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► To cite this version:

Mario Altieri, Olivier Séréé, Thierry Lobbedez, Philippe Segol, Armand Abergel, et al.. Risk factors of de novo malignancies after liver transplantation: a French national study on 11004 adult patients. *Clinics and Research in Hepatology and Gastroenterology*, 2021, 45 (4), pp.101514. 10.1016/j.clinre.2020.07.019 . hal-03671648

HAL Id: hal-03671648

<https://hal.science/hal-03671648v1>

Submitted on 15 Mar 2023

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Risk factors of *de novo* malignancies after liver transplantation:

a French national study on 11004 adult patients

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Keywords: liver transplantation; *de novo* malignancies; competing risk.

Word count = 2388

Abbreviations:

ALD: Alcohol-related Liver Disease
CI: Confidence Interval
HCC: Hepato Cellular Carcinoma
LT: Liver Transplantation
PSC: Primary Sclerosing Cholangitis
SIR: Standardized Incidence Ratio
SHR: SubHazard Ratio

Conflict of interest statement: no conflict of interest to declare.

Financial support statement: Chiesi gave financial support for the analysis of data.

Authors contributions:

Mario Altieri and Jérôme Dumortier had the idea of the project and participated in analysis and interpretation of data.

Olivier Séréé, Thierry Lobbedez, Xavier Blaizot and Guy Launoy performed methodology and statistical analysis of data.

Mario Altieri, Olivier Séréé and Jérôme Dumortier participated in writing of the manuscript.

Mario Altieri, Philippe Segol, Armand Abergel, Olivier Boillot, Karim Boudjema, Filomena Conti, Olivier Chazouillères, Audrey Coilly, Maryline Debette-Gratien, Sébastien Dharancy, François Durand, Christophe Duvoux, Claire Francoz, Jean Gugenheim, Jean Hardwigen, Pauline Housel-Debry, Nassim Kamar, Marianne Latournerie, Pascal Lebray, Vincent Leroy, Martine Neau-Cransac, Georges-Philippe Pageaux, Sylvie Radenne, Ephrem Salamé, Faouzi Saliba, Didier Samuel, Claire Vanlemmens, Camille Besch and Jérôme Dumortier were liver transplant centers medical managers and approved the final version of the manuscript.

Abstract

Background: After liver transplantation (LT), *de novo* malignancies are one of the leading causes of late mortality. The aim of the present retrospective study was to identify the risk factors of *de novo* malignancies in a large cohort of LT recipients in France, using Fine and Gray competing risks regression analysis.

Methods: The study population consisted in 11004 adults transplanted between 2000 and 2013, who had no history of pre-transplant malignancy, except primary liver tumor. A Cox model adapted to the identification of prognostic factors (competitive risks) was used.

Results: From the entire cohort, one (or more) *de novo* malignancy was reported in 1480 LT recipients (13.45%). The probability to develop a *de novo* malignancy after LT was 2.07% at 1 year, 13.30% at 5 years, and 28.01% at 10 years. Of the known reported malignancies, the most common malignancies were hematological malignancy (22.36%), non-melanoma skin cancer (19.53%) and lung cancer (12.36%). According to Fine and Gray competing risks regression multivariate analysis, were significant risk factors for post-LT *de novo* malignancy: recipient age (Subdistribution Hazard Ratio (SHR)=1.03 95%CI 1.03-1.04), male gender (SHR=1.45 95%CI 1.27-1.67), non-living donor (SHR=1.67 95%CI 1.14-2.38), a first LT (SHR=1.35 95%CI 1.09-1.69) and the type of initial liver disease (alcohol-related liver disease (SHR=1.63 95%CI 1.22-2.17), primary sclerosing cholangitis (SHR=1.98 95%CI 1.34-2.91), and primary liver tumor (SHR=1.88 95%CI 1.41-2.54)). Initial immunosuppressive regimen had no significant impact.

Conclusion: The present study confirms that LT recipient characteristics are associated with the risk of *de novo* malignancy and this underlines the need for personalized screening in order to improve survival.

Introduction

Liver transplantation (LT) is the treatment of end-stage chronic liver disease and severe acute liver failure. During the past 3 decades, progresses in reanimation, surgery, medical management including immunosuppression, led to improved survival (1). In France, for the 1993-2016 period, the survival of LT patients (n=19942) was 85.2% at one year, 73.6% at five years, and 62.6% at ten years. During this period, there was a significant improvement in early post-operative survival, but survival after the first year remained similar (2). This can be explained by the occurrence of late complications such as sepsis, recurrence of initial disease (mainly hepatitis C), *de novo* malignancies, and cardiovascular diseases that are known to be the main causes of late mortality (3-5), *de novo* malignancies accounting for approximately 20% of deaths (6).

Compared with the general population, the excess risk of post-LT *de novo* malignancies occurrence is well known with an estimated risk 1.4 to 11.55 times greater (7-19). Risk factors for *de novo* malignancies include immunosuppression therapy, but also a number of patient-related factors including age, gender, oncogenic viral infections, history of tobacco and alcohol use, and initial liver disease. Recently, using extensive data from the French national Agence de la Biomédecine database, we quantified the risk of solid organ *de novo* malignancies (excluding non-melanoma skin cancers) after LT: the incidence of *de novo* malignancies among all LT patients between 1993 and 2012 was compared to that observed in the French population, standardized on age, gender, and calendar period (standardized incidence ratio, SIR) (20). Among the 11226 LT patients included in the study, 1200 *de novo* malignancies were diagnosed (10.7%). The risk of death was approximately two times higher in patients with *de novo* malignancy (48.8% vs. 24.3%). The SIR for all *de novo* solid organ malignancies was 2.20. Following this first analysis, the aim of the present study was to identify the risk factors of *de novo* malignancies in a part of the same large cohort of LT recipients in France, using Fine and Gray competing risks regression analysis.

Materials and methods

Study Population

Adult patients who underwent a LT between January 2000 and December 2013 were identified from the national database of the French *Agence de la Biomédecine*, whose main purpose is the allocation of grafts, identification of biological and clinical information about transplantation, and follow-up of patients transplanted in France. Patients who died within 30 days (because these deaths are mainly related to post-operative complications), as well as those diagnosed with cancer within 30 days after LT (because these cancers were considered as independent from transplantation), were excluded. Patients who presented a primary liver tumor were included, but those who presented recurrence of the primary liver tumor after LT were excluded.

The data on post-LT malignancies were extracted from the Cristal database, which is completed once a year for each patient from the clinical charts of each transplant center. The Cristal data base is locally implemented by an independent clinical study technician, from the *Agence de la Biomédecine*. The presence of cancer is identified, together with the date of diagnosis, and is coded using a thesaurus, with the possibility to add free text. The thesaurus used was mapped to the International Classification of Diseases, 10th Revision (ICD-10). The vital status is also specified in the Cristal register.

Statistical analysis

Baseline characteristics among LT recipients were computed. These characteristics were described using proportions for categorical variables and means with associated standard deviations for continuous variables. An omnibus χ^2 tests were performed for comparison of categorical variables and 2-sample t tests were performed for continuous variables.

Multivariate analysis using competing risks regression was performed to examine the association between clinical characteristics and post-transplant malignancies. The primary outcome of interest was time to the first report of post-transplant cancer. Because patients who died during the follow-up were no longer able to experience the outcome of interest, death event was treated as a competing event. The first time to cancer was modeled with Fine and Gray competing risk methods (21). All

patients were censored at the end of the study period on December 31, 2013. Subgroup analyses were then performed to evaluate the risk of specific subgroups on post-transplant malignancy. Risk factors included in the multivariate model were recipient characteristics, donor characteristics, initial immunosuppressive regimen, and etiology of initial liver disease. Results of the regression analysis were expressed in subhazard ratio (SHR) and confidence intervals. All reported p values were 2-tailed, and a p value at or less than 0.05 was considered to be statistically significant. We used 95% confidence intervals. Statistical analyzes were performed with R 3.3.3 (R Foundation for Statistical Computing), and survival and cmprsk packages.

Results

Study population

The study population consisted in 11004 adult LT recipients (2000-2013), from whom 1480 (14.45%) presented at least one post-transplant *de novo* malignancy (Figure 1). The median duration of follow-up was 3.55 years for patients without post-transplant *de novo* malignancy diagnosis and 3.71 years for patients with. The probability to develop a *de novo* malignancy after LT was 2.07% at 1 year, 13.30% at 5 years, and 28.01% at 10 years (Figure 2). Of the known reported malignancies, the most common malignancies were hematological malignancy, non-melanoma skin cancer and lung cancer (Table 1). Out of 11004 included LT recipients, 2552 had died by December 31, 2013, including 619 who had presented a *de novo* malignancy. Significant clinical characteristics associated with post-LT *de novo* malignancy included: age at LT, gender, type of initial liver disease, number of LT, donor age and type of initial immunosuppressive therapy (calcineurin inhibitor (CNI) and antimetabolite types) (Table 2).

Cox regression analysis

According to Cox regression multivariate analysis (Table 3), were significant risk factors for post-LT *de novo* malignancy: age, male gender, non-living donor, main type of initial liver disease (alcohol-related liver disease (ALD), primary sclerosing cholangitis (PSC), primary liver tumor and other liver disease) and initial use of mycophenolate. Were significant factors for post-LT better survival: female gender, type of initial liver disease (hepatitis B, PSC, other cirrhosis, congenital liver disease). Were significant factors for post-LT worse survival: recipient age, a number of LT ≥ 2 and use of anti-lymphocyte antibodies. Finally, were significant risk factors for post-LT *de novo* malignancy or death: recipient age, donor age, a number of LT ≥ 2 , initial liver disease (all protective: hepatitis B, PSC, congenital liver disease), initial use of mycophenolate and of anti-lymphocyte antibodies.

Fine and Gray competing risks regression analysis

According to Fine and Gray competing risks regression multivariate analysis (Table 4), were significant risk factors for post-LT *de novo* malignancy: recipient age, male gender, non-living donor,

a first LT, and the type of initial liver disease (ALD, PSC and primary liver tumor). The type of initial immunosuppressive regimen had no significant impact.

Discussion

Summarizing the impact of *de novo* malignancies after LT, Daniel *et al.* (2017) reported long-term outcome of almost 90000 LT recipients and found that early deaths (within 1 year post-transplant) were related to infections and cardiovascular events, whereas malignancy-related deaths increased after year 1, *de novo* malignancies being more frequent than recurrent cancers, mainly hepatocellular carcinoma (71% vs. 28%) (22). We conducted the present retrospective study with the aim to identify the risk factors of *de novo* malignancies in a large cohort (>11000) of LT recipients in France. We used both Cox and Fine and Gray regression analysis because different insights can be learned from each analysis. Nevertheless, Fine–Gray is a regression model for the cumulative incidence function and it should be used when prediction is the focus (23, 24).

The overall incidence of *de novo* malignancies has been reported to range from 3.1 and 14.4%, with a cumulative risk that progressively increases with post-transplant time, rising from 20% at 10 years to 55% at 15 years (25). This is in accordance with our results: the probability to develop a *de novo* malignancy after LT was 2.07% at 1 year, 13.30% at 5 years, and 28.01% at 10 years. Nevertheless, interpretation of available data must take into account the variability of patient-related factors able to influence malignancy type and incidence, including age, gender, geographical considerations, and the predominant initial liver disease and its associated morbidities. In addition, immunosuppressive strategies can significantly differ from a cohort to another. Finally, all kinds of *de novo* malignancies are not systematically captured in all large cohort studies, according to available (and missing) data. We confirm herein that non-melanoma skin cancers and post-transplant lymphoproliferative disorders (PTLD) are the most common *de novo* malignancies after LT (in our population are identified all hematological malignancies and not only PTLD), as reported recently by Rademacher *et al.*, skin tumors and PTLD representing 26% and 15% of *de novo* malignancies, respectively, after a mean follow-up of 28 years (26).

We also confirm herein that patient-related factors are the strongest determinants of post-LT *de novo* malignancies, including age, gender and initial liver disease (and associated morbidities). We did not investigate in the present study specific risk factors for each type of malignancies; nevertheless we

previously reported the role of age, sex and initial ALD on the risk of different types of *de novo* malignancies after LT (20). Sinking an open door, older age is a well-described risk factor for cancer, with the exception in the field of organ transplantation of PTLD which preferentially occur in young recipients, with a strong correlation with EBV infection (9). The most relevant risk factor of *de novo* malignancies in our population was the initial liver disease, recalling the analysis of the American Scientific Registry of Transplant Recipients (SRTR) data. HCV-, ALD- and non-alcoholic steatohepatitis (NASH)- related liver diseases were associated with the occurrence of *de novo* malignancies (19). This suggests the impact of synergistic risk factors, the most important being probably tobacco and alcohol consumption, obesity and diabetes. In our national database, as many others previously, such seminal data are not available and cannot be included in analysis. In France, NASH-related liver disease was a rare indication for LT until recent years and are included in the item “other cirrhosis” and cannot be analyzed separately. More interestingly, HCV-related liver disease was the second more frequent initial liver disease in our population, but was not associated with *de novo* malignancies. Not surprisingly, ALD as a leading cause for LT in France, was associated with the highest risk of *de novo* malignancies. It can be hypothesized that a vast majority of patients transplanted for primary liver tumor had underlying ALD and therefore SHR associated with ALD and primary liver tumor are very close. History of ALD probably explains the high incidence of alcohol/tobacco-related malignancies, such as lung, lip-mouth-pharynx-larynx, esophagus. In addition, similarly to ALD patients, patients undergoing LT for PSC were exposed to a greater risk of *de novo* malignancies as previously reported (5). It may be explained by the association with inflammatory bowel disease, and therefore an increased risk of colorectal cancer, but also of skin, renal, hematological and pancreatic cancer (27, 28). Interestingly, Rademacher *et al.* (2017) reported a surprising lower incidence of *de novo* malignancies after LT for PSC, possibly influenced by the low rate of smokers recipients, and a different prevalence of IBD or pre-liver transplant colectomy (26). Regarding gender, *de novo* malignancies are more frequent in men. Even if ALD and PSC LT recipients are predominantly males, the impact of gender remains significant in multivariate analysis; we hypothesize that this is probably due to the deleterious impact of alcohol, tobacco, metabolic

syndrome in men transplanted for non-ALD non-PSC indications. Finally, we confirm herein the protective impact of re-transplantation on *de novo* malignancies occurrence (19); it can be hypothesized that this is due to a strong selection of patients, erasing the weight of time spent under immunosuppressive therapy, in case of late re-transplantation.

Immunosuppressive therapy precisely! We did not identify any role for initial immunosuppressive regimen on occurrence of *de novo* malignancies. Analysis of maintenance immunosuppression should be more relevant, but hard to perform as such data were not available in our data base. It can be underline that interpretation of such data is highly questionable regarding frequent and multiple changes of drugs during years of post-transplantation follow-up. Nevertheless, in a single center report on 368 LT recipients with initial ALD, we noticed that tobacco consumption (both past and current) was associated with a significant increased risk of *de novo* solid organ malignancy, whereas maintenance immunosuppressive regimen including mTOR inhibitors was associated with a decreased risk (29). Very recently, Bhat *et al.* (2019) analyzed data from the Scientific Registry of Transplant Recipients database comprising all 108412 adult LT recipients across the United States between 1987 and March 2015 (median follow-up of 6.95 years) (30). Potential risk factors for malignancies after LT were assessed using Cox regression analysis for the outcome of time to first malignancy. *De novo* malignancies occurred in 9783 patients (9.02%), including 41.3% of skin, 14.0% of hematological and 44.7% of solid organ. The 10-year probability of *de novo* malignancy was 11.5%. On multivariable analysis, age, male gender, white race, multiorgan transplantation, previous malignancy and initial liver disease (ALD, autoimmune, NASH and PSC) were associated with higher risk of post-LT *de novo* malignancy, but type of immunosuppression was not, strongly recalling our main results.

Undoubtedly, the increased risk and mortality associated with *de novo* malignancies underlines the need for surveillance strategies to detect tumors at earlier stages, leading to more effective treatments and better survival. Screening protocols proposal for the detection of *de novo de novo* malignancies in LT population include an annual skin examination (for skin cancers), an annual CT scan in active tobacco smokers (for lung cancers), an annual colonoscopy in PSC patients with inflammatory bowel disease and a colonoscopy 2 years after LT in patients above 50 years (for colorectal cancers), an

annual clinical ears, nose, throat examination in smokers (for lip-mouth-pharynx-larynx cancers), an annual ultrasound examination (for renal cancers) and a compliance monitoring of routine health maintenance screening (for breast and prostate cancers) (13, 31-37).

In conclusion, the present study performed on a large cohort with long follow-up, despite some limitations (lack of data on maintenance immunosuppressive regimen, tobacco consumption, co-morbidities such as diabetes and obesity), confirms that LT recipients characteristics are associated with the risk of *de novo* malignancy (age, gender, and initial liver disease) and this underlines the need for personalized screening in order to improve survival.

Acknowledgements

The authors thank all French liver transplant centers and the *Agence de la Biomédecine* for having authorized access to data.

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Table 1. Type of post-LT *de novo* malignancies

| Malignancies | n | (%) |
|------------------------------|------|-----------|
| Hematological | 331 | (22.36%) |
| Skin | 289 | (19.53%) |
| Lung | 183 | (12.36%) |
| Lip-Mouth Pharynx and Larynx | 108 | (7.30%) |
| Prostate | 74 | (5.00%) |
| Colorectal | 73 | (4.93%) |
| Esophagus | 48 | (3.24%) |
| Breast | 34 | (2.30%) |
| Kidney | 21 | (1.42%) |
| Pancreas | 19 | (1.28%) |
| Bladder | 16 | (1.08%) |
| Kaposi sarcoma | 12 | (0.81%) |
| Melanoma | 8 | (0.54%) |
| Stomach | 7 | (0.47%) |
| Central Nervous System | 7 | (0.47%) |
| Thyroid | 7 | (0.47%) |
| Others | 114 | (7.70%) |
| Unknown site | 129 | (8.72%) |
| Total | 1480 | (100.00%) |

Table 2 : Characteristics of the study population (n=11004)

| | | No de novo malignancy (n=9524) | De novo malignancy (n=1480) | <i>p</i> * |
|--|--------------------------------|-----------------------------------|--------------------------------|------------|
| Follow-up (years) | Q1 / Med / Q3 | 1.04 / 3.55 / 7.18 | 1.76 / 3.71 / 6.29 | < .001 |
| Age at LT (years) | Q1 / Med / Q3 | 46.08 / 53.81 / 60.02 | 50.13 / 55.99 / 61.06 | < .001 |
| Gender | Male | 6 768 (71,1%) | 1 174 (79,3%) | < .001 |
| | Female | 2 756 (28,9%) | 306 (20,7%) | |
| Nb of LT | 1 | 8 820 (92,6%) | 1395 (94,3%) | 0.05 |
| | 2 | 652 (6,8%) | 82 (5,5%) | |
| | 3 | 48 (0,5%) | 2 (0,1%) | |
| | 4 | 4 (0,0%) | 1 (0,1%) | |
| Type of initial liver disease | Metabolic disease | 394 (4,1%) | 30 (2,0%) | < .001 |
| | Alcohol-related | 3 024 (31,8%) | 566 (38,2%) | |
| | Viral hepatitis B | 384 (4,0%) | 48 (3,2%) | |
| | Viral hepatitis C | 1 420 (14,9%) | 168 (11,4%) | |
| | Primary sclerosing cholangitis | 257 (2,7%) | 46 (3,1%) | |
| | Other cirrhosis | 761 (8,0%) | 85 (5,7%) | |
| | Acute liver failure | 466 (4,9%) | 36 (2,4%) | |
| | Congenital liver disease | 201 (2,1%) | 20 (1,4%) | |
| | Other liver disease | 336 (3,5%) | 43 (2,9%) | |
| | Primary liver tumor | 2 281 (24,0%) | 438 (29,6%) | |
| Donor age (years) | Q1 / Med / Q3 | 36.00 / 50.00 / 63.00 | 33.00 / 47.00 / 59.00 | < .001 |
| Donor type | Living | 228 (2,4%) | 28 (1,9%) | 0.26 |
| | Death | 9 126 (95,8%) | 1431 (96,7%) | |
| | NA | 170 (1,8%) | 21 (1,4%) | |
| Initial immunosuppressive treatment after LT | CNI | | | < .001 |
| | Tacrolimus | 8 069 (84,7%) | 1233 (83,3%) | |
| | Ciclosporine | 1 381 (14,5%) | 245 (16,6%) | |
| antimetabolite | NA | 74 (0,8%) | 2 (0,1%) | < .001 |
| | Azathioprine | 99 (1,0%) | 21 (1,4%) | |
| | Mycophenolate | 6 798 (71,4%) | 825 (55,7%) | |
| | None | 2 543 (26,7%) | 631 (42,6%) | |
| corticosteroids | NA | 84 (0,9%) | 21 (1,4%) | 0.71 |
| | yes | 9 106 (95,6%) | 1430 (96,6%) | |
| | no | 328 (3,4%) | 48 (3,2%) | |
| anti-lymphocytes antibodies | NA | 90 (0,9%) | 2 (0,1%) | 0.40 |
| | yes | 467 (4,9%) | 65 (4,4%) | |
| | no | 8 975 (94,2%) | 1 413 (95,5%) | |
| | NA | 82 (0,9%) | 2 (0,1%) | |

* *p* of heterogeneity (khi2 test)

Table 3: Impact of potential risks factors for malignancy occurrence and death: results of Cox regression analysis

| | | Cancer | | Death | | Cancer or Death | |
|--|--------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| | | HR (95% CI) | | HR (95% CI) | | HR (95% CI) | |
| | | Bivariate | Multivariate | Bivariate | Multivariate | Bivariate | Multivariate |
| Age (years) | | 1.04 (1.04-1.05) | 1.03 (1.03-1.04) | 1.02 (1.02-1.02) | 1.02 (1.01-1.02) | 1.02 (1.02-1.03) | 1.02 (1.02-1.03) |
| Gender | M vs. F | 1.67 (1.47-1.89) | 1.47 (1.30-1.69) | 1.33 (1.22-1.47) | 1.22 (1.10-1.33) | 1.35 (1.25-1.45) | 1.23 (1.14-1.35) |
| Nb of LT | >1 vs. 1 | 0.77 (0.62-0.96) | 0.85 (0.68-1.07) | 1.74 (1.55-1.96) | 1.79 (1.58-2.03) | 1.48 (1.33-1.66) | 1.53 (1.36-1.72) |
| Donor age (year) | | 1.00 (1.00-1.01) | 1.00 (1.00-1.01) | 1.01 (1.01-1.01) | 1.01 (1.00-1.01) | 1.01 (1.01-1.01) | 1.01 (1.00-1.01) |
| Donor type | Living vs. Death | 0.52 (0.36-0.76) | 0.72 (0.49-1.06) | 0.77 (0.60-0.99) | 0.80 (0.61-1.04) | 0.71 (0.57-0.89) | 0.79 (0.62-1.00) |
| Type of initial liver disease | | | | | | | |
| | Metabolic disease | 1 (reference) |
| | Alcohol-related | 2.32 (1.61-3.35) | 1.55 (1.07-2.25) | 0.97 (0.80-1.19) | 0.86 (0.69-1.06) | 1.15 (0.95-1.38) | 0.94 (0.77-1.14) |
| | Viral hepatitis B | 1.20 (0.76-1.89) | 0.98 (0.62-1.56) | 0.50 (0.37-0.68) | 0.46 (0.34-0.63) | 0.62 (0.48-0.82) | 0.56 (0.42-0.73) |
| | Viral hepatitis C | 1.54 (1.04-2.27) | 1.19 (0.80-1.76) | 1.36 (1.10-1.67) | 1.18 (0.95-1.46) | 1.41 (1.16-1.71) | 1.19 (0.98-1.46) |
| | Primary sclerosing cholangitis | 1.88 (1.19-2.99) | 1.82 (1.14-2.91) | 0.47 (0.33-0.68) | 0.48 (0.33-0.69) | 0.71 (0.53-0.95) | 0.69 (0.51-0.94) |
| | Other cirrhosis | 1.45 (0.96-2.20) | 1.25 (0.80-1.94) | 0.91 (0.68-1.21) | 0.62 (0.47-0.83) | 0.81 (0.65-1.02) | 0.76 (0.59-0.97) |
| | Acute liver failure | 1.04 (0.64-1.69) | 1.23 (0.75-2.01) | 0.76 (0.57-1.00) | 0.83 (0.62-1.11) | 0.88 (0.68-1.13) | 0.98 (0.76-1.27) |
| | Congenital liver disease | 1.21 (0.68-2.14) | 1.28 (0.72-2.28) | 0.35 (0.22-0.57) | 0.39 (0.24-0.64) | 0.56 (0.39-0.81) | 0.60 (0.41-0.88) |
| | Other liver disease | 1.59 (1.00-2.53) | 1.62 (1.01-2.61) | 0.91 (0.68-1.21) | 0.98 (0.73-1.32) | 1.05 (0.81-1.36) | 1.12 (0.86-1.45) |
| | Primary liver tumor | 3.03 (2.10-4.39) | 1.99 (1.36-2.91) | 1.12 (0.91-1.38) | 0.92 (0.74-1.14) | 1.39 (1.15-1.68) | 1.07 (0.88-1.31) |
| Initial immunosuppressive treatment after LT | | | | | | | |
| CNI | Ciclo vs. Tacro | 0.98 (0.85-1.12) | 0.94 (0.80-1.10) | 1.09 (0.98-1.21) | 1.04 (0.93-1.17) | 1.05 (0.96-1.15) | 1.02 (0.92-1.12) |
| antimetabolite | None | 1 (reference) |
| | Mycophenolate | 1.13 (1.02-1.26) | 1.20 (1.06-1.35) | 1.03 (0.95-1.12) | 1.01 (0.92-1.11) | 1.11 (1.03-1.19) | 1.11 (1.03-1.21) |
| | Azathioprine | 0.77 (0.50-1.20) | 1.02 (0.70-1.48) | 1.12 (0.83-1.52) | 1.28 (0.99-1.64) | 1.01 (0.77-1.32) | 1.12 (0.89-1.41) |
| corticosteroids | yes vs. no | 0.96 (0.72-1.28) | 1.05 (0.78-1.43) | 0.84 (0.68-1.03) | 0.84 (0.68-1.04) | 0.88 (0.73-1.06) | 0.91 (0.75-1.10) |
| anti-lymphocytes antibodies | yes vs. no | 0.86 (0.67-1.10) | 0.97 (0.75-1.25) | 1.34 (1.14-1.57) | 1.34 (1.14-1.58) | 1.21 (1.05-1.40) | 1.25 (1.08-1.44) |

Table 4. Impact of potential risks factors for malignancy occurrence: results of the adjusted Fine and Gray model

| | | risks factors for malignancy | |
|--|--------------------------------|------------------------------|-------------------------|
| | | SHR* (95% CI) | |
| | | Bivariate | Multivariate |
| Age (years) | | 1.04 (1.03-1.04) | 1.03 (1.03-1.04) |
| Gender | M vs. F | 1.61 (1.41-1.82) | 1.45 (1.27-1.67) |
| Nb of LT | 1 vs. >1 | 1.30 (1.04-1.61) | 1.35 (1.09-1.69) |
| Donor age (years) | | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| Donor type | Death vs. Living | 1.79 (1.23-2.56) | 1.67 (1.14-2.38) |
| Type of initial liver disease | | | |
| | Metabolic disease | 1 (reference) | 1 (reference) |
| | Alcohol-related | 2.14 (1.61-2.86) | 1.63 (1.22-2.17) |
| | Viral hepatitis B | 1.22 (0.82-1.81) | 1.05 (0.71-1.55) |
| | Viral hepatitis C | 1.25 (0.91-1.71) | 1.03 (0.75-1.41) |
| | Primary sclerosing cholangitis | 1.94 (1.32-2.86) | 1.98 (1.34-2.91) |
| | Other cirrhosis | 1.41 (0.97-2.04) | 1.31 (0.91-1.89) |
| | Acute liver failure | 0.95 (0.62-1.45) | 1.11 (0.72-1.70) |
| | Congenital liver disease | 1.23 (0.74-2.05) | 1.36 (0.82-2.25) |
| | Other liver disease | 1.42 (0.95-2.13) | 1.48 (0.98-2.23) |
| | Primary liver tumor | 2.61 (1.95-3.49) | 1.88 (1.41-2.54) |
| Initial immunosuppressive treatment after LT | | | |
| CNI | Ciclo vs. Tacro | 0.98 (0.86-1.13) | 0.92 (0.80-1.06) |
| antimetabolite | None | 1 (reference) | 1 (reference) |
| | Mycophenolate | 0.86 (0.61-1.21) | 0.92 (0.65-1.31) |
| | Azathioprine | 1.00 (0.90-1.10) | 0.96 (0.87-1.07) |
| corticosteroids | yes vs. no | 1.01 (0.76-1.34) | 1.04 (0.78-1.39) |
| anti-lymphocytes antibodies | yes vs. no | 0.80 (0.62-1.02) | 0.88 (0.68-1.14) |

* Subdistribution Hazard Ratio with death as competing risks outcomes

Legends for figures

Figure 1: Flow chart of the patients included in the study.

Figure 2: Cumulative probability of *de novo* malignancy after LT (Kaplan-Meier estimates)



