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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Decision tree analysis to stratify risk of de novo non-melanoma skin cancer following liver transplantation

Tomohiro Tanaka[1] · **Michael D. Voigt**[1]

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Abstract

Purpose Non-melanoma skin cancer (NMSC) is the most common de novo malignancy in liver transplant (LT) recipients; it behaves more aggressively and it increases mortality. We used decision tree analysis to develop a tool to stratify and quantify risk of NMSC in LT recipients.

Methods We performed Cox regression analysis to identify which predictive variables to enter into the decision tree analysis. Data were from the Organ Procurement Transplant Network (OPTN) STAR files of September 2016 ($n = 102984$).

Results NMSC developed in 4556 of the 105984 recipients, a mean of 5.6 years after transplant. The 5/10/20-year rates of NMSC were 2.9/6.3/13.5%, respectively. Cox regression identified male gender, Caucasian race, age, body mass index (BMI) at LT, and sirolimus use as key predictive or protective factors for NMSC. These factors were entered into a decision tree analysis. The final tree stratified non-Caucasians as low risk (0.8%), and Caucasian males > 47 years, BMI < 40 who did not receive sirolimus, as high risk (7.3% cumulative incidence of NMSC). The predictions in the derivation set were almost identical to those in the validation set ($r^2 = 0.971$, $p < 0.0001$). Cumulative incidence of NMSC in low, moderate and high risk groups at 5/10/20 year was 0.5/1.2/3.3, 2.1/4.8/11.7 and 5.6/11.6/23.1% ($p < 0.0001$).

Conclusions The decision tree model accurately stratifies the risk of developing NMSC in the long-term after LT.

Keywords De novo malignancy · Skin cancer · Non-melanoma · Liver transplantation · Decision tree

Introduction

De novo malignancy is common in transplant recipients (Vogt et al. 2002); it occurs in about 10% of liver transplant recipients at 10 years (Collett et al. 2010); Non-melanoma skin cancer [NMSC, basal cell carcinoma (BCC) or squamous cell carcinoma (SCC)] is the most common malignancy in transplant recipients (Jensen et al. 2010; Belloni-Fortina et al. 2012; Haagsma et al. 2001); and may occur in up to 37% within 10 years after transplantation. This is a 30–100-times greater incidence than the general population (Herrero 2009). These skin cancers are also more aggressive than those in the general population. NMSC causes significant morbidity ranks in the top 5 most costly cancers in the United States (Soltani-Arabshahi and Tristani-Firouzi 2013; Housman et al. 2003). Although risk factors for NMSC following LT are well described (Mithoefer et al. 2002; Bellamy et al. 2001; McCaughan and Vajdic 2013; Garrett et al. 2017), these factors cannot easily be used to stratify or quantify an individual's risk (Belloni-Fortina et al. 2012; McCaughan and Vajdic 2013).

Multiple methods that make use of artificial intelligence or machine learning have greatly improved the accuracy of predictive analytics. The drawback of many of these techniques is that the algorithms are opaque black boxes which are difficult to translate into clinically useful algorithms. Decision tree analysis is an exception, as it is a form of machine learning that establishes hierarchical trees that are simple to understand and interpret, and are easy to use to individualize each patient's care. This method has been used in variety of scientific papers including oncology (Leiter et al. 2004; Kurosaki et al. 2012; Garzotto et al. 2005; Valera et al. 2007). We therefore used decision tree analysis to see if it could provide a more accurate and intuitive algorithm to stratify and quantify the long term risk of NMSC post-liver transplant using variables available from peritransplant

✉ Tomohiro Tanaka
tomohiro-tanaka@uiowa.edu

[1] Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA, USA

period, with a view to providing more personalized care such as starting chemoprophylaxis, altering immune suppression regimens, and providing increased surveillance in high risk patients (Kim et al. 2016).

Methods

This study was approved by the University of Iowa Institutional Review Board (IRB #201701798). We analyzed deceased donor liver transplants, based on Organ procurement Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) STAR file as of September 30, 2016. This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C. The content of the analysis is the responsibility of the authors' alone and does not necessarily reflect the views or policies of the Department of Health and Human Services. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government.

Patients

We reported categorical data as median and interquartile range, and continuous data as mean and standard deviation. In the comparison of NMSC and unaffected groups, we used two-sided Student's *t* test for continuous data and analysis of variance or Chi-test as appropriate for categorical data as appropriate.

We entered the following variables which were available from peritransplant period into a Cox regression model to identify predictors of de novo skin cancer: recipient's gender and age at LT, race, liver disease diagnosis, presence of hepatocellular cancer (HCC), final laboratory model for end stage liver disease (MELD) score, body mass index (BMI),human leukocyte antigen (HLA) mismatch, donor age, blood group ABO compatibility, cold ischemic time, acute cellular rejection (ACR) within 30 days post-LT, thymoglobulin induction, basiliximab induction, choice of immune suppression at discharge from first transplant admission, use of sirolimus or mycophenolate mofetil (MMF). Our primary outcome was the time to diagnosis of skin cancer. Those variables were selected from basic demographics and also based on previous research showing an effect on post-transplant skin cancer. Those were selected based on basic characteristics available from the database and previous research showing an effect on skin cancer post-transplant.

Data-mining analysis

Into the decision tree analysis, we entered the variables which Cox regression identified as the independent positive or negative predictors of developing NMSC after LT. We used JMP Pro 11 (SAS Institute, Cary, NC, USA) to data-mine 105,984 deceased donor liver transplants in the UNOS/OPTN data files. We randomly divided the data into a model building set used to generate the model, and a validation set to validate the model. The model building set consisted of two-thirds of the patients ($n = 70{,}656$) and the validation set of complement of one-third ($n = 35{,}328$). We have previously documented the methods elsewhere (Tanaka et al. 2015; Kurosaki et al. 2010). Briefly, this analysis belongs to a family of nonparametric regression methods based on binary recursive partitioning of data to produce a model in the form of a tree structure. It incrementally divides the data into smaller subsets which are optimized according to the amount of information gained by each subsequent partition into a subset. The software uses entropy analysis to explore the data to search for optimal split variables, and build the optimal decision tree that will classify all subjects into particular subgroups. These subgroups are homogeneous with respect to their ability to predict a certain stratum of risk of developing NMSC post-liver transplant. Initially the entire study population is split into subgroups that stratify the risk of developing NMSC; then each of these subgroups can be further subdivided such that the sub-subgroups better stratify the risk of NMSC. Further subdivisions are made if the sub-sub-groups improve the classification of the risk of de novo skin cancer post-LT. We imposed a restriction that the terminal subgroups resulting from any given split must contain at least 500 patients. The decision tree analysis stopped when either no additional information was gained by a split, or the subset size fell below 500. The resulting final subgroups were the most homogeneous with respect to a stratum of risk of de novo skin cancer. The model classified patients into subgroups with different skin cancer incidence rates in a flowchart form. The accuracy and reproducibility of the model that was derived in the model building set was validated in the randomly selected validation set. I addition we used Kaplan-Meier analysis to compare the cumulative incidence of NMSC for each derived subgroup, as each subgroup represented a specific (high, intermediate or low) level of risk and used the log rank statistic for significance. Cox hazard model was then used in the generation of the predictive index using model derivation set (Chen and George 1985). Area under the ROC curve (AUROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the generated predictive index in the validation set.

Of all the 105,984 patients, 2147 (0.02%) had 1 or 2 missing value(s) in the variables: decision tree model classifies missing values as a separate category that can be analyzed with the other categories. Otherwise missing values were treated with imputation by the personal mean score.

Results

De novo NMSC developed in 4556 (4.2%) of the 105,984 recipients, at a median follow up of 6.7 years, giving an incidence rate of 1285 per 100,000 person-years. Two thousand and seventy subjects had basal cell cancer (BCC), 3022 had squamous cell and 536 had both. The rate of NMSC was 2.9/6.3/13.5% at 5/10/20 years, respectively. Mean age at diagnosis was 63 (± 2.9) years. The patient characteristics are shown in Tables 1 and 2.

The Cox regression identified male gender, Caucasian race, older age, lower BMI at LT, and lack of sirolimus at discharge from initial transplant surgery as significant risk factors for NMSC ($p < 0.05$, respectively). Choice of immunosuppressant other than sirolimus, etiology of liver disease or episode of acute cellular rejection within 6 month post-LT were not associated with the risk (Table 3).

Using these identified risk factors, we performed decision tree analysis using the randomly selected model building dataset ($n = 70,656$). All variables were similar (with no statistic difference) when comparing the model building and validation sets (Table 2). The decision tree analysis identified 6 subgroups that optimally stratified the risk after identifying the best cutoff levels for each factor (Fig. 1). The strongest initial predictor was Caucasian ethnic group. Non-Caucasians had a 0.8% risk of developing NMSC vs 5.6% in Caucasians. Increased age was the second strongest predictor. Among Caucasians, the model showed that recipients ≥ 47-years-old at LT had a NMSC rate of 6.4% vs only 3.1% in patients younger than 47. In Caucasians older than 47, male vs female gender (7.2 vs 4.6%), BMI < 40 (7.3 vs 4.4%) and not receiving sirolimus (7.4 vs 5.5%) serially stratified patients in the intermediate risk groups. Separate sub-analysis was also performed to evaluate the development of de novo squamous cell carcinoma (SCC). The multivariate Cox regression model and the decision tree was the same as that of the overall de novo NMSC (same variables with the same cutoff levels), except the use of the sirolimus was not chosen in the decision tree model: non-Caucasian had a 0.5% risk of de novo SCC vs 5.0% in Caucasian male older than 47-years-old with BMI < 40 at LT.

Table 1 Clinical characteristics of the recipients with ($n = 4556$) and without ($n = 101,428$) DNNMSC

	Without de novo NMSC ($n = 101,428$)	With de novo NMSC ($n = 4556$)	*p*
Male gender, *n* (%)	65,058 (64)	3413 (75)	< 0.001
Age at liver transplant	51.8 (0.03)	55.5(0.16)	< 0.001
Caucasian, *n* (%)	74,547 (73)	4347 (95)	< 0.001
Liver etiology at LT, *n* (%)			
ALD	19,329 (19)	1033 (23)	< 0.001
PSC/PBC	10,864 (11)	571 (13)	
AIH	3220 (3.2)	146 (3.2)	
Other	68,015 (67)	2806 (62)	
HCC at LT, *n* (%)	14,377 (14)	577 (13)	0.004
MELD at LT	21.5 (0.04)	20.4 (0.19)	0.002
BMI at LT	28.3 (0.29)	27.8 (1.31)	0.7
HLA mismatch	4.6 (0.005)	4.5 (0.02)	0.002
Donor age	38.6 (0.05)	39.0 (0.25)	0.12
Cold ischemic time (h)	7.6 (0.013)	7.5 (0.64)	0.2
ACR within 30 days, *n* (%)	12,678 (12)	529 (12)	0.7
On thymo induction, *n* (%)	6153 (6)	223 (5)	0.008
On basiliximab induction, *n* (%)	9322 (9)	397 (9)	0.27
On FK at discharge (vs CsA), *n* (%)	70,780 (70)	3283 (72)	0.9
On Sirolimus[a], *n* (%)	2960 (3)	100 (2)	0.003
On MMF[a], *n* (%)	52,607 (52)	2509 (55)	< 0.001
Follow-up period (years)[b]	6.71 (0.016)	6.27 (0.079)	< 0.001

Data presented as mean (± SD) unless otherwise indicated

NMSC non-melanoma skin cancer, *ALD* alcoholic liver disease, *PSC* primary sclerosing cholangitis, *PBC* primary biliary cholangitis, *AIH* autoimmune hepatitis, *HCC* hepatocellular carcinoma. *ACR* acute cellular rejection, *MMF* mycophenolate mofetil

[a]At last follow up or at the diagnosis of skin cancer, whichever comes first

[b]Till death, lost follow up or occurrence of the de novo skin cancer, whichever comes first

Table 2 Clinical characteristics of the model building cohort ($n=70,656$) and validation cohort ($n=35,328$)

	Building ($n=70,656$)	Validation ($n=35,328$)	p
Male gender, *n* (%)	45,614 (67)	22,857 (65)	0.64
Age at liver transplant	52 (0.04)	52 (0.06)	0.57
Development of de novo NMSC, *n* (%)	3069 (4.3)	1478 (4.2)	0.68
Age at first de novo NMSC	63 (2.7)	62 (3.6)	0.41
Caucasian, *n* (%)	52,605 (74)	26,289 (74)	0.84
Liver etiology at LT, *n* (%)			
ALD	13,695 (19)	6667 (19)	0.06
PSC/PBC	7682 (11)	3753 (11)	
AIH	2262 (3)	1104 (3)	
Other	47,017 (66)	23,804 (67)	
HCC at LT, *n* (%)	9969 (14)	4958 (14)	0.62
MELD at LT	21.5 (0.05)	21.5 (0.07)	0.98
BMI at LT	28.0 (0.02)	28.1 (0.03)	0.65
HLA mismatch	4.6 (0.006)	4.6 (0.008)	0.72
Donor age	38.7 (0.06)	38.5 (0.09)	0.12
ABO, *n* (%)			0.56
Identical	65,158 (93)	32,529 (92)	
Compatible	4858 (7)	2487 (7)	
Mismatch	618 (0.9)	300 (0.9)	
Cold ischemic time (h)	7.6 (0.02)	76 (0.03)	0.66
ACR within 30 days, *n* (%)	8908 (12)	4299 (12)	0.06
On thymo induction, *n* (%)	4218 (6)	2158 (6)	0.37
On basiliximab induction, *n* (%)	6475 (9)	3244 (9)	0.92
On FK at discharge (vs CsA), *n* (%)	49,333 (80)	24,730 (80)	0.93
On Sirolimus[a], *n* (%)	2363(3.3)	1086 (3.1)	0.42
On MMF[a], *n* (%)	36,779 (52)	18,337 (52)	0.64
Follow-up period (years)[b]	6.7 (0.2)	6.7 (0.3)	0.52

Data presented as mean (± SD) unless otherwise indicated

NMSC non-melanoma skin cancer, *ALD* alcoholic liver disease, *PSC* primary sclerosing cholangitis, *PBC* primary biliary cholangitis, *AIH* autoimmune hepatitis, *HCC* hepatocellular carcinoma, *ACR* acute cellular rejection, *MMF* mycophenolate mofetil

[a]At last follow up or at the diagnosis of skin cancer, whichever comes first

[b]Till death, lost follow up or occurrence of the de novo skin cancer, whichever comes first

Based on this decision tree analysis, we identified three levels of risk for de novo NMSC [low (L), intermediate (Ia, Ib, Ic and Id) and high (H)] with rates varying from 0.8 to 7.4%. The low risk group (group L) included only non-Caucasians. The high risk group (group H) included Caucasian males, who were older than 47 at LT, who had a BMI ≤ 40, and who did not receive sirolimus. The intermediate risk groups [intermediate risks (Groups Ia, b, c and d)] were those with some but not all of the factors (Fig. 1).

When we applied the yardstick derivated by decision tree analysis which were developed in the model building set to the randomly selected independent validation set of 35,328 patients, NMSC developed in 0.74% of the low risk group, 7.2% of the high risk group and 2.96% (Group Ia), 4.7% (Group Ib), 3.5% (Group Ic), 4.8% (Group Id) in the intermediate risk group. We validated the model by comparing the results of model building set with those of the validation set; the rates of NMSC for each subgroup of patients in this comparison were closely correlated ($r^2=0.971$, $p<0.0001$) (Fig. 2) which indicates the accuracy of this model in predicting the stratum of risk.

Kaplan–Meier analysis demonstrates that the low-, intermediate- and high-risk groups had significantly different cumulative hazards of developing NMSC (Fig. 3). The 5/10/20-year NMSC cumulative rates were 0.5/1.2/3.3, 2.1/4.8/11.7 and 5.6/11.6/23.1% in the 3 risk groups respectively ($p<0.0001$]).

We also performed separate Kaplan–Meier analysis to assess the actual impact of the sirolimus, which was the only post-transplant variable, in different risk groups: among those with Caucasian race, which were chosen as the most potent risk factor per the current decision tree model, the

Table 3 Multivariate cox hazard model to identify risk factors associated with de novo NMSC

	HR	95% CI	*p*
Male gender	1.82	1.06–3.25	0.029
Age at LT	1.06	1.03–1.09	< 0.001
Caucasian (vs others)	2.0	1.04–4.5	0.036
Liver etiology at LT			0.27
ALD vs others	1.32	0.74–2.28	
PSC/PBC/AIH vs others	3.50	0.80–10.3	
HCC at LT	0.95	0.48–1.78	0.88
MELD at LT	0.45	0.09–2.1	0.32
BMI at LT	0.96	0.92–0.99	0.045
HLA mismatch	0.85	0.71–1.01	0.07
Donor age	1.01	0.99–1.02	0.42
ABO mismatch	2.0	0.61–12.1	0.50
Cold ischemic time (h)	0.99	0.90–1.06	0.78
ACR within 30 days	1.32	0.70–2.34	0.38
On thymo induction	0.75	0.26–1.37	0.54
On basiliximab induction	1.58	0.88–2.7	0.12
On FK at discharge (vs CsA)	1.13	0.41–4.7	0.83
On Sirolimus[a]	0.52	0.01–0.73	0.023
On MMF[a]	1.05	0.63–1.85	0.84

HR hazard ratio, *ALD* alcoholic liver disease, *PSC* primary sclerosing cholangitis, *PBC* primary biliary cholangitis, *AIH* autoimmune hepatitis, *HCC* hepatocellular carcinoma. *ACR* acute cellular rejection, *MMF* mycophenolate mofetil

[a]At last follow up or at the diagnosis of skin cancer, whichever comes first

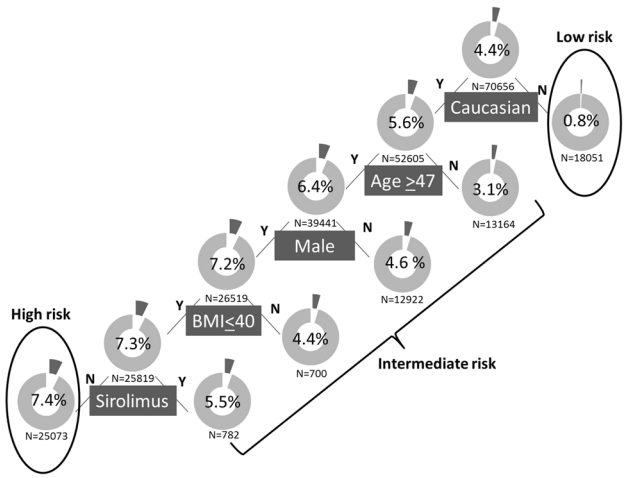

Fig. 1 Decision tree model developed in the model building set. Boxes indicate the factors used to differentiate patients and the cutoff values for each group. Pie charts indicate the incident rate of NMSC for each group of recipients. Those groups were classified into three subgroups based on the incident rate

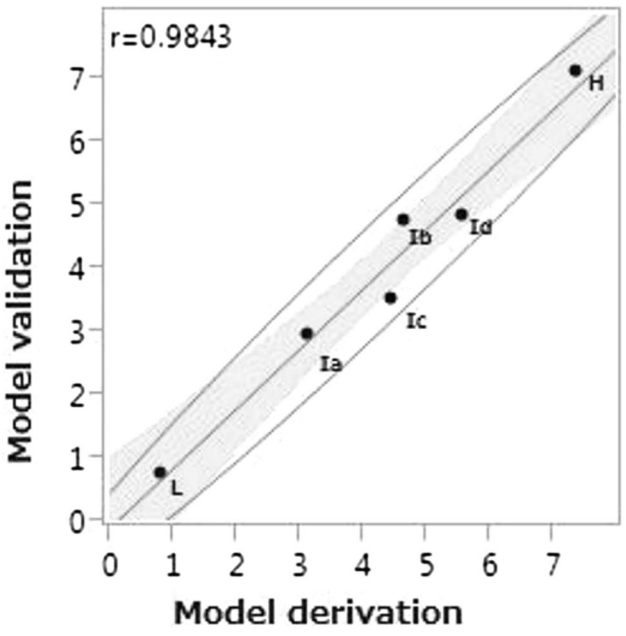

Fig. 2 Correlation between model derivation and validation. The yardstick proposed by decision tree analysis was validated in the rest of the dataset with close correlation ($r^2 = 0.971$, $p < 0.0001$)

use of sirolimus protected patients against de novo NMSC (10-year development rate of 11.9% in those who were on it ($n = 88{,}911$) versus 8.7% in those without ($n = 2606$), $p = 0.042$). In non-Caucasian, those who were on sirolimus did not develop any NMSC during follow up period ($n = 454$), but those without ($n = 14{,}031$) showed 10-year development rate of 1.3%.

Generation of a predictive index was then attempted: In the model building cohort, Cox hazard model was used to predict NMSC within the follow-up period and showed Caucasian race was with hazard ratio (HR) 5.92 ($p < 0.0001$), age < 47 at LT with HR 2.876 ($p < 0.001$), Male gender with HR 1.854 ($p < 0.0001$), BMI at LT < 40 with HR 1.40 (< 0.0001) and use of sirolimus with HR 1.22 ($p = 0.01$). This generated the equation: Predictive index = (Caucasian race × 1.779) + [(Age at LT) ≥ 47 × 1.056] + (Male gender × 0.596)+[(BMI at LT ≤ 40) × 0.3364] + (Use of sirolums × 0.2). A cutoff score of 3.0 predicted the de novo NMSC with a sensitivity of 91%, a specificity of 42%, a positive predictive value of 5.7%, and a negative predictive value of 99% (AUROC 0.731, $p < 0.001$).

Discussion

De novo malignancy is one of the most common causes of death after liver transplantation (Watt et al. 2009, 2010). The risk of malignancy is two to four times higher in transplant recipients than in age- and sex-matched control

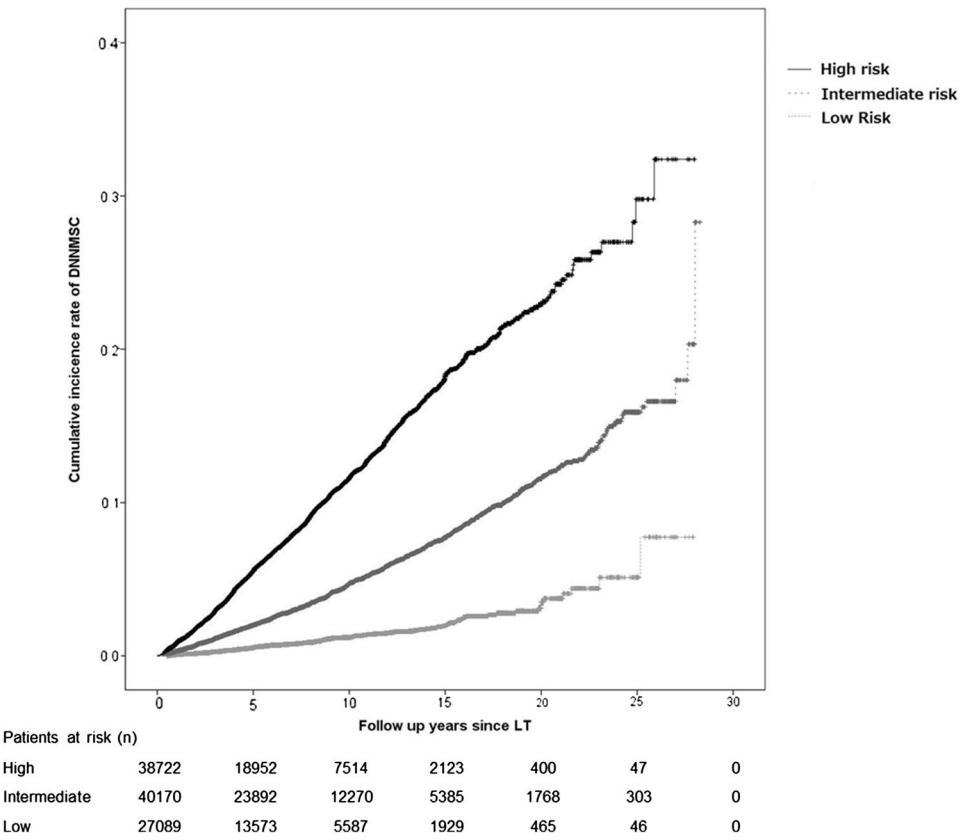

Fig. 3 Incidence rate of NMSC among groups with low-, intermediate- and high-risk groups. Cumulative incidence rate of such skin cancer at 5/10/20 year was 0.5/1.2/3.3, 2.1/4.8/11.7 and 5.6/11.6/23.1% in those with low-, intermediate- and high-risk, respectively ($p < 0.0001$)

subjects (Lanzino et al. 1997; Kaneko et al. 2013). This may be due to impaired immune surveillance in those on immunosuppression (Swann and Smyth 2007). De novo NMSC is one of the most common malignancies following LT, with an overall incidence of 16–22.5% (Unlu et al. 2015; Herrero et al. 2005). Our data confirms the high cumulative incidence of NMSC which was 13.5% after a mean of 20-years post-transplant. Our data also illustrate the magnitude of this increased risk: there were 1285 NMSC per 100,000 person-years in our liver transplant cohort, versus an expected rate of 38 per 100,000 person-years in the general US adult population (Tejera-Vaquerizo et al. 2016). This high rate is important because patients with NMSC could have worse post-transplant survival than those without NMSC (Herrero et al. 2005; Aberg et al. 2008), especially in case of SCC under immunosuppressive agents (Mithoefer et al. 2002).The incidence of BCC was four times higher than the incidence of SCC amongst the general population in the United States (Christenson et al. 2005), but we observed more cases with SCC than BCC in the dataset. There were several other studies investigating post-SOT (including LT) cohort observed the reverse ratio of BCC to SCC (Mithoefer et al. 2002; Hartevelt et al. 1990; Euvrard et al. 1995; Krynitz et al. 2013), which might be related to the pattern of exposure to ultraviolet radiation with more strict instruction for sunscreen, or again the immunosuppressive treatment in transplant recipients (Naldi et al. 2000).

There are several known risk factors for developing NMSC in liver transplant recipients, including older age, male gender, fair-skin, prior sun exposure, actinic keratosis, smoking, history of autoimmune hepatitis, human papilloma virus infection, and excessive alcohol use (Mithoefer et al. 2002; Bellamy et al. 2001; McCaughan and Vajdic 2013). Garrett et al. (2017) recently reported that increased age, white race, male sex, and thoracic organ transplantation increased the risk of skin cancer post-solid organ transplantation (SOT), and suggested that this information could be used to inform risk stratification and screening guidelines for post-transplant skin cancers. Lowenstein et al. also reviewed prediction tools for NMSC post-kidney transplantation (Lowenstein et al. 2017). However, clinical providers cannot quantify the absolute risk based on the presence or absence of these risk factors alone or in combination.

Decision tree analysis is a method to classify individuals into homogeneous subgroups; it generates a transparent algorithm in the form of a tree-structure that is intuitive and easily used clinically (Many other forms of artificial intelligence generate opaque black box algorithms that cannot be applied clinically) (Leiter et al. 2004; Kurosaki et al. 2012; Garzotto et al. 2005; Valera et al. 2007). We used the independent risk factors that we had initially identified by Cox

Regression analysis, to enter in to the Decision tree analysis. These factors were: Caucasian men, age at transplant, BMI, and not receiving sirolimus after transplant. The decision tree analysis ranked the risk factors and found optimal cut-offs to provide the greatest discrimination among subsets. The optimum age was > 47, and the optimum BMI was < 40. The highest risk group had a 7.4% cumulative incidence of NMSC and the lowest risk subgroup had a cumulative incidence of only 0.8%. Many researchers have put a lot of efforts to formulate regression models for prediction of NMSC post-transplant (Lowenstein et al. 2017). These prediction models are useful for identifying high-risk patients but are somewhat complicated to use at the bedside because they require calculations to be performed. Our prediction model is used simply by incorporating basic patients' data into the decision tree and following the flowchart. These prediction models based on factors easily accessible in routine clinical settings help physicians identify the high-, intermediate- or low-risk individuals and use this stratification to modify surveillance, care and immune suppression, and educate the individual about their specific risk, even since pre-LT.

Sirolimus use was shown to protect patients from getting NMSC in our study to some extent (but not from getting SCC, presumably due to lack of decent sample size in that sub-analysis). This finding is in keeping with many studies showing reduced risk of de novo malignancy in recipients that use the mammalian target of rapamycin (mTOR) instead of a calcineurin inhibitor (CNI) for immune suppression. Data from multiple studies have been synthesized in several meta-analyses: the meta-analysis by Knoll et al. showed that mTOR use reduced NMSC rates in transplant recipients (Knoll et al. 2014), that by Kauffman et al. showed mTOR inhibitors were associated with reduced de novo malignancy across the board, including NMSC in kidney recipients (Kauffman et al. 2005) and the meta-analysis by Liang et al. showed reduce de novo malignancy in LT recipients (Liang et al. 2012). However, this topic is controversial, and some studies did not show a protective effect of mTOR on NMSC. There were no actual data in our dataset regarding the reasons why sirolimus was introduced to those respective recipients, either. Never-the-less our decision tree analysis identified mTOR inhibitor use as one of the 5 most important variables that predict the risk of NMSC. Results from clinical trials comparing CNI to mTOR suggest that patients at high risk for skin cancer derive the greatest benefit from changing to an mTOR early, before they have developed multiple lesions (Geissler 2015). Our results support using an mTOR but in addition, the decision tree can help practitioners identify the high risk patients.

We also identified lower BMI as a risk factor for NMSC. This is in keeping with studies of non-transplant patients that showed that obesity protected against the development of NMSC (Pothiawala et al. 2012; Tang et al. 2013), possibly because obesity is associated with less sun exposure (Rigel 2008; Trost et al. 2002).

Patients with history of alcohol consumption, as the underlying etiology of liver disease, were reported to have higher risk in developing NMSC after transplantation (Bellamy et al. 2001; Modaresi Esfeh et al. 2012), although it was not observed in our current study, presumably because the UNOS STAR file did not include actual daily amount, frequency or length of alcohol consumption prior to LT.

The decision tree analysis provides practitioners with a simple and easy to use tool to accurately stratify and quantify risk of NMSC in liver transplant recipients. Patients at high risk can potentially be managed differently. Current guidelines recommend that SOT recipients have annual skin exam surveillance for NMSC (McCaughan and Vajdic 2013). However high risk patients could potentially be considered for more frequent surveillance or additional interventions, such as retinoid chemoprophylaxis, or changes in intensity or type of immune suppression (Kim et al. 2016). In addition, this result also could be utilized in enrolling patients at high risk in interventional studies to prove safety and efficacy and lack of harm. Further research is warranted in this topic. Those with the predictive index less than 3.0 could have less frequent surveillance based on its high sensitivity and negative predictive value, however even our lowest risk group, with 124 cases/100,000 person-years have an age adjusted incidence of NMSC that is four times more than would be expected in the general population (38 cases per 100,000 person-years) (Tejera-Vaquerizo et al. 2016). Thus, even the low risk group should be followed according to current guidelines, with annual skin examinations for cancer surveillance at this point.

The decision tree model showed that patients with high-risk for de novo NMSC had 7.4% of the development, and 3.1–5.5% in patients with intermediate-risk during the follow up period, however, the Kaplan Meier analysis showed that 10 and 20 years cumulative development rate were much higher than those. This is mainly based on the nature of decision tree analysis (this is not a probability model to represent times-to-event), and the analysis was conducted by the population with median follow up period of 6.7 years. Thus, it probably is reasonable to see much higher rate of NMSC in later post-transplant years. In addition, the patient with Caucasian race who were < 47 years old had lowest development rate of NMSC amongst the Intermediate risk group. It could be argued that the higher rate of the development rate of NMSC in High- and the rest of the Intermediate-risk group was associated with their getting older during the study period, which should increase the risk of NMSC.

A limitation of our study is that model building (derivation) and validation sets were not from entirely independent cohorts. However, the model building and validation

sets were randomly derived a priori, with no patients overlapping in the two sets, and the sets had identical distribution of variables: with no statistical differences in any of the variables in the model building and validation sets. A second limitation is that the decision tree analysis was performed using retrospectively and voluntary collected registry- based database (UNOS STAR file), which originally is not designed specifically to track cancer incidence. We were not able to assess pre-existing NMSC as a potential risk factor (Lowenstein et al. 2017) because the data was obtained only in approximately 10% of the cases ($n = 11{,}916$). Also we were not able to evaluate smoking history or human papilloma virus (Chockalingam et al. 2015; Euvrard et al. 2003) as the UNOS STAR file do not include such information. We could not control for intensity of immunosuppression over time or be certain of how long patients who were discharged on sirolimus remained on it either. In addition, it did not allow us to accurately identify those who died of NMSC or who lost follow up. A third limitation is that the OPTN does not collect data on everolimus use at discharge. Some subjects who were not using sirolimus may have received everolimus. If we assume that both mTOR inhibitors (everolimus and sirolimus) have similar antineoplastic properties, then those on everolimus would have been protected, but would have been analyzed in the non-sirolimus group. This would weaken the signal of the protective effect of mTOR inhibitors, but would certainly not invalidate the observation that sirolimus protects against developing NMSC.

In conclusion, our study confirms the importance of the known risk factors of Caucasian race, older age, and male gender as risk factors, but identifies the new variables of sirolimus and obesity (both protective) in establishing an individual's risk of getting NMSC. We have confirmed those with very high risk of developing NMSC after liver transplantation. However, even the lowest risk group has 4 times the risk of the general population. Annual surveillance for skin cancer seems to be an appropriate minimum recommendation for all post-LT patients including the lowest risk group, but the highest group might need more frequent surveillance. We have used decision tree analysis to derive simple and easy to use tool to accurately stratify and quantify risk of NMSC post-LT. It gives specific guidance about age cutoff (> 47) and BMI cutoff (Pothiawala et al. 2012) for optimal risk stratification. This decision tree could help providers to individualize care of their liver transplant recipients.

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Compliance with ethical standards

Conflict of interest Author Tomohiro Tanaka declares that he has no conflict of interest. Author Michael Voigt declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Aberg F, Pukkala E, Hockerstedt K, Sankila R, Isoniemi H (2008) Risk of malignant neoplasms after liver transplantation: a population-based study. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver. Transpl Soc 14(10):1428–1436

Bellamy CO, DiMartini AM, Ruppert K, Jain A, Dodson F, Torbenson M et al (2001) Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. Transplantation 72(4):619–626

Belloni-Fortina A, Piaserico S, Bordignon M, Gambato M, Senzolo M, Russo FP et al (2012) Skin cancer and other cutaneous disorders in liver transplant recipients. Acta dermato-venereologica 92(4):411–415

Chen CH, George SL (1985) The bootstrap and identification of prognostic factors via Cox's proportional hazards regression model. Stat Med 4(1):39–46

Chockalingam R, Downing C, Tyring SK (2015) Cutaneous squamous cell carcinomas in organ transplant recipients. J Clin Med 4(6):1229–1239

Christenson LJ, Borrowman TA, Vachon CM, Tollefson MM, Otley CC, Weaver AL et al (2005) Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. Jama 294(6):681–690

Collett D, Mumford L, Banner NR, Neuberger J, Watson C (2010) Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transpl 10(8):1889–1896

Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M et al (1995) Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol 33(2 Pt 1):222–229

Euvrard S, Kanitakis J, Claudy A (2003) Skin cancers after organ transplantation. N Engl J Med 348(17):1681–1691

Garrett GL, Blanc PD, Boscardin J, Lloyd AA, Ahmed RL, Anthony T et al (2017) Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. JAMA Dermatol 153(3):296–303

Garzotto M, Park Y, Mongoue-Tchokote S, Bledsoe J, Peters L, Blank BH et al (2005) Recursive partitioning for risk stratification in men undergoing repeat prostate biopsies. Cancer 104(9):1911–1917

Geissler EK (2015) Skin cancer in solid organ transplant recipients: are mTOR inhibitors a game changer? Transpl Res 4:1

Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ et al (2001) Increased cancer risk after liver transplantation: a population-based study. J Hepatol 34(1):84–91

Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP (1990) Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 49(3):506–509

Herrero JI (2009) De novo malignancies following liver transplantation: impact and recommendations. Liver Transpl 15(Suppl 2):S90–S94

Herrero JI, Espana A, Quiroga J, Sangro B, Pardo F, Alvarez-Cienfuegos J et al (2005) Nonmelanoma skin cancer after liver transplantation. Study of risk factors. Liver Transpl 11(9):1100–1106

Housman TS, Feldman SR, Williford PM, Fleischer AB Jr, Goldman ND, Acostamadiedo JM et al (2003) Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol 48(3):425–429

Jensen AO, Svaerke C, Farkas D, Pedersen L, Kragballe K, Sorensen HT (2010) Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. Acta dermato-venereologica 90(5):474–479

Kaneko J, Sugawara Y, Tamura S, Aoki T, Sakamoto Y, Hasegawa K et al (2013) De novo malignancies after adult-to-adult living-donor liver transplantation with a malignancy surveillance program: comparison with a Japanese population-based study. Transplantation 95(9):1142–1147

Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD (2005) Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation 80(7):883–889

Kim C, Cheng J, Colegio OR (2016) Cutaneous squamous cell carcinomas in solid organ transplant recipients: emerging strategies for surveillance, staging, and treatment. Semin Oncol 43(3):390–394

Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R et al (2014) Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. BMJ 349:g6679

Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattstrom C, Wilczek H et al (2013) Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—a Swedish population-based study. Int J Cancer 132(6):1429–1438

Kurosaki M, Hosokawa T, Matsunaga K, Hirayama I, Tanaka T, Sato M et al (2010) Hepatic steatosis in chronic hepatitis C is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage and response to interferon therapy. Hepatol Res 40(9):870–877

Kurosaki M, Hiramatsu N, Sakamoto M, Suzuki Y, Iwasaki M, Tamori A et al (2012) Data mining model using simple and readily available factors could identify patients at high risk for hepatocellular carcinoma in chronic hepatitis C. J Hepatol 56(3):602–608

Lanzino G, Cloft H, Hemstreet MK, West K, Alston S, Ishitani M (1997) Reversible posterior leukoencephalopathy following organ transplantation. Description of two cases. Clin Neurol Neurosurg 99(3):222–226

Leiter U, Buettner PG, Eigentler TK, Garbe C (2004) Prognostic factors of thin cutaneous melanoma: an analysis of the central malignant melanoma registry of the german dermatological society. J Clin Oncol 22(18):3660–3667

Liang W, Wang D, Ling X, Kao AA, Kong Y, Shang Y et al (2012) Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis. Liver Transpl 18(1):62–69

Lowenstein SE, Garrett G, Toland AE, Jambusaria-Pahlajani A, Asgari MM, Green A et al (2017) Risk prediction tools for keratinocyte carcinoma after solid organ transplantation: a review of the literature. Br J Dermatol 177(5):1202–1207

McCaughan GW, Vajdic CM (2013) De novo malignant disease after liver transplantation? Risk and surveillance strategies. Liver Transpl 19(Suppl 2):S62–S67

Mithoefer AB, Supran S, Freeman RB (2002) Risk factors associated with the development of skin cancer after liver transplantation. Liver Transpl 8(10):939–944

Modaresi Esfeh J, Hanouneh IA, Dalal D, Tabba A, Lopez R, Pagadala M et al (2012) The incidence and risk factors of de novo skin cancer in the liver transplant recipients. Int J Org Transpl Med 3(4):157–163

Naldi L, Fortina AB, Lovati S, Barba A, Gotti E, Tessari G et al (2000) Risk of nonmelanoma skin cancer in Italian organ transplant recipients. A registry-based study. Transplantation 70(10):1479–1484

Pothiawala S, Qureshi AA, Li Y, Han J (2012) Obesity and the incidence of skin cancer in US Caucasians. CCC 23(5):717–726

Rigel DS (2008) Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. J Am Acad Dermatol 58(5 Suppl 2):S129-32

Soltani-Arabshahi R, Tristani-Firouzi P (2013) Chemoprevention of nonmelanoma skin cancer. FPS 29(5):373–383

Swann JB, Smyth MJ (2007) Immune surveillance of tumors. J Clin Investig 117(5):1137–1146

Tanaka T, Kurosaki M, Lilly LB, Izumi N, Sherman M (2015) Identifying candidates with favorable prognosis following liver transplantation for hepatocellular carcinoma: Data mining analysis. J Surg Oncol 112(1):72–79

Tang JY, Henderson MT, Hernandez-Boussard T, Kubo J, Desai M, Sims ST et al. Lower skin cancer risk in women with higher body mass index: the women's health initiative observational study. Cancer Epidemiol Biomark Prev. 2013;22(12):2412–2415

Tejera-Vaquerizo A, Descalzo-Gallego MA, Otero-Rivas MM, Posada-Garcia C, Rodriguez-Pazos L, Pastushenko I et al (2016) Skin cancer incidence and mortality in Spain: a systematic review and meta-analysis. Actas Dermo-sifiliograficas 107(4):318–328

Trost SG, Owen N, Bauman AE, Sallis JF, Brown W (2002) Correlates of adults' participation in physical activity: review and update. Med Sci Sports Exerc 34(12):1996–2001

Unlu O, Roach EC, Okoh A, Olayan M, Yilmaz B, Uzunaslan D et al (2015) Skin cancer in immunosuppressed transplant patients: vigilance matters. World J Hepatol 7(4):717–720

Valera VA, Walter BA, Yokoyama N, Koyama Y, Iiai T, Okamoto H et al (2007) Prognostic groups in colorectal carcinoma patients based on tumor cell proliferation and classification and regression tree (CART) survival analysis. Ann Surg Oncol 14(1):34–40

Vogt DP, Henderson JM, Carey WD, Barnes D (2002) The long-term survival and causes of death in patients who survive at least 1 year after liver transplantation. Surgery 132(4):775–780 **(discussion 80)**

Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ (2009) Long-term probability of and mortality from de novo malignancy after liver transplantation. Gastroenterology 137(6):2010–2017

Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR (2010) Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transpl 10(6):1420–1427