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Vitamin D status and risk of infections after liver transplantation in the Swiss Transplant Cohort Study

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Abbreviations:

BMI, body mass index

CsA, cyclosporine A

DBD, donation after brain death

EC-MPA, enteric-coated mycophenolate

IQR, interquartile range

MELD, model of end stage liver disease

MMF, mycophenolate mofetil

IRR, incidence rate ratio

RRT, renal replacement therapy

STCS, Swiss Transplant Cohort Study

Tac, tacrolimus

25-OHD, 25-OH vitamin D

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Abstract

Main problem

Increasing evidence indicates a role of vitamin D in the immune system affecting response to infections. We aimed to characterize the role of vitamin D status, i.e. deficiency (25-OH vitamin D [25-OHD] < 50nmol/l) and no deficiency (25-OHD ≥ 50nmol/l) in incident infections after liver transplantation.

Methods

In 135 liver transplant recipients blood samples drawn at time of liver transplantation and 6 months afterwards were used to determine 25-OHD levels. Incident infections episodes were prospectively collected within the STCS database. Poisson regression was applied to address associations between vitamin D status and incident infections.

Results

Vitamin D deficiency was common at time of transplantation and 6 months afterwards without a significant change in median 25-OHD levels. In univariable analyses vitamin D deficiency was a risk factor for incident infections in the first 6 months post-transplant (IRR 1.52, 95% CI 1.08-2.15, *P*=0.018) and for bacterial infections occurring after 6 up to 30 months post-transplant (IRR 2.29, 95% CI 1.06-4.94, *P*=0.034). These associations were not detectable in multivariable analysis with adjustment for multiple confounders.

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Conclusions

Efforts to optimize vitamin D supplementation in liver transplant recipients are needed. Our data question the role of vitamin D deficiency in incident infections.

(ClinicalTrials.gov number: NCT01204944)

Introduction

Vitamin D deficiency is highly prevalent in patients with end-stage organ failure including patients listed for organ transplantation [1-3]. The majority of vitamin D is synthesized in the skin via ultraviolet light exposure, only a small proportion is ingested by food intake. 25-position hydroxylation of vitamin D takes place in the liver forming 25-OH vitamin D (25-OHD) which is used as an indicator of vitamin D status [4]. In the kidneys an additional 1-position hydroxylation is performed resulting in the biologically active form 1, 25-$(OH)_2$ vitamin D [4].

Besides its well-established role for bone metabolism, vitamin D has been linked to infections [5], cardiovascular diseases and overall survival [6, 7] in the general population. In chronic liver disease vitamin D deficiency has been associated with the degree of liver dysfunction [8], infections [9] and even mortality [8, 9]. Some data suggest an influence of vitamin D on infections in solid organ transplant recipients [10, 11]. Beyond assessment of the vitamin D status at time of transplantation and 6 months after transplantation, our study specifically addressed the question whether vitamin D deficiency is associated with incident infections in liver graft recipients. We divided a total observation period of 2.5 years into two periods, the

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first 6 months after transplantation and 6 months post-transplant until 2.5 years post-transplant. Our analysis took the vitamin D status at time of transplantation and at 6 months post-transplant for the first period and the second period into account, respectively.

Patients and methods

Study design, population and patient-related data

This study was performed within the Swiss Transplant Cohort Study (STCS, www.stcs.ch, ClinicalTrials.gov number: NCT01204944). The STCS prospectively collects data and biosamples from all 6 transplant centers in Switzerland (i.e. Basel, Bern, Geneva, St. Gallen, Lausanne and Zurich). Since May 2008 all solid organ transplants have been registered within the STCS database, for data analysis and sampling an informed consent is obtained. Enrollment is > 93% of all transplantations in Switzerland [12]. The STCS was approved by the Ethic Committees of all participating institutions. Liver transplantations of enrolled participants were performed between May 2008 and July 2011. Enrolment included liver transplant recipients within the STCS, available plasma samples and ongoing informed consent at the follow up of 2.5 years after transplantation. With the exception of information about vitamin D supplementation, which was retrospectively added by patient chart review, all other data were prospectively collected. Dedicated professionals supervised by transplant infectious diseases physicians prospectively record infections every 6 months in the first year post-transplant and afterwards every year. For analysis of the association between vitamin D levels and infections, only clinical relevant infections, i.e. symptomatic and, if possible, resulting in targeted treatment, were considered. Clinical presentations interpreted suggestive of an infectious etiology and prompting initiation of antimicrobial treatment by the treating

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physicians were rated as probable infections, if routine diagnostics remained without identification of a pathogen. For the subgroup analysis of bacterial infections, we defined proven bacterial infections as clinically apparent infections combined with detection of the causative bacterium and initiation of targeted antimicrobial treatment.

Laboratory analysis

For laboratory analyses, prospectively collected blood samples of the participating transplant recipients were retrieved from the STCS biobank. Blood samples drawn at the time of transplant and samples obtained 6 months post-transplant were used for centralized, uniform measurement at the Institute of Clinical Chemistry of the University Hospital Zurich. 25-OH vitamin D measurement was performed with Roche Diagnostics Vitamin D total assay on Cobas® 8000 (Roche Diagnostics, Mannheim, Germany).

Vitamin D status was categorized as deficiency, if 25-OH vitamin D < 50nmol/l (20ng/ml), whereas 25-OH vitamin D levels ≥ 50nmol/l were considered as no deficiency.

Statistical analysis

All statistical analyses were performed with R (version 3.3.2). Continuous variables were reported as median and interquartile range (IQR), categorical variables as absolute numbers and frequencies (%). Statistical testing was performed with two-sided tests, *P*-values < 0.05 were considered significant. Wilcoxon rank-sum test was used for comparison of continuous variables between two groups, whereas Wilcoxon matched-pairs signed-rank test was applied

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for pairwise comparisons. Multiple group comparison was performed with Kruskal-Wallis test. Linear relationships were assessed by Pearson correlation. Categorical variables were compared using Fisher's Exact test. For investigation of the association between vitamin D levels and incident infections, we defined two observation periods. The first period referred to the timespan from transplantation to 6 months post-transplant, for this analysis vitamin D values measured at time of transplantation were considered. The second period comprised the timespan beginning after 6 months post-transplant until 30 months post-transplant, for this period, 25-OH vitamin D values determined at 6 months after transplantation were taken into account. For analysis regarding defined time periods, patients with shorter follow up either due to death or lost to follow up were excluded (5 out of 135 liver recipients for an observation period up to 30 months). Poisson regression was applied to identify risk factors associated with infections. In the univariable analysis we tested the variables age, sex, type of graft (whole vs. split), vitamin D status (no deficiency vs. deficiency), use of induction immunosuppression, body mass index (BMI) and self-reported mobility. In addition, model of end stage liver disease (MELD) and Child-Pugh score were added exclusively for the analysis on vitamin D levels peri-transplant and incident infections within the first 6 months after transplantation, as prior research highlighted relevance of these parameters in cirrhotic patients as well as in the early post-transplant period [13, 14]. If number of events was sufficient, all these variables were taken into the multivariable model with the exception of variables showing co-linearity. For the analysis of the association between vitamin D levels and incident proven bacterial infections after 6 up to 30 months after transplantation, we decided to limit our multivariable analysis on 5 independent variables with respect to the number of events (n=49) to avoid over-adjustment. The present model was chosen under consideration of best fit and the prerequisite of inclusion of vitamin D levels. Vitamin D supplementation at time transplant and 6 months after transplantation were intentionally not

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considered in analysis, as we addressed the associations with vitamin D levels itself and not the presence of supplementation therapy.

Results

Patients' characteristics

Of the 135 participants 64.4% were males, 132 (97.8%) were Caucasian. Median age of liver recipients was 54 years (IQR 45-61). The most common reasons for liver transplantation were hepatitis C (n=30, 22.2%), alcohol abuse (n=28, 20.7%), hepatitis B (n=15, 11.1%) or incidence of hepatocellular carcinoma (n=22, 16.3%). 126 (93.3%) grafts derived from deceased donors, 6 (4.4%) from living related donors and 3 (2.2%) from a living unrelated donor. At time of transplantation median model of end stage liver disease (MELD) score was 20 (IQR 14-28). Induction immunosuppression was administered in 90 (66.7%) participants. Peri-transplant 24 (17.8%) participants received cholecalciferol (median dose 800IU) and 2 (1.5%) participants 1, 25-dihydroxycholecalciferol (median dose 0.25µg). Six months post-transplant 55 (40.7%) liver recipients obtained supplementation with cholecalciferol (median dose 800IU) and 2 (1.5%) participants with 1, 25-dihydroxycholecalciferol (median dose 0.125 µg).

Vitamin D status

Peri-transplant the majority of liver transplant recipients showed a deficiency of 25-OHD (n=96, 71.1%). In 39 (28.9%) individuals 25-OHD levels of at least 50nmol/l were detected. Six months post-transplant 88 (66.2%) patients had vitamin D deficiency. No vitamin D

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deficiency was present in 45 (33.8%) individuals (Figure 1). 25-OHD measured peri-transplant (median 32.5nmol/l, IQR 12.6-55.8nmol/l) and 6 months post-transplant (median 35.4nmol/l, IQR 19.7-62.7nmol/l) did not significantly differ (*P*=0.067). At transplantation 88.0% of liver recipients without vitamin D supplementation showed 25-OHD values < 50nmol/l (vs. 50.0% of recipients treated with vitamin D analogues). Six months after transplantation 50.0% of liver recipients with supplementation therapy and 77.5% without supplementation were vitamin D deficient (25-OHD < 50nmol/l).

Vitamin D status and infections

Infections within the first 6 months post-transplant of liver recipients

Overall 190 infections affecting 94 participants occurred within the first 6 months after liver transplantation: 98 (51.6%) bacterial, 41 (21.6%) viral, 6 (3.2%) fungal infections, 1 (0.5%) parasitic infection and 44 (23.2%) suspected infections prompting antimicrobial treatment, in which identification of the causative pathogen was not successful (Figure 2). The most common, by bacterial infections affected sites were the gastrointestinal tract (n=40, 40.8%), bacteremia (n=22, 22.5%), urinary tract (n=13, 13.3%) and respiratory tract (n=5, 5.1%) (Figure 3).

Univariable Poisson regression showed an increased risk of infection for administration of induction immunosuppression (IRR 1.48, 95%CI 1.07 to 2.05; *P*=0.019), higher MELD (IRR 1.04, 95%CI 1.02 to 1.06; *P*<0.001) or Child-Pugh score (IRR 1.08, 95%CI 1.01 to 1.16; *P*=0.017) and vitamin D deficiency (IRR 1.52, 95%CI 1.08 to 2.15; *P*=0.018) (Table 2). No association with incident infections were found for age, sex, type of liver graft, BMI and self-

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reported mobility at time of transplantation. With regard to co-linearity between MELD and Child-Pugh score, only MELD score was added to the multivariable model (r=0.435, P<0.001). In multivariable analysis higher MELD score (IRR 1.03, 95%CI 1.01 to 1.05; P=0.003) correlated positively with risk of incident infections, whereas male sex was protective (IRR 0.67, 95%CI 0.45 to 0.98; P=0.040). No significant association with vitamin D levels was detected.

Restricting Poisson regression to bacterial infections identified a positive correlation with increasing MELD (univariable IRR 1.05, 95%CI 1.03 to 1.07; P<0.001), Child-Pugh score (univariable IRR 1.17, 95%CI 1.06 to 1.28; P=0.001) as well as higher BMI (univariable IRR 1.04, 95%CI 1.00 to 1.08; P=0.037) (Table 3). In a multivariable model male sex was associated with a lower risk of incident infections (IRR 0.52, 95%CI 0.30 to 0.91; P=0.021), but none of the additionally investigated variables, including vitamin D levels at time of transplantation, showed a significant association.

Infections after 6 up to 30 months after liver transplantation

A total of 158 infections affecting 68 individuals were recorded in this observation period, composed of 49 (31.0%) bacterial infections, 24 (15.2%) viral infections, 4 (2.5%) fungal infections and 81 (51.3%) infections without identification of the causative pathogen (Figure 2). Bacterial infections most frequently were bacteremia (n=13, 26.5%) or affected the gastrointestinal tract (n=9, 18.4%), respiratory tract (n=8, 16.3%) or the skin and mucous membranes (n=8, 16.3%) (Figure 3).

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In univariable analysis increasing age protected from infections (IRR per decade 0.83, 95%CI 0.76 to 0.92; *P*<0.001), whereas vitamin D status, sex, type of liver graft, use of induction immunosuppression, BMI at 6 months post-transplant and self-reported mobility 6 months after transplantation did not show a significant association with incident infections. Multivariable analysis identified increased risk of incident infections in transplant recipient reporting major limitations in self reported mobility 6 months after transplantation (IRR 3.62, 95%CI 1.01 to 12.90; *P*=0.047), solely.

Focusing exclusively on bacterial infections vitamin D deficiency (IRR 2.29, 95%CI 1.06 to 4.94; *P*=0.034) and male sex (IRR 3.34, 95%CI 1.41 to 7.92; *P*=0.006) increased risk of incident infections, but increasing age (IRR 0.84, 95%CI 0.70 to 1.00; *P*=0.049) was protective in univariable analysis (Table 3). Multivariable analysis only confirmed the positive correlation between male sex and incident infections (IRR 2.99, 95%CI 1.17 to 7.63; *P*=0.022). Notably, vitamin D status (IRR 1.09, 95%CI 0.45 to 2.66; *P*=0.844) lost its association after adjustment.

Discussion

In our study vitamin D status of liver allograft recipients was determined by uniform, centralized measurement utilizing prospectively collected samples gathered at the time of transplantation and 6 months post-transplant. Vitamin D deficiency was highly prevalent at both time points, transplantation and 6 months post-transplant. In longitudinal measurements, no significant change in 25-OHD levels was observed in liver graft recipients. Multivariable analyses did not confirm an association of vitamin D levels with incident infections or proven bacterial infections.

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In chronic liver disease vitamin D deficiency is common [9]. Several reasons may contribute to persisting vitamin D deficiency after transplantation. Physicians might have prescribed an insufficient dose of vitamin D, which could be aggravated by an increased demand (compared to non-transplant patients) to reach normal vitamin D levels. Recent reports indicated that an initial loading dose is beneficial to replenish vitamin D levels [15]. Notably, none of our patients received a loading dose. Furthermore, transplant patients are instructed to avoid sun exposure, because of the increased risk of skin cancer due to immunosuppression, which results in omission of the most important vitamin D source. This hypothesis is also supported by the absence of a seasonal influence on 25-OHD 6 months post-transplant (Supplemental Table 1). In our opinion, malcompliance with prescribed supplementation therapy seems unlikely, but there was no assessment for compliance with supplementation therapy. Approaches to improve vitamin D supplementation therapy might benefit from a better knowledge of pharmacokinetics in transplant recipients [16, 17].

Several studies support a link between vitamin D and antimicrobial effects; an impact on both innate and adaptive immunity is postulated. 1, 25-$(OH)_2$ vitamin D can be produced by monocytes and macrophages via CYP27B1-hydroxylase using 25-OHD as necessary substrate. The produced 1, 25-$(OH)_2$ vitamin D activates vitamin D receptor-directed genes such as cathelicidin and results in killing of the ingested pathogen [18, 19]. The active form of cathelicidin, LL-37, has been shown to be able to disrupt bacterial membranes and viral envelopes [20]. This mechanism seems not to be limited to monocytes and macrophages. Increasing evidence is present for barriers like skin [21], gut [22] and lung [23] being capable of using this pathway. This pathway might be hampered if an insufficient amount of 25-OHD is available. In cirrhotic patients a positive correlation between vitamin D deficiency and incident infections has been reported previously [9, 24]. In the present study, univariable

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analyses showed an association of vitamin D deficiency and incident infections within the first 6 months (first observation period) and bacterial infections after 6 up to 30 months post-transplant. However, multivariable analyses could not confirm these associations indicating that adjustment for confounders vanished the observation.

Limitations of our study are the retrospective assessment of vitamin D supplementation. The strengths include serial 25-OHD measurement with uniform methods, the prospective study design and the availability of follow-up data up to 2.5 years post-transplant for almost all study participants.

In conclusion, our study challenges the postulated role of vitamin D in infections after liver transplantation, as this association got lost after adjustment for multiple confounders. Despite supplementation therapy a relevant proportion of our patients were deficient or severely deficient, a finding in need of action.

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Tables

Table 1: Baseline characteristics

Variable	
Age (median (IQR))	54y (45-61)
Sex (n, %)	Male 87 (64.4%) Female 48 (35.6%)
Ethnicity (n, %)	Caucasian 132 (97.8%) Asian 2 (1.5%) African 1 (0.7%)
Underlying disease (n ,%)	Hepatitis C 30 (22.2%) Alcohol abuse 28 (20.7%) Hepatocellular carcinoma 22 (16.3%) Hepatitis B 15 (11.1%) Extrahepatic biliary atresia 5 (3.7%) Primary biliary cirrhosis 5 (3.7%) Extrahepatic biliary atresia 5 (3.7%) Cholangiocarcinoma 4 (3.0%) Primary sclerosing cholangitis 4 (3.0%) Other 17 (12.6%)
MELD (median (IQR))	20 (14-28)
Child – Pugh stage[*] (n, %)	A 44 (32.6%) B 42 (31.1%) C 29 (21.5%)
Hepatorenal syndrome (n, %)	Present, no RRT 18 (13.3%) Present, RRT 12 (8.8%) Absent, no RRT 98 (72.6%) Unknown 7 (5.2%)
Type of donation (n, %)	Deceased donor: DBD 126 (93.3%) Living donor: related 6 (4.4%) living unrelated 3 (2.2%)
Type of transplant (n, %)	Whole liver 121 (89.7%) Split liver 14 (10.4%)
Induction therapy (n, %)	Basiliximab 89 (65.9%)[##] Rituximab 1 (0.7%) None 45 (33.3%)
Maintenance immunosuppression[#] (n, %)	Tac+MMF+steroids 17 (12.6%) Tac+MMF 24 (17.8%) Tac solely 17 (12.6%) CsA+MMF+steroids 8 (5.9%) CsA+MMF 20 (14.8%) CsA solely 7 (5.2%) MMF+steroids 4 (3.0%) Other regimen 38 (28.1%)
Vitamin D supplementation (n, %)	peri-transplant** cholecalciferol 24 (17.8%) 1, 25-dihydroxycholecalciferol 2 (1.5%) None 108 (80.0%) 6 months post-transplant*** cholecalciferol 55 (40.7%)

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	1, 25-dihydroxycholecalciferol 2 (1.5%) None 70 (51.9%)

[#] at 6 months post-transplant

[##] 1 combined with glucocorticoids, 1 combined with rituximab

* data for 20 participants missing

** data for 1 participant missing

*** data for 8 participants missing

Abbreviations: CsA: cyclosporine A, DBD: donation after brain death, EC-MPA: enteric-coated mycophenolate, MELD: Model for End-Stage Liver Disease, MMF: mycophenolate mofetil, RRT: renal replacement therapy, Tac: tacrolimus

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Table 2: Poisson regression analysis of risk for infections within the first 6 months post-transplant and after 6 up to 30 months post-transplant

	first 6 months post-transplant				after 6 up to 30 months post-transplant			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*
Vitamin D status[#]								
No deficiency	Reference		Reference		Reference		Reference	
Deficiency	1.52 (1.08 to 2.15)	0.018	1.19 (0.79 to 1.81)	0.408	1.15 (0.81 to 1.64)	0.430	1.19 (0.75 to 1.91)	0.461
Age								
Per decade increase	0.99 (0.90 to 1.09)	0.875	0.93 (0.79 to 1.08)	0.323	0.83 (0.76 to 0.92)	<0.001	0.93 (0.77 to 1.14)	0.498
Sex								
Female	Reference				Reference		Reference	
Male	0.79 (0.59 to 1.06)	0.114	0.67 (0.45 to 0.98)	0.040	1.36 (0.95 to 1.96)	0.094	1.19 (0.75 to 1.89)	0.464
MELD score*								
Per point increase	1.04 (1.02 to 1.06)	<0.001	1.03 (1.01 to 1.05)	0.003				
Child-Pugh score*								
Per point increase	1.08 (1.01 to 1.16)	0.017						
Type of graft								
whole liver	Reference				Reference		Reference	
split liver	1.02 (0.64 to 1.62)	0.944	1.31 (0.64 to 2.70)	0.465	1.56 (0.97 to 2.50)	0.065	1.15 (0.54 to 2.45)	0.726
Induction immunosuppression	Reference		Reference		Reference		Reference	
None	1.48 (1.07 to 2.05)	0.019	1.53 (1.00 to 2.34)	0.052	1.23 (0.86 to 1.76)	0.262	0.89 (0.56 to 1.41)	0.620
Any								
BMI[#]								
Per point increase	1.02 (0.99 to 1.05)	0.204	1.01 (0.97 to 1.05)	0.678	0.98 (0.94 to 1.01))	0.218	1.03 (0.97 to 1.08)	0.353
Mobility[#]								
No problems	Reference		Reference		Reference		Reference	
Some problems	1.00 (0.71 to 1.42)	0.996	0.84 (0.58 to 1.20)	0.333	1.16 (0.77 to 1.76)	0.474	1.07 (0.68 to 1.69)	0.758
Confined to bed	2.04 (0.82 to 5.04)	0.125	1.25 (0.48 to 3.25)	0.645	3.16 (1.00 to 10.04))	0.051	3.62 (1.01 to 12.90)	0.047

MELD: model of end stage liver disease

* at time of transplantation

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[#] assessment at time of transplantation and at 6 months post-transplant used for analysis of incident infections within first 6 months post-transplant and after 6 up to 30 months post-transplant, respectively

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Table 3: Poisson regression analysis of risk for bacterial infections within the first 6 months post-transplant and after 6 up to 30 months post-transplant

	first 6 months post-transplant				after 6 up to 30 months post-transplant			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*
Vitamin D status[#]								
No deficiency	Reference		Reference		Reference		Reference	
Deficiency	1.49 (0.92 to 2.41)	0.106	0.96 (0.54 to 1.70)	0.879	2.29 (1.06 to 4.94)	0.034	1.09 (0.45 to 2.66)	0.844
Age								
Per decade increase	1.00 (0.88 to 1.15)	0.973	0.99 (0.78 to 1.25)	0.901	0.84 (0.70 to 1.00)	0.049	0.79 (0.56 to 1.11)	0.170
Sex								
Female	Reference				Reference		Reference	
Male	0.80 (0.53 to 1.20)	0.278	0.52 (0.30 to 0.91)	0.021	3.34 (1.41 to 7.92)	0.006	2.99 (1.17 to 7.63)	0.022
MELD score*								
Per point increase	1.05 (1.03 to 1.07)	<0.001	1.02 (0.99 to 1.06)	0.131				
Child-Pugh score*								
Per point increase	1.17 (1.06 to 1.28)	0.001						
Type of graft								
whole liver	Reference		Reference		Reference			
split liver	1.32 (0.74 to 2.37)	0.349	1.20 (0.41 to 3.52)	0.741	0.47 (0.11 to 1.95)	0.299		
Induction immunosuppression	Reference		Reference		Reference			
None	1.46 (0.93 to 2.30)	0.103	1.48 (0.78 to 2.81)	0.227	1.17 (0.61 to 2.24)	0.641		
Any								
BMI[#]								
Per point increase	1.04 (1.00 to 1.08)	0.037	1.03 (0.96 to 1.10)	0.403	0.96 (0.89 to 1.03)	0.228	0.95 (0.86 to 1.04)	0.267
Mobility[#]								

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No problems	Reference		Reference		Reference		Reference	
Some problems	0.91 (0.55 to 1.51)	0.711	0.73 (0.43 to 1.23)	0.239	1.54 (0.73 to 3.23)	0.256	1.63 (0.75 to 3.50)	0.216
Confined to bed	0.84 (0.12 to 6.12)	0.862	0.49 (0.06 to 3.77)	0.493	4.05 (0.54 to 30.27)	0.173	3.70 (0.40 to 34.04)	0.248

MELD: model of end stage liver disease

* at time of transplantation

[#] assessment at time of transplantation and at 6 months post-transplant used for analysis of incident infections within first 6 months post-transplant and after 6 up to 30 months post-transplant, respectively

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Figure legends

Figure 1: Distribution of 25-OH vitamin D values of liver transplant recipients peri-transplant and 6 months post-transplant

Figure 2: Infections occurring in the first 6 months after transplantion and more than 6 up to 30 months post-transplant

Figure 3: Site of infection in bacterial infections after liver transplantation

Appendices

The members of the Swiss Transplant Cohort Study are: Patrizia Amico, John-David Aubert, Vanessa Banz, Guido Beldi, Christian Benden, Christoph Berger, Isabelle Binet, Pierre-Yves Bochud, Elsa Boëly, Heiner Bucher, Thierry Carell, Emmanuelle Catana, Yves Chalandon, Sabina de Geest, Olivier de Rougemont, Michael Dickenmann, Michel Duchosal, Laure Elkrief, Thomas Fehr, Sylvie Ferrari-Lacraz, Christian Garzoni, Paola Gasche Soccal, Christophe Gaudet, Emiliano Giostra, Déla Golshayan, Karine Hadaya, Jörg Halter, Dominik Heim, Christoph Hess, Sven Hillinger, Hans H. Hirsch, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Richard Klaghofer, Michael Koller (Head of the data center), Bettina Laesser, Roger Lehmann, Christian Lovis, Pietro Majno; Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Pascal Meylan, (Head, Biological samples management group), Paul Mohacsi, Philippe Morel, Ulrike Mueller, Nicolas J Mueller (Chairman Scientific Committee), Helen Mueller-McKenna (Head of local data management), Antonia Müller, Thomas Müller, Beat Müllhaupt, Manuel Pascual (Executive office), Jakob Passweg, Klara Posfay-Barbe, Juliane

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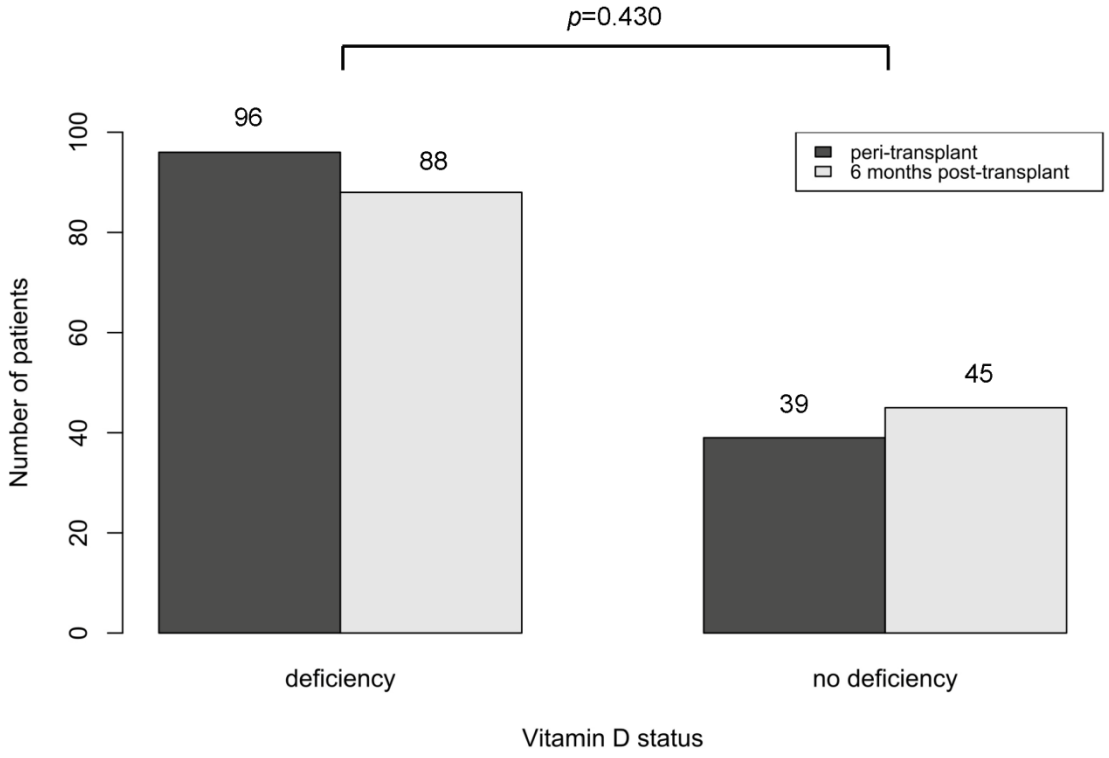

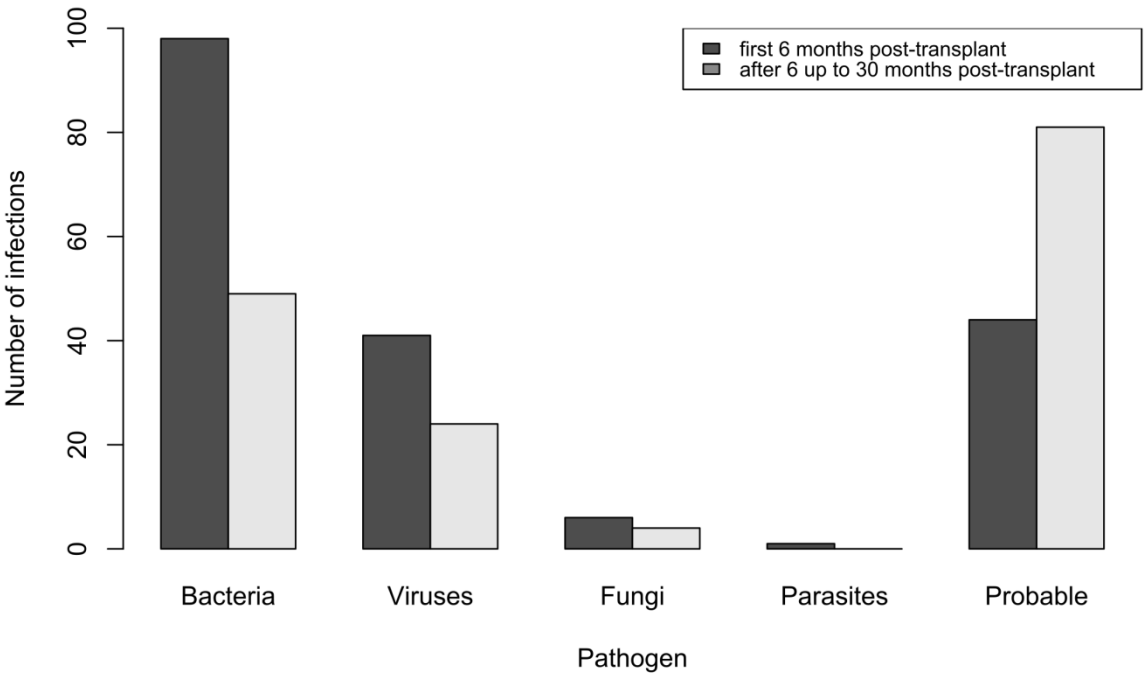

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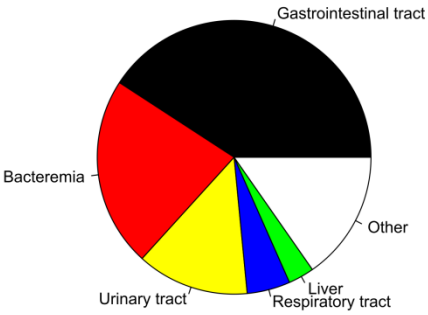
Bacterial infections first 6 months post-transplant



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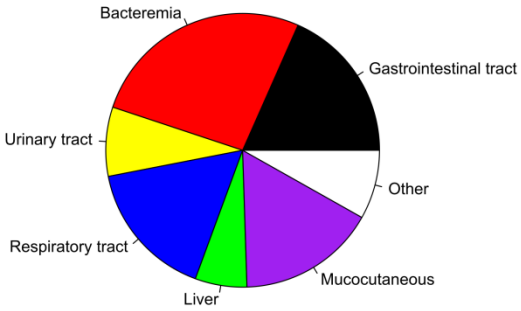

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