Title Page:

Cancer after liver transplantation in children and young adults – A population-based study from four Nordic countries

Authors:

Fredrik Åberg[1], Helena Isoniemi[1], Eero Pukkala[2,3], Hannu Jalanko[4], Allan Rasmussen[5], Hans H. Storm[6], Nicolai Schultz[5], William Bennet[7], Nils Ekvall[8], Bo-Göran Ericzon[9], Silvia Malenicka[10], Steinar Tretli[11], Pål-Dag Line[12,13], Kirsten Muri Boberg[12,13,14], Anniken Østensen[16,13], Tom Hemming Karlsen[12,13,14,15], Arno Nordin[1]

Affiliations:

1) Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Helsinki, Finland

2) Finnish Cancer Registry – Institute for Statistical and Epidemiological Cancer Research, Helsinki Finland

3) Faculty of Social Sciences, University of Tampere, Tampere, Finland

4) Department of Pediatric Nephrology and Transplantation, Children's Hospital, Helsinki University Hospital, Helsinki, Finland

5) Department of Surgical Gastroenterology and Transplantation, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

6) Danish Cancer Society, Copenhagen, Denmark

7) Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden

8) Department of Pediatrics, Institute of Clinical Sciences, The Sahlgrenska Academy at University of Gothenburg and Queen Silvia Children's Hospital, Gothenburg, Sweden

9) Division of Transplantation Surgery, Karolinska Institutet and Karolinska University Hospital Huddinge, Stockholm, Sweden

10) Department of Pediatrics, Astrid Lindgren´s Children's Hospital Huddinge, B57, Karolinska University Hospital Huddinge, 141 86 Stockholm, Sweden

11) The Norwegian Cancer Registry, Oslo, Norway

12) Department of Transplantation Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway

13) Institute of Clinical Medicine, University of Oslo, Oslo, Norway

14) Norwegian PSC Research Center, Department of Transplantation Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Rikshospitalet, Oslo, Norway

15) Research Institute of Internal Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway

16) Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

Key words: Liver transplantation, pediatrics, hepatology

Footnote Page:

Abbreviations: LT, liver transplantation; SIR, standardized incidence ratio

Grants and Financial Support:

This study is indebted all of those who collaborate in maintaining the Nordic Liver Transplant Registry and the cancer registries in each country. This study was supported by Scandiatransplant Research Grant and a grant from Mary and Georg Ehrnrooth Foundation.

Conflicts of interest:

Corresponding author:

Fredrik Åberg, MD, PhD

Address: HUCH Meilahti Hospital, PB 340, 00029 HUS, Finland

Telephone: +358 40 578 0625

Fax: +3589174975

E-mail: Fredrik.Aberg@helsinki.fi

Abstract

Cancer after liver transplantation (LT) constitutes a threat also for young recipients, but cancer risk factors are usually absent in children and large studies on cancer risk profile in young LT recipients are scarce. Data of patients younger than 30 years who underwent LT 1982-2013 in the Nordic countries was linked with respective national cancer registries to calculate standardized incidence ratios (SIR). Thirty-seven cancer cases were observed in 923 patients with 7846 person-years of follow-up. The SIR for all cancer types, compared to matched general population, was 9.8 (males 12.4 and females 7.8). Cumulative incidence of cancer adjusted for the competing risk of death was 2% at 10, 6% at 20, and 22% at 25 years post LT. Non-Hodgkin lymphoma was the most common cancer type (n=14) followed by colorectal (n=4) and hepatocellular cancer (n=4). Age was a significant risk factor for cancer, and the absolute risk of most cancers (except for lymphoma) increased considerably in young adults older than 20 years. The cancer risk pattern is different in pediatric and young LT patients compared to adult recipients. The striking increase in cancer incidence in young adulthood after the second decade of life deserves further consideration in transition programs.

Abstract word count: 199

Main body text:

Introduction

An increased risk for cancer after solid organ transplantation is well established (1, 2, 3). This increased risk is chiefly attributed to lifelong immunosuppression, but the cancer risk pattern is markedly modified by patient-specific factors such as age, history of alcohol abuse, smoking, and transplant indication (4).

In pediatric and young liver transplant (LT) recipients risk-modifying factors are often absent or different from the typical adult LT recipients. The cancer risk pattern in young patients is therefore likely to differ from the pattern in older patients. In addition, the immune system may not be fully developed in children. However, there is a lack of large studies investigating the spectrum of post-LT cancers and risk factors specifically in pediatric and young adult patients. In studies involving both adults and children (1, 3), risk factors specific to children and young adults are usually not reported. Most studies of pediatric populations have focused on post-transplant lymphoproliferative disease (5, 6, 7), but few have assessed other types of cancer. The largest studies on this topic included all types of solid-organ transplant patients (7, 8, 9) or only kidney transplant patients (10), but there are no large studies on young LT patients.

In this Nordic multicenter study, we analyzed the incidence and types of post-LT cancer among patients transplanted before 30 years of age, and compared the cancer risk to the matched general population.

Material and methods

Patient data were derived from the Nordic LT Registry, which includes records of all LT patients in Finland, Sweden, Norway, and Denmark since 1982. Nordic LT Registry data are maintained by the Nordic Liver Transplant Group and stored at Scandiatransplant in Aarhus University Hospital, Denmark. Scandiatransplant is the official organ exchange organization in the Nordic countries. The study protocol was approved by the appropriate institutional review boards in each country.

The study included all patients who underwent LT at ages 0-30 years between 1982 and 2013. The data included date of birth, sex, date of LT and re-LT, indication for LT, country of LT, and immunosuppressive medication used during the first month post-LT.

Cancer diagnosis was identified via the national cancer registry in each country and linked to our study patients using the unique personal identity number. Follow-up for cancer started at the date of the first LT and ended at death, emigration or study closure 31 December 2013. Neoplasms are recorded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). Regarding hematologic neoplasms, only definite malignant cases were considered, which excludes non-destructive (early lesion) lymphoproliferative disorders.

The cancer registration system in the Nordic countries is virtually complete (11) and the computerized record linkage procedure precise (12) thus providing unbiased control data and accurate comparisons for the study. Basal cell carcinoma was not included in the non-melanoma skin cancer category.

Statistical analysis

The numbers of cancer cases and person-years at risk were counted by 5-year age groups, separately for each calendar year and country. The expected number of cases of all cancers combined and of specific cancer types were calculated by multiplying the number of person-years in each sex and age-group by the corresponding cancer incidence rate in each country during the period of observation. The standardized incidence ratio (SIR) was calculated by dividing the observed number of cases by the expected number of cases. The 95% confidence intervals (CI) for the SIR were based on the assumption that the number of observed cases followed a Poisson distribution (13).

Hepatocellular cancer diagnosis recorded in cancer registries within 6 months post-LT was considered as pre-LT cancer that had been confirmed with a delay (n=7), and was thus excluded from the de novo post-LT cancer count. Cumulative incidence was calculated with the competing-risk method according to Fine and Gray (14) with mortality held as a competing risk. Age-adjusted hazards ratios by Cox regression analyses were calculated for sex, country and era of LT, indication, and type of immunosuppression. Any type of post-LT cancer was considered as outcome variable. Non-Hodgkin lymphoma was also analyzed separately. *P*-values < 0.05 were considered statistically significant.

Results

The study comprised 923 patients with 7846 person-years of follow-up. Of patients, 464 (50%) were male and 544 (59%) had undergone LT after the year 2000 (Table 1). The most common LT indication was biliary atresia (26%) (Table 1). Information on immunosuppressive medication was available for 652 patients (71%) in Nordic LT registry.

During the study follow-up, we observed 37 de-novo cancer cases. Non-Hodgkin lymphoma was the most common cancer type (n=14). The distribution of cancer types is shown in Figure 1. The cumulative incidence of de-novo cancer after adjustment for the competing risk of death was 2% at 10 years, 6% at 20 years, and 22% at 25 years post-LT in patients at risk (Figure 2).

Of all cancers, 8 (22%) occurred within 2 years post-LT, 14 (38%) 2-9 years, and 15 (41%) 10 years post-LT (Figure 3). The occurrence of cancer in relationship to age and time after LT is shown in Figure 4. Cancer types other than lymphomas were very rare in patients younger than 20 years (Figure 4).

Of non-Hodgkin lymphomas, 11 (79%) occurred in male patients. Ten cases (71%) were observed in patients younger than 30 years. All 3 kidney cancers occurred in females older than 30 years at cancer diagnosis. Both cases of non-melanoma skin cancer occurred in males and after 10 years post-LT (both at age >30). Only 1 of 4 colorectal cancers was diagnosed at younger age than 30 years and at less than 10 years post-LT. Three of 4 colorectal cancers occurred in patients transplanted for primary sclerosing cholangitis. All de novo liver cancers occurred more than 4 years post-LT (mean 6.7 years) at a mean age of 24 years with 3 of 4 liver cancers occurring in males.

SIRs

The overall SIR for all cancer types was 9.8 (95% CI 6.8-13.3); for males 12.4 (95% CI 7.5-19.4) and for females 7.8 (95% CI 4.6-12.3), respectively. SIRs for cancer types with at least 2 observed cases are shown in Table 2. SIRs and cancer incidence rates according to age group are shown in Table 3.

Risk factor analysis

By Cox regression analysis, increasing age and mycophenolate use were the only factors significantly associated with increased post-transplant overall cancer risk (Table 4). When non-Hodgkin lymphoma was considered, male sex was the only significant age-adjusted risk factor (hazards ratio 5.2, 95% CI 1.2-23.4, P=0.03).

Discussion

Although post-LT cancer rates proved to be 10-fold higher in young LT recipients compared to the general population, absolute cancer risk was very low with approximately 3-7 cases per 100 patients during a 10-year follow-up. The cumulative incidence of cancer was only 2% 10 years post-LT, but increased considerably during the second decade, reaching 22% 25 years post-LT for patients at risk. Non-Hodgkin lymphoma was the most common cancer type across all ages and all follow-up periods, followed by hepatocellular, colorectal, and kidney cancer. Overall, we found that post-LT cancer, other than lymphoma, becomes a much more relevant issue in young adults (older than 20 years) compared to children, regardless of time elapsed post-LT.

Our findings have direct clinical implications. Firstly, the sharp increase in cancer risk after the second decade of life is in practice after transition to adult care. This issue merits further consideration in transition programs and in the further follow-up of young LT patients. Secondly, clinicians should evaluate exposure to known cancer risk factors, such as alcohol use, smoking, and obesity, and be vigilant for any new symptoms potentially attributed to cancer. Thirdly, the immunosuppression regimen deserves also to be reviewed on a regular basis.

Previous studies have reported cancer incidences of 0.3-1.1 per 100 person-years of follow-up in pediatric kidney transplant recipients (8, 10), and 0.9 per 100 person-years of follow-up in pediatric LT recipients (8). Our cancer incidence of 0.3-0.7 per 100 person-years, depending on age, is within the range reported by others. Francis and colleagues reported a cumulative incidence of all cancers of 27% at 25 years after first kidney transplantation (10), which is also fairly close to the cumulative incidence in our study.

Previously reported SIRs for all cancer types vary from 12.5-19.1 (7, 8), and the SIR for non-skin cancers was 8.2 in one study (10). The largest study involving all types of pediatric solid-organ transplant recipients found elevated SIRs for non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, myeloma, and cancers of the kidney, thyroid, liver, testis, soft tissue, ovary, bladder, and vulva (7). Non-Hodgkin lymphoma was the most common cancer type in all of these studies, accounting for 30-80% of all cancer cases (7,8,9, 15) and with SIRs ranging from 46-212 (7, 8, 10).

These studies differ from our study by including either all types of organ transplants or only kidney transplants, including only patients transplanted at ages 0-18 and in the age structure of patients and length of follow-up (7, 8, 9, 10, 15). Although LT patients were included in some studies (7, 8, 9), it is difficult to draw conclusions on the cancer risk pattern specifically for young LT patients, because analyses were mostly performed in groups combining all types of solid-organ transplants. Cancer SIR is heavily influenced by the age structure of the patient cohort and length of follow-up. SIRs generally decrease with age although absolute excess risk may rise, because cancer incidence in the background population also rises with age. The somewhat lower cancer SIRs observed in our study are therefore possibly explained by our inclusion of young adults (aged 18-30 at LT). Young adults may differ from pediatric patients, as well as middle-aged and older adults in the length of

environmental exposures (alcohol, smoking etc), co-morbidity, and with regards to LT indication. No specific cancer surveillance guidelines exist for young adult LT patients.

Despite of elevated cancer SIRs in young LT recipients, a recent Nordic study found no increased mortality from cancer among 1-year surviving pediatric LT patients compared to matched general population (16). This may be due to a successful cancer treatment in most of these cases. However, the relatively few number of cancer cases and limited follow-up after cancer diagnosis or treatment restricts firm conclusions.

It is difficult to predict which young LT patient will develop cancer since no risk factor was strongly associated with cancer. Higher age increased the risk for any cancer, which was also shown in a recent study (10). A higher lymphoma risk was observed in male patients. The relatively small number of cases precluded risk factor analyses for other specific types of cancer.

The reason for an increased cancer risk with antimetabolite use (mycophenolate or azathioprine) was unclear, and multivariate analyses were not possible due to limited number of cases. The risk estimates were also increased for non-Hodgkin lymphoma, but non-significant. Antimetabolites may affect viral replication and mycophenolate has been associated with post-transplant cytomegalovirus disease (17, 18). Viral disease is implicated in the pathophysiology of many pediatric post-transplant cancers, thus providing a possible mechanism for the association seen in our study between antimetabolite use and cancer. In adult transplant cohorts, the effect of mycophenolate on cancer risk is controversial (19, 20). However, data on immunosuppression was available only from the first post-LT month and only for 71% of patients. We were unable to analyse whether antimetabolite use continued in the long term, and whether antimetabolite use was associated with different calcineurin-inhibitor exposure compared to those without antimetabolite

use. Cancer incidence could thus not be weighed on cumulative load of immunosuppression, and our findings must be interpreted with severe caution.

We also observed an elevated SIR for colorectal cancer. This finding could be related to the inclusion of a relatively large proportion of patients with primary sclerosing cholangitis (11%), many of whom have concomitant inflammatory bowel disease. The majority (75%) of colorectal cancers occurred in patients with primary sclerosing cholangitis older than 30 years of age and several years post-LT. Frequent colonoscopy surveillance is recommended for such patients.

In adult transplant recipients, skin cancer is the most common post-transplant cancer type (1, 2). However, we observed only 2 cases of non-melanoma skin cancer and no case of melanoma. Thus, skin cancer is extremely rare in pediatric LT patients, but, similar to previous reports (8, 10, 21, 22), becomes a relevant risk in young adulthood (>25-30 years of age).

Strengths of this study includes the long follow-up (up to 31 years), large sample of LT recipients, and the completeness of cancer data within the Nordic LT registry and the national cancer registries, as well as the unique ability to combine data from several countries. All Nordic LT patients under 30 years of age were included, without any exclusions, and each patient could be successfully linked with cancer-registry data. The NORDCAN classification system, adapted by the cancer registries in all Nordic countries, allow for straightforward combination of data across countries (23).

A clear limitation of the study is the small number of cancer events which prevents conclusive analysis of individual cancers. Several risk factors for cancer could not be adjusted for in the present analyses, such as presence of inflammatory bowel disease (risk factor for colorectal cancer), viral status (Epstein Barr virus – lymphoma risk), and environmental risk factors (alcohol use,

obesity, smoking etc). Moreover, the registry data did not include information on the long-term type and doses of immunosuppression.

Conclusions

A unique cancer risk pattern exists among pediatric and young LT recipients. Non-Hodgkin lymphoma is the most common cancer type in these patients. The risk of other cancers increases considerably in young adulthood, after the second decade of life, compared to childhood, and this merits consideration in transition programs. This also calls for strategies to reduce cancer risk, and such strategies may include cancer surveillance recommendations specific to young adult transplant recipients. Larger studies are required to better clarify risk factors for specific cancer types in young transplant recipients; this can likely be achieved only by combining transplant cohorts from several countries.

Figure legends:

Figure 1. Number of cases observed for various cancer types after liver transplant.

Figure 2. Cumulative incidence of de novo cancer post-liver transplantation after adjustment for mortality as a competing risk. Patients at risk at different time-points are shown in parentheses.

Figure 3. The occurrence of various cancer types by time after liver transplantation.

Figure 4. The occurrence of non-Hodgkin lymphoma and other de novo cancers after liver transplantation in relationship to age and time since transplant. The area under the dotted red line signifies cancers that were diagnosed before 20 years of age.

References

1. Engels EA, Pfeiffer RM, Fraumeni JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306: 1891-1901.

2. Nordin A, Åberg F, Pukkala E, et al. Decreasing incidence of cancer after liver transplantation - A Nordic population-based study over 3 decades. Am J Transpl 2017; 00: 1-12. https://doi.org/10.1111/ajt.14507

3. Collett D, Mumford L, Banner NR, et al. Comparison of the incidence of malignancy in recipients of different types of organ: A UK registry audit. Am J Transpl 2010; 10: 1889-1896.

4. Burra P, Rodriguez-Castro KI. Neoplastic disease after liver transplantation: focus on de novo neoplasms. World J Gastroenterol 2015; 21: 8753-8768.

5. Ng VL, Alonso EM, Bucuvalas JC, et al. Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: report of the studies of pediatric liver transplantation experience. J Pediatr 2012; 160: 820-826.

6. Goss JA, Shackleton CR, McDiarmid SV, et al. Long-term results of pediatric liver transplantation - an analysis of 569 transplants. Ann Surg 1998; 228: 411-420.

7. Yanik EL, Smith JM, Shiels MS, et al. Cancer risk after pediatric solid organ transplantation. Pediatrics 2017; 139; DOI: 10.1542/peds.2016-3893

8. Simard JF, Baecklund E, Kinch A, et al. Pediatric organ transplantation and risk of premalignant and malignant tumors in Sweden. Am J Transpl 2011; 11: 146-151.

9. Debray D, Baudouin V, Lacaille F, et al. De novo malignancy after solid organ transplantation in children. Transplant Proc 2009; 41: 674-675.

10. Francis A, Johnson DW, Craig JC, Wong G. Incidence and predictors of cancer following kidney transplantation in childhood. Am J Transpl 2017; 17: 2650-2658.

11. Pukkala E, Engholm G, Højsgaard Schmidt LK, et al. Nordic Cancer registries – an overview of their procedures and data comparability. Acta Oncol 2017, DOI: 10.1080/0284186X.2017.1407039

12. Pukkala, E.: Nordic biological specimen bank cohorts as basis for studies of cancer causes and control – quality control tools for study cohorts with more than 2 million sample donors and 130,000 prospective cancers. In: Dillner, J. (ed.): Methods in Biobanking. Methods in Molecular Biology, 2011, Volume 675. Totowa, Humana Press 2011, pp. 61-112.

13. Breslow NE, Day NE. Statistical methods in cancer research, Volume II – The design and analysis of cohort studies. IARC Sci Publ 1987; 82: 1–406.

14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.

15. Koukourgianni F, Harambat J, Ranchin B, et al. Malignancy incidence after renal transplantation in children: a 20-year single-centre experience. Nephrol Dial Transplant 2010; 25: 611-616.

16. Åberg F, Gissler M, Karlsen TH, et al. Differences in long-term survival among liver transplant recipients and the genral population: a population-based Nordic study. Hepatology 2015; 61: 668-677.

17. Sarmiento JM, Dockrell DH, Schwab TR, et al. Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. Clin Transplant 2000; 14: 136-138.

18. Brennan DC, Legendre C, Patel D, et al. Cytomegalovirus incidence between everolimus versus mycophenolate in de novo renal transplants: Pooled analysis of three clinical trials. Am J Transpl 2011; 11: 2453-2462.

19. Crane GM, Powell H, Kostadinov R, et al. Primary CNS lymphoproliferative disease, mycophenolate and calcineurin inhibitor usage. Oncotarget 2015; 6: 33849-33866.

20. Robson R, Cecka JM, Opelz G, et al. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. Am J Trans 2005; 5: 2954-2960.

21. Coutinho HM, Groothoff JW, Offringa M, et al.. De novo malignancy after paediatric renal replacement therapy. Arch Dis Child 2001; 85: 478–483.

22. Euvrad S, Kanitakis J, Cochat P, Claudy A. Skin cancers following pediatric organ transplantation. Dermatol Surg 2004; 30: 616-621.

23. Engholm G, Ferlay J, Christensen N, et al. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol. 2010; 49: 725-736.

.

.

Table 1. Demographic characteristics of the study cohort.

	N	%
Age at transplant		
0-14 years	503	54%
15-29 years	420	46%
Female	459	50%
Male	464	50%
Country		
Sweden	387	42%
Norway	186	20%
Finland	182	20%
Denmark	168	18%
Era of LT		
1980-1999	379	41%
2000-2013	544	59%
Indication for transplantation		
Biliary atresia	236	26%
Acute liver failure	170	18%
Primary sclerosing cholangitis	106	11%
Metabolic liver disease *	121	13%
Liver tumor	74	8%
Autoimmune hepatitis	48	5%
Other	168	18%
Immunosuppression during first month post-LT		

Cyclosporine	216	33%
Tacrolimus	419	64%
Antimetabolite		
Azathioprine	209	32%
Mycophenolate	203	31%
None	244	37%
Steroids (yes vs no)	626	95%
IL2-receptor antibody (yes vs no)	91	14%
ATG/OKT antibody (yes vs no)	39	6%

* The following diagnoses are coded as "metabolic" in the Nordic Liver Transplant Registry: Wilson disease, hemochromatosis, alfa-1 antitrypsin deficiency, glycogen storage disease, familial hypercholesterolemia, tyrosinemia, primary hyperoxaluria, familial amyloidotic polyneuropathy, porphyria, cystic fibrosis, familial intrahepatic cholestasis (PFIC).

Table 2. Observed and expected numbers of cancers and standardized incidence ratios (SIRs) with 95% confidence intervals (CI) for cancer types with at least 2 observed cases.

Cancer type	Observed	Expected	SIR	95% CI
All types*	37	3.8	9.8	6.8-13.3
Non-Hodgkin lymphoma	14	0.2	86.0	47.0-144
Hepatocellular	4	0.02	200	53.8-512
Colorectal	4	0.2	26.7	7.2-68.3
Kidney	3	0.1	46.5	9.6-135
Skin, non-melanoma*	2	0.1	39.3	4.8-141

*Excludes basal cell carcinoma.

Table 3. Incidence rates and standardized incidence ratios (SIRs) for cancer after liver transplantation by age group (age at cancer diagnosis).

Age, years	Observed	Person-years of follow-up	Incidence (per 100 person-years)	SIR	95% CI
0-14	9	2698	0.3	20.9	9.6-39.7
15-29	14	3232	0.4	12.3	6.8-20.8
30+	14	1917	0.7	6.1	3.3-10.3
All	37	7846	0.5	9.8	6.8-13.3

Table 4. Factors associated with post-transplant de novo cancer by Cox regression analysis adjusted for age.

	Hazards ratio	95% CI	P
Age at transplant (per 1 year increment)	1.04	1.01-1.08	**0.01**
Female	1.04	0.55-1.99	0.90
Country			
Sweden	0.57	0.21-1.58	0.28
Norway	0.93	0.30-2.89	0.90
Finland	2.12	0.81-5.51	0.13
Denmark	Reference		
Decade of LT			
1980-1999	0.55	0.22-1.38	0.20
2000-	Reference		
Indication for transplantation			
Biliary atresia	Reference		
Acute liver failure	0.30	0.08-1.16	0.08
Primary sclerosing cholangitis	0.42	0.10-1.72	0.23
Metabolic liver disease	0.61	0.20-1.88	0.39
Liver tumor	1.16	0.30-4.52	0.83
Autoimmune hepatitis	0.48	0.09-2.59	0.39
Other	0.74	0.25-2.23	0.59
Immunosuppression during first month post LT			
Cyclosporine (vs tacrolimus)	1.13	0.44-2.88	0.80

Antimetabolite (vs no)	3.33	1.00-11.5	**0.049**
Azathioprine	3.39	0.90-12.8	0.07
Mycophenolate	3.27	0.84-12.8	0.09
None	Reference		
Steroids	0.98	0.13-7.36	0.99
IL2-receptor antibody	2.89	0.93-9.04	0.07
ATG/OKT antibody	0.00	0.00-	0.98