the liver transplant recipients than in other transplants group (368 days for liver, versus 1703 days for kidney ($p<0.001$), 2357 days for lung ($p<0.001$), not reached for heart ($p=0.02$)). The proportion of patients for whom seroprotection was persistent at one year was 50% [CI95% 0.39-0.63] for liver transplant recipients, 79% [CI95% 0.69-0.90] for kidney recipients, 91% [CI95% 0.77-0.95] for lung recipients and 63% [CI95% 0.42-0.95] for heart recipients (figure 11).

Figure 11: Kaplan-Meier estimates of the loss of seroprotection after SOT by transplanted organ



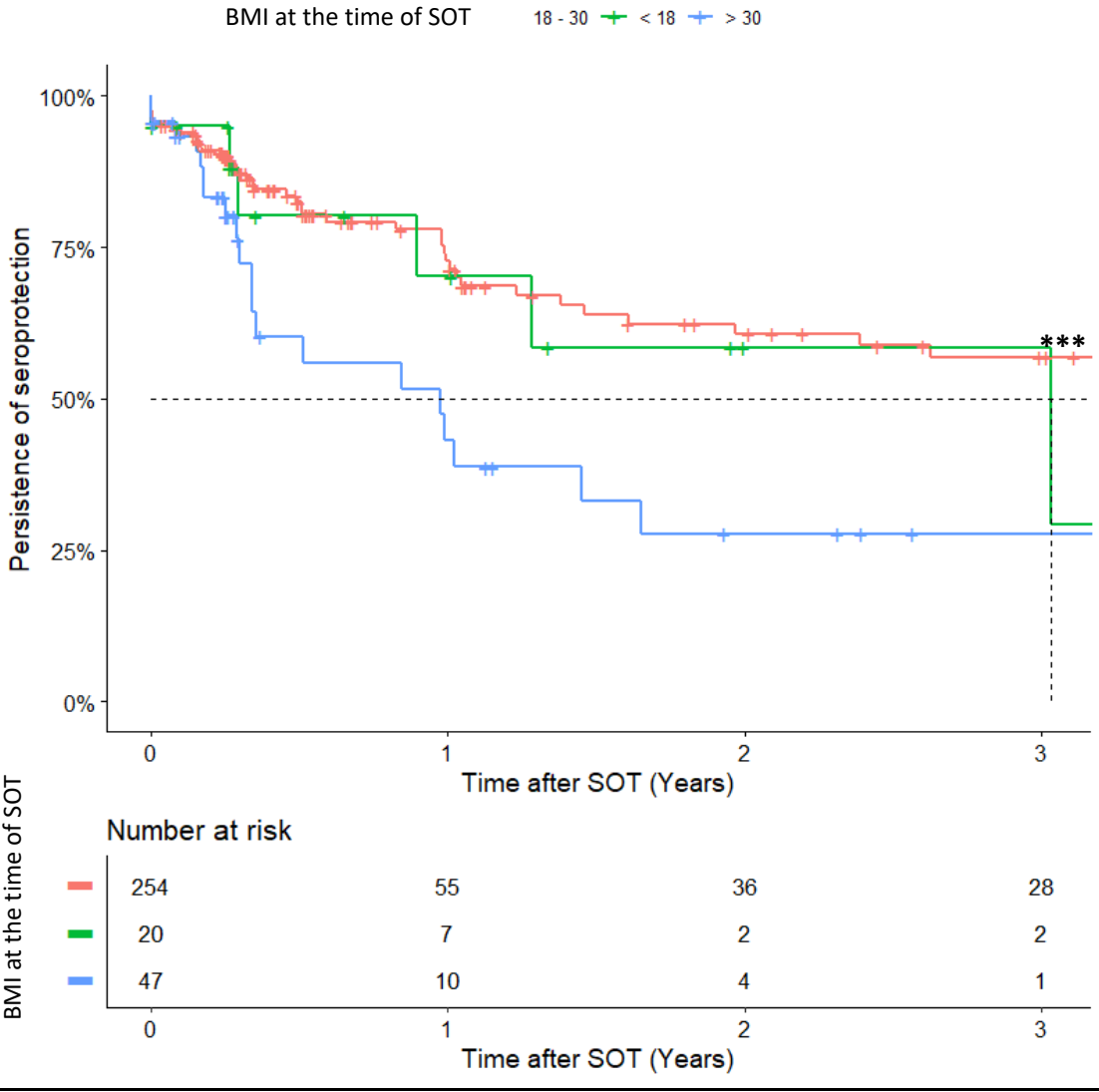
by stratified log-rank test, * p<0.001, **p<0.01, *p<0.05 (p-value for the difference between liver transplantation and each of the other organ transplantation)*

- **BMI**

BMI above 30 kg/m² at the time of SOT was significantly associated with seroprotection loss compared with a BMI between 18 and 30 kg/m² (HR 2.50 [CI95% 1.50; 4.16], p=0.002). Conversely, having a BMI <18 kg/m² was not significantly

associated with the loss of seroprotection (HR 1.39 [CI95% 0.63; 3.40]). The proportion of patients for whom seroprotection was persistent at one year was 73% [CI95% 0.42-0.65] for the patients with BMI between 18-30 kg/m², 70% [CI95% 0.48-1.00] for the patients with a BMI under 18 kg/m², and 43% [CI95% 0.1-0.28] for those with BMI above 30 kg/m² (figure 12).

Figure 12: Kaplan-Meier estimates of loss of seroprotection after SOT according to BMI at time of SOT

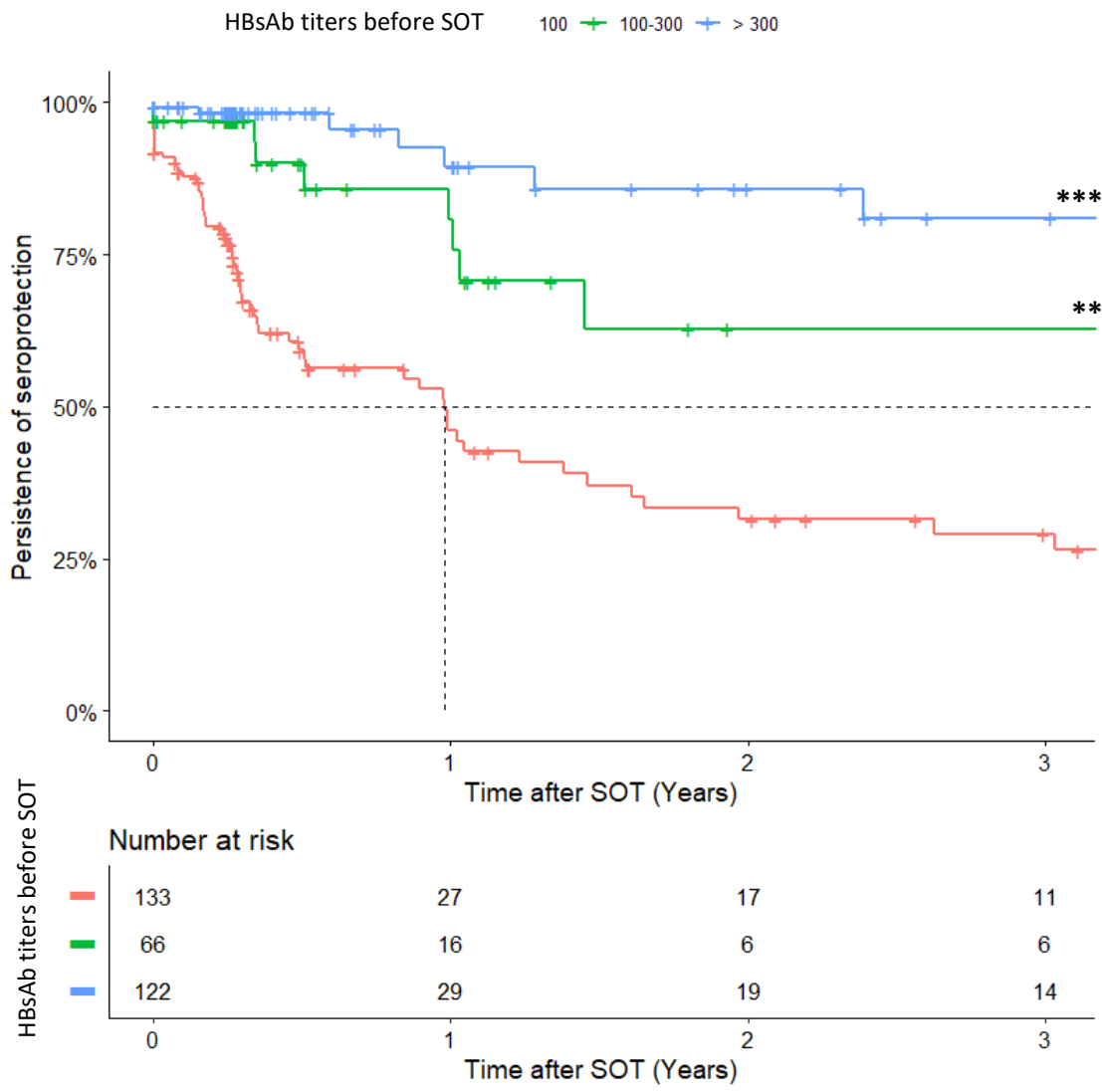


* by stratified log-rank test, *** p<0.001, **p<0.01, *p<0.05 (p-value for the difference between BMI 18-30 and each category), BMI: body mass index (kg/m²), SOT: solid organ transplantation

- *HBsAb titers before transplantation*

HBsAb titers before transplantation were associated with the risk of seroprotection loss. Indeed, HBsAb titers between 100-300 UI/L and HBsAb >300UI/L were associated with a lower risk of seroprotection loss versus HBsAb titers before transplantation under 100 UI/L (respectively HR 0.41 [CI95% 0.23; 0.73], HR 0.14 [CI95% 0.07; 0.28], $p < 0.001$). Moreover, 81% [CI95% 0.67-0.97]) of the patients with HBsAb titers between 100 and 300 UI/L maintained a seroprotection at one year after transplantation, as well as 89% [CI95% 0.80-1.00] of patients with HBsAb above 300UI/L; conversely, only 46% [CI95% 0.36-0.59] of patients with HBsAb under 100 UI/L before transplantation maintained HBsAb levels >10UI/L one year after SOT (figure 13).

Figure 13: Kaplan-Meier estimates of the loss of seroprotection after SOT by pre-transplant HBsAb value



* by stratified log-rank test, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ (p-value for the difference between HBsAb <100 and each category) HBsAb: Anti-hepatitis B virus surface antigen antibodies (UI/L), SOT: solid organ transplantation

- *Additional factors*

Being over 50 years at the time of transplantation versus younger was associated with seroprotection loss in univariate analysis (HR 2.36 [CI95% 1.49; 3.73], $p < 0.001$).

The use of tacrolimus during the induction immunosuppressive therapy was associated with a higher risk of loss of seroprotection (HR 2.19 [CI95% 1.05; 4.57], $p=0.04$); conversely, use of antithymocyte globulins (ATG) during the induction immunosuppressive therapy was protective against seroprotection loss (HR 0.40, [CI95% 0.25; 0.642], $p=0.001$). The use of MMF in maintenance immunosuppressive therapy was also protective against seroprotection loss (HR 0.49 [CI95% 0.32; 0.76], $p=0.01$). Interestingly, the use corticosteroids in maintenance therapy was protective (HR 0.31 [CI95% 0.21; 0.50], $p<0.001$) while its use during the induction phase of IST was associated with a higher risk of loss of protection (HR 3.51 [CI95% 2.22; 5.53], $p<0.001$).

Table 3: Patient characteristics distribution according to seroprotection loss or persistence after SOT and risk factors of seroprotection loss in univariate and multivariate analysis with Cox regression

<i>n</i> = 321	HBsAb >10 UI/L		HBsAb <10 UI/L		Univariate			Multivariate		
	<i>n</i> = 231	71.9%	<i>n</i> = 90	28.1%	HR [§]	95% CI	p-value*	HR [§]	95% CI	p-value*
Gender										
Male	141	61.0	63	70.0	1			-	-	
Female	90	39.0	27	30.0	1.01	[0.63 ; 1.58]	1.0	-	-	
Transplanted organ										
Liver	171	74.1	26	28.9	1			1		
Kidney	41	17.7	56	62.2	0.26	[0.16 ; 0.42]	<0.001	0.20	[0.12 ; 0.34]	<0.001
Lung	10	4.3	3	3.3	0.18	[0.06 ; 0.60]		0.15	[0.04 ; 0.50]	
Heart	9	3.9	5	5.6	0.33	[0.13 ; 0.85]		0.33	[0.13 ; 0.83]	
Age at the time of SOT (Years)										
<50	112	48.5	30	33.3	1			-	-	
>50	119	51.5	60	66.7	2.36	[1.49 ; 3.73]	<0.001	-	-	
Pre-transplant HBsAb value (UI/L)										
<100	67	29.0	66	73.3	1			1		
100-300	52	22.5	14	15.6	0.41	[0.23 ; 0.73]	<0.001	0.32	[0.18 ; 0.60]	<0.001
300-1000	112	48.5	10	11.1	0.14	[0.07 ; 0.28]		0.10	[0.05 ; 0.21]	
BMI at the time of SOT (kg/m²)										
18 - 30	192	83.1	62	68.9	1			1		
<18	13	5.6	7	7.8	1.39	[0.63 ; 3.40]	0.002	3.28	[1.42 ; 7.61]	0.01
>30	26	11.3	21	23.3	2.50	[1.50 ; 4.16]		1.39	[0.83 ; 2.34]	
Induction IST										
ATG	151	65.4	27	30	0.40	[0.25 ; 0.642]	0.001	-	-	
basiliximab	23	10.0	1	1.1	0.21	[0.03 ; 1.45]	0.1	-	-	
ciclosporine	8	3.5	5	5.6	0.71	[0.29 ; 1.77]	0.5	-	-	
tacrolimus	208	90.0	82	91.1	2.19	[1.05 ; 4.57]	0.04	-	-	
MMF	199	86.1	84	93.3	2.21	[0.96 ; 5.10]	0.06	-	-	
mTOR	20	8.7	2	2.2	0.67	[0.16 ; 2.76]	0.6	-	-	
corticosteroide	49	21.2	61	67.8	3.51	[2.22 ; 5.53]	<0.001	-	-	
Maintenance IST										
ciclosporine	11	4.9	5	5.9	1.16	[0.47 ; 2.90]	0.7	-	-	
AZA	3	1.2	2	2.2	1.12	[0.27 ; 4.60]	0.9	-	-	
tacrolimus	208	93.3	81	91	0.94	[0.45 ; 1.95]	0.9	-	-	
MMF	176	78.9	58	65.2	0.49	[0.32 ; 0.76]	0.002	-	-	
mTOR	28	12.6	8	9.0	0.72	[0.35 ; 1.51]	0.4	-	-	
corticosteroide	166	74.4	31	34.8	0.31	[0.21 ; 0.50]	<0.001	-	-	

* by Wald test, - Not included in multivariate model (not significant influence), SOT: solid organ transplantation, HBsAb: Hepatitis B surface antibody, IST: Immunosuppressive therapy, BMI: body mass index, ATG: antithymocyte globulins, MMF: mycophenolate mofetil, AZA: Azathioprine, mTOR: mechanistic target of rapamycin

- ***Risk factors of seroprotection loss after SOT: Multivariate analysis***

In order to better understand the factors contributing to the observed seroprotection loss amongst transplanted patients, we developed a Cox regression model (table 3 and figure 14).

- *Transplanted organ*

When adjusting the analysis on BMI at time of SOT and pre transplantation HBsAb titers, liver recipients lost earlier their seroprotection than kidney, lung and heart recipients (respectively to HR 0.20 [CI95% 0.12; 0.34]), HR 0.15 [CI95% 0.04; 0.50] and HR 0.33 [CI95% 0.13; 0.83], $p < 0.001$ for each). Liver transplantation was associated with an increased risk of seroprotection loss compared to kidney recipients (HR 4.96, CI95% [2.98-8.25], $p < 0.001$). Conversely, lung transplantation and heart transplantation were not significantly associated with seroprotection loss versus kidney transplantation (respectively, HR 0.73 [CI95% 0.21- 2.49] and HR 1.61 [CI95% 0.61- 4.28] $p < 0.001$).

- *Pre-transplantation HBsAb titers*

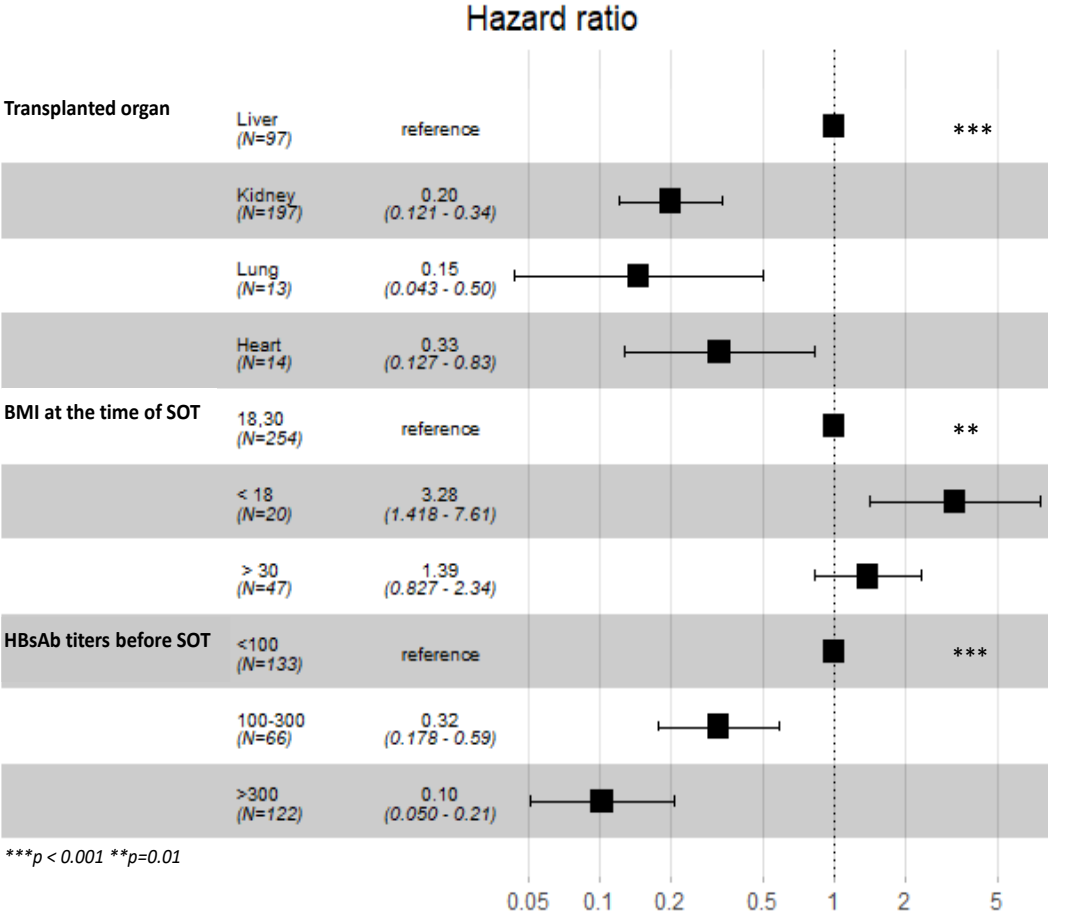
After adjustment on transplanted organ group and BMI at SOT, pre-transplantation HBsAb titers between 100 and 300 UI/L or above 300 UI/L were significantly associated with a decreased risk of seroprotection loss compared with HBsAb titers under 100 UI/L (respectively HR 0.32 [CI95% 0.18-0.60]) and HR 0.10 [CI95% 0.05- 0.21], $p < 0.001$).

- *BMI*

After adjustment on transplanted organ and pre-transplant HBsAb titer, having a BMI at the time of SOT under 18 kg/m² was significantly associated with an increased risk of seroprotection loss, compared to a BMI between 18 and 30 kg/m² (HR 3.28,

[CI95% 1.42-7.61], p=0.01). While BMI above 30 kg/m² was associated in univariate analysis with seroprotection loss compared with a BMI between 18-30 kg/m², this difference was no longer significant after adjustment (HR 1.39 IC95% [0.83; 2.34]).

Figure 14: Forest plot for Cox model: Hazard Ratio for seroprotection loss



SOT: Solid organ transplantation, HBsAb: Hepatitis B surface antibody, IST: Immunosuppressive therapy, BMI: body mass index, ATG: antithymocyte globulins, MMF: mycophenolate mofetil, AZA: Azathioprine, mTOR: mechanistic target of rapamycin

DISCUSSION

Through this large retrospective cohort study we collected data on 321 solid organ transplant recipients between 2009 and 2019 vaccinated against HBV before transplantation. We described the evolution of HBsAb titers, aiming to identify the factors associated with the seroprotection loss (HBsAb <10UI/L).

We observed that 28.0% (90/321) of patients lost this seroprotection during follow-up, with a median time from SOT of 104 days (IQR 92-381); this proportion was 19.3% (62/321) at 1 year and 23.1% (74/321) at 2 years post-transplantation. In our study, the highest risk of loss of seroprotection was in the first 30 days post transplantation. The probability to maintain seroprotection one year after transplantation was 67% (95% CI 0.60-0.75) and 50% (IC 95% 0.41-0.63) three years after SOT. In our cohort, protective antibody levels decrease over time, with the steepest decline in the immediate aftermath of the transplantation, and a slower diminution afterwards. The highest rates of antibody loss were observed immediately after transplantation. Patients had lost 34.0% of their pre-transplantation HBsAb levels 30 days after transplantation and 81.0% at 3 years. This observation may be linked to a vaccination or a booster dose injected just before the first pre-transplantation dosage analysed; indeed, some authors have described a rapid anti-HBs titre decay in the first months after primary vaccine schedule or booster and much slower afterward (29,30). It would also be interesting to know whether patients with very high levels of antibodies benefited from a complete vaccination schedule shortly before their transplant due to a lack of previous immunity or a vaccination booster, in order to adjust our result on these variables.

Although our data are limited, these results show that it is necessary to closely monitor the HBsAb titers during the first years post-transplantation, in order to propose a boost injection if needed. This loss of protection is consistent with the literature. Indeed, some studies (15,31) reported that among patients vaccinated before a liver transplantation, more than 30% lost their seroprotection during the post-transplant follow-up period. Moreover, in a retrospective cohort of kidney recipients vaccinated before transplantation, 25% of patients lost their protective anti-HBsAb titers during the year after SOT (24).

We have identified clinical risk factors (liver transplantation, pre-transplantation HBsAB titers $<100\text{UI/L}$, and BMI under 18 kg/m^2) associated with the increased loss of protective antibodies in multivariate analyses. To our knowledge, the impact of the type of transplanted organ had not been evaluated regarding the persistence of long-term protection after HBV vaccination. Data from studies on vaccination against other pathogens are also limited on this point; one study describes a decreased persistence of vaccine protection against hepatitis A in kidney transplantation compared to liver transplantation (32). Thus, further studies are needed. The authors of this hepatitis A study suspected a negative impact of ciclosporin A (principally used for kidney transplant recipients, versus tacrolimus in liver transplant recipients). The population of solid organ transplant recipients is heterogeneous with different immunosuppressive regimens depending on the type of transplant. However, the association between the type of transplanted organ and the persistence of seroprotection in our study is not explained by the immunosuppressive regimen. Indeed, despite the fact that some immunosuppressive schedules are associated with seroprotection loss in univariate analysis, this association is not reproduced after adjustment on transplanted organ, HBsAb titer before SOT and BMI. A lack of statistical power cannot be excluded due

to the disparity in patient treatments, leading to a small number of patients in some IST categories. In addition, we collected data on maintenance therapy only during the first 6 months post SOT and it is possible that more precise data on the immunosuppressive regimen and IST plasmatic dosages may show an association.

The association between the transplanted organ and seroprotection persistence could also be explained by characteristics that we were not able to collect in our retrospective work. Transplanted patients have heterogeneous comorbidities (33,34). Moreover, the disease that led to the SOT can be associated with heavy pre-transplantation IST (35,36), which could influence the seroprotection persistence.

Moreover, this difference in risk could be linked to the intrinsic immune role of the organ transplanted. More so than other solid organs that are transplanted, the liver, as an immunologically active organ, interacts with and thereby modulates the host immune response: it is an important organ for maintaining the systemic homeostasis of T lymphocytes and regulating their apoptosis, it is the site of complex immune mechanisms maintaining a state of immune tolerance while being able to deploy an effective response against external pathogens (37). The assay of immunological markers could be of interest to better characterise the risk factors associated with the persistence of seroprotection. HbsAb titers are only one component of the immune response to vaccines (38). It is used as a proxy marker for protection. To measure the long-term response to HBV vaccine, others studies used in vitro B and T cell activity testing, and show that HBV protection could be present despite a decrease in anti-hepatitis B surface antibodies over time (39). Immunological mechanisms are complex during transplantation, and cellular response may play a role in the protection

conferred by vaccines; it would therefore be interesting to use other methods to comprehensively assess the immune protection in organ transplant patients.

In our cohort, the higher the antibody level is during the pre-transplant period, the longer the seroprotection is maintained. This observation is consistent with the literature in the general population. Different mathematical models are proposed to describe the dynamics of HBsAb levels. Best fits to calculate the antibody decay are found with bi-logarithmic functions, emphasizing the role of initial HBsAb titers (determined after completing the vaccination protocol) on the evolution over time (30). Our data suggest that it is important to obtain antibody levels above 100 IU/L in transplantation candidates.

The impact of low BMI in patient with seroprotection loss could be explained by the relationship between nutrition and the immune functions (40). However, reviews on the immune function in children with malnutrition underlines the great heterogeneity of the data but suggested (except for severely malnourished children) that malnutrition has globally little or no effect on vaccine responses (41,42). Obesity is reported as a risk factor for lower levels of HBsAb after vaccination in the general population (43). In our study, patients with BMI >30 kg/m² have indeed lower pre-transplantation HBsAb titers, and were more likely to lose seroprotection in univariate analysis, but this association disappeared after adjustment on the initial antibody level and the type of organ transplanted.

Our study has several limitations. First, due to its retrospective nature, we were unable to collect information on the vaccination schedule and dose; at least, we know that all our patients were well vaccinated against hepatitis B since pre-transplantation HBs antibody levels were higher than 10UI/L and negative infection markers were

assessed. Secondly, follow-up time was heterogeneous. Since the risk of loss of protection rises with time, we used a Cox model to take into account these different follow-up times. Thirdly, we have including patients transplanted very recently, in order to obtain a better homogeneity of clinical practices (e.g. in terms of vaccination and immunosuppressant regimes). However, this lead for some patients to a very short follow-up times resulting in a lot of non-informative censoring.

Finally, due to the constant evolution of solid organ transplant management and new vaccine possibilities (like new adjuvants and DNA vaccine with the aims of higher seroconversion rates and longer persistence of seroprotection (44,45)), studies on the long-term persistence of seroprotection in these populations are necessary. They will allow to offer more appropriate monitoring for at-risk patients.

CONCLUSION

Although our data are limited, these results show that it is necessary to closely monitor the HBsAb titers during the first year post-transplantation, not to miss a need for a boost injection, particularly in the liver transplant population, patients with a BMI under 18 kg/m² and organ transplant patients who had antibody levels under 100UI/L prior to transplantation. It is therefore necessary to strive to obtain the highest possible antibody levels before transplantation, using a double-dose vaccination regimen and additional doses if necessary, in order to limit the risk of seroprotection loss after transplantation.

THÈSE SOUTENUE PAR : LEJEUNE SOPHIE

TITRE : ÉVOLUTION DES TAUX D'ANTICORPS ANTI-HBS ET IDENTIFICATION DES FACTEURS DE RISQUE DE PERTE DE LA SÉROPROTECTION CHEZ LES TRANSPLANTÉS D'ORGANES SOLIDES PRÉALABLEMENT VACCINÉS CONTRE L'HÉPATITE B

CONCLUSION :

La surveillance annuelle de la persistance de la protection vaccinale contre l'hépatite B est recommandée chez les transplantés d'organes solides. La persistance de cette protection est toutefois méconnue au sein de cette population.

Nous avons analysé les données de 321 patients transplantés d'organe solide suivi dans notre centre entre 2009 et 2019, négatifs pour l'antigène anti-HBs et l'anticorps anti-HBc, et présentant un taux d'anticorps HBs (AChBs) avant la greffe >10 IU/L (témoignant d'une vaccination contre l'hépatite B). Nous avons étudié la dynamique des taux d'AChBs après la transplantation, et les facteurs associés à la persistance de la séroprotection (AChBs <10UI/L).

Après transplantation d'organe solide, au cours du suivi (médiane 104 jours, quartiles 92-381), la perte de séroprotection était observée chez 90/321 (28,0%) patients. En analyse univariée, la transplantation hépatique, l'âge de plus de 50 ans lors de la greffe, l'indice de masse corporelle (IMC) de plus de 30 kg/m² lors de la greffe, un taux d'AChBs pré-transplantation inférieur à 100UI/L, un traitement d'induction par ATG ou tacrolimus ou corticoïdes, et un traitement de maintenance par MMF ou corticoïdes étaient associés à la perte de la séroprotection. En analyse multivariée, l'organe transplanté, le taux d'AChBs pré-transplantation et l'IMC étaient associés avec la persistance de la séroprotection : en effet, les transplantations rénale (HR 0,20 [IC95% 0,12; 0,34]), pulmonaire (HR 0,15 [IC95% 0,04; 0,50]) et cardiaque (HR 0,33 [IC95% 0,13; 0,83]) étaient associées à un risque moindre perte de la séroprotection que la transplantation hépatique (p<0,001) ; de même, ce risque était diminué pour les patients avec un taux d'AChBs avant la transplantation d'organe compris entre 100 et 300 UI/L (HR 0,32 [IC95% 0,18-0,60]) ou supérieur à 300 UI/L (HR 0,10 [IC95% 0,05-0,21]) par rapport à des taux inférieurs à 100 UI/L (p<0,001) ; enfin, les patients avec un IMC inférieur à 18 kg/m² présentaient un risque plus élevé de perte de la séroprotection (HR 3,28 [IC95% 1,42-7,61]) que les patients avec un IMC entre 18 et 30 (p= 0,05).

Bien que nos données soient limitées, ces résultats montrent qu'il est nécessaire de suivre de près les titres d'HBsAb pendant les premières années suivant la transplantation, pour ne pas manquer la nécessité de la réalisation d'un rappel vaccinal, en particulier en cas de greffe hépatique, d'IMC inférieur à 18 kg/m² et de taux d'anticorps inférieur à 100UI/L avant la transplantation. De surcroît, il est nécessaire de s'efforcer d'obtenir les niveaux d'anticorps les plus élevés possibles avant la transplantation, en utilisant un schéma vaccinaux doubles doses et des injections supplémentaires si nécessaires, afin de limiter le risque de perte de séroprotection après la transplantation.

VU ET PERMIS D'IMPRIMER

Grenoble, le :

LE DOYEN

Pr. Patrice MORAND



LE PRÉSIDENT DE LA THÈSE

Pr. Patrice MORAND



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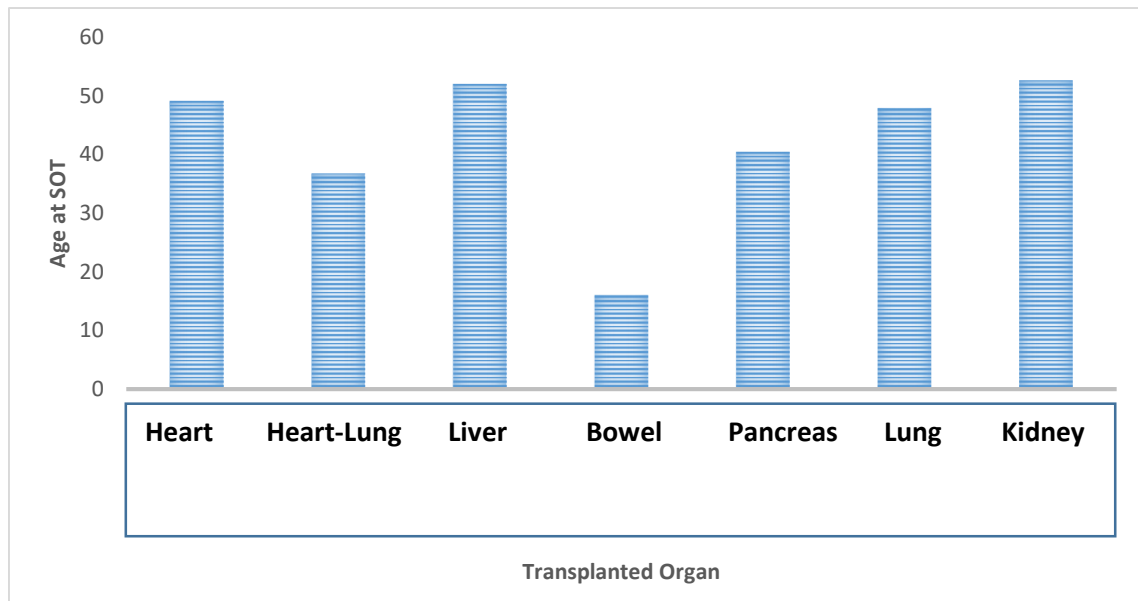
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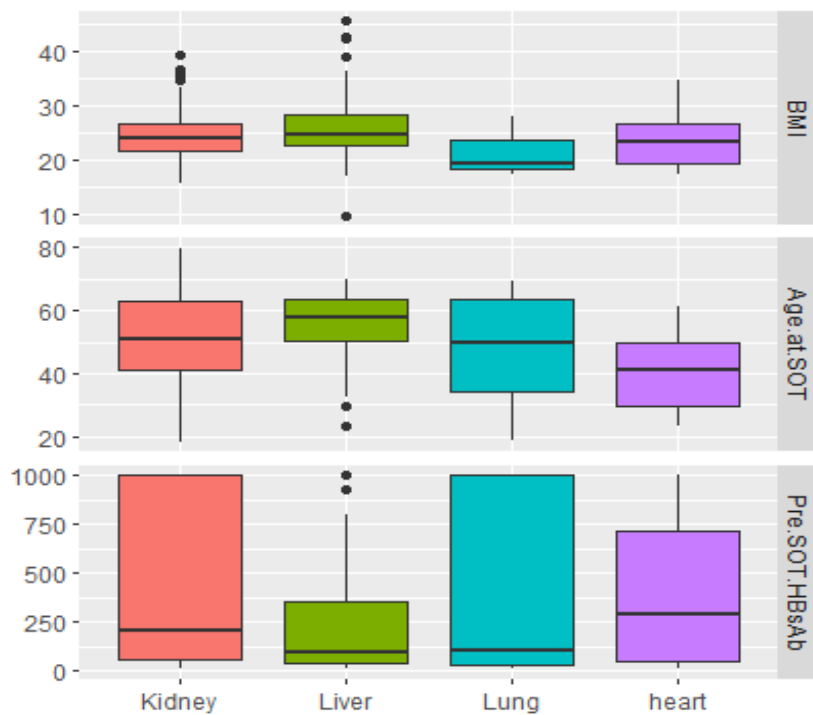
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ANNEXES

Supplementary figure 1: Age at SOT in 2017 (Agence de bio médecine)

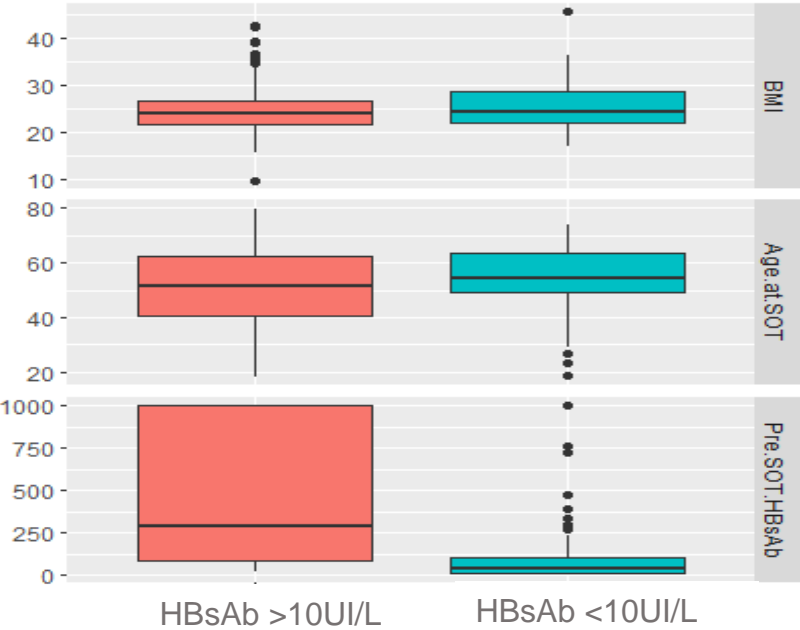


Supplementary figure 2: Distribution of HBsAb dosage in pre-transplantation, age at SOT and BMI according to the transplanted organ (n = 321)



SOT: Solid organ transplantation, HBsAb: Hepatitis B antibody BMI: Body mass index

Supplementary figure 3: Distribution of BMI at SOT, age at SOT and HBsAb dosage in pre-transplantation according to loss or persistence of seroprotection after SOT (n = 321)



SOT: Solid organ transplantation, HBsAb: Hepatitis B antibody BMI: Body mass index

Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. ”