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Original Article

ORIGINAL ARTICLE

Comparison of different algorithms for the assessment of cardiovascular risk after kidney transplantation by the time of entering waiting list

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ABSTRACT

Background. The prevalence of cardiovascular disease is high among patients with chronic kidney disease and cardiovascular events (CVE) remain the leading cause of death after kidney transplantation (KT). We performed a retrospective analysis of 389 KT recipients to assess if the European Society of Cardiology Score (ESC-Score), Framingham Heart Study Score (FRAMINGHAM), Prospective Cardiovascular Munster Study Score (PROCAM-Score) or Assessing cardiovascular risk using Scottish Intercollegiate Guidelines Network Score (ASSIGN-Score) algorithms can predict cardiovascular risk after KT at the time of entering the waiting list.

Methods. 389 KT candidates were scored by the time of entering the waiting list. Pearsons chi-square test, cox regression analysis and survival estimates were performed to evaluate the reliability of the cardiovascular scoring models after successful KT.

Results. During a follow-up of 8 ± 5.8 years, 96 patients (30%) died due to cardiovascular problems, whereas 13.9% suffered non-fatal CVE. Graft loss occurred in 84 patients (21.6%). Predictors of CVE, survival and graft loss were age and the length of end-stage kidney disease. All scores performed well in assessing the risk for CVE ($P < 0.01$). Receiver-operating characteristic analysis using the ESC-SCORE, as an example, suggested a cut-off for risk stratification and clinical decisions.

Conclusions. We found all tested scores were reliable for cardiovascular assessment. We suggest using cardiac scores for risk assessment before KT and then taking further steps according to current guidelines.

Keywords: ASSIGN, cardiovascular risk assessment, ESC-SCORE, FRAMINGHAM, kidney transplantation, PROCAM

INTRODUCTION

Cardiovascular events (CVE) remain the leading cause of mortality in patients with chronic kidney disease (CKD). The prevalence of cardiovascular disease (CVD) is very high among patients with CKD, especially those on haemodialysis [1–3]. Besides CKD, independent risk factors include serum

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cholesterol, smoking, diabetes, hypertension, male sex and a family history of CVD, and the accumulation of these factors leads to a higher overall risk (OR) [4–6]. In addition to these traditional risk factors, others such as the duration of renal replacement therapy (RRT), graft function after transplantation, rejection episodes, chronic inflammation and side effects of immunosuppressive medication increase the cardiovascular (CV) risk, especially in this population. Large randomized controlled trials as the Assessment of lescol in Renal Transplantation (ALERT) Study and the Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) Study have shown this before [3, 7–10]. Though Pilmore *et al.* showed significantly lower rates of CVD after kidney transplantation compared with RRT [11], the incidence still reached up to 30% [12, 13]. Almost 40% of kidney transplant recipients experience an event during the first 3 years [13]. The cumulative 3-year incidence of myocardial infarction ranged from 4.7% to 11.1% [14], while CVEs remain the most common cause of short- and long-term mortality even after successful KT [15]. Therefore, the assessment of CV risk is important when preparing CKD patients for KT. Invasive diagnostic methods, such as coronary arteriography, may properly predict the risk for CVE before and after KT and allow interventional treatment, but cannot predict other vascular events, such as stroke or peripheral arterial disease (PAD). Additionally, they include a risk of complications, especially nephrotoxicity by contrast agents. Therefore, non-interventional evaluation strategies are needed to predict CV risk and select candidates who will best benefit from transplantation.

For this purpose, different scoring algorithms have been developed to help physicians optimize risk factor management. The FRAMINGHAM [16] assesses the 10-year risk for myocardial infarction based on age, cholesterol, blood pressure, smoking status and treatment for hypertension. The PROCAM [17], which is based on the FRAMINGHAM equation, predicts the 10-year OR for coronary heart disease based on serum cholesterol, blood sugar, blood pressure, history of smoking and familiar predisposition. In addition, the ESC-SCORE [18] is a modification of the PROCAM that takes into account regional factors being responsible for over- or underestimation by the PROCAM. The ESC-SCORE was established to predict the 10-year risk of all fatal CVE. The PROCAM and FRAMINGHAM have additional scores for stroke. The ASSIGN also considers gender, left ventricular hypertrophy, cigarettes per day and regional factors to assess CVD [19]. The reliability of these scores is often limited, by excluding either the female sex, certain age groups or local particularities. None of these scores is validated in CKD or kidney transplant recipients, and the FRAMINGHAM score appears to underestimate the CV risk after KT [20]. The American Heart Association and the American College of Cardiology Foundation (AHA/ACC Foundation) stated eight risk factors to assess the need for cardiac disease evaluation and management in kidney and liver transplantation candidates, endorsed by the American Society of Transplant Surgeons, the American Society of Transplantation (AST) and the National Kidney Foundation. The risk factors are: age >60 years, smoking, dyslipidaemia, hypertension, diabetes mellitus, known coronary artery disease (CAD), left ventricular hypertrophy and being in end-stage kidney disease (ESKD) for >12 months [21]. However, no cumulative amount or threshold was determined for these risk factors to recommend invasive testing. Since there are only recommendations, most German transplantation centres have developed their own, strongly varying, strategies.

Reuter *et al.* [22] assessed the PROCAM, FRAMINGHAM and ESC-SCORE in a cohort of 347 CKD patients who were wait-listed for KT. The study included a follow-up of 4.1 years and identified an increasing ESC-SCORE as a robust prognosticator for overall and event-free survival (EFS) from CVE. Patients were followed-up during the waiting period and after successful transplantation, if they received a kidney graft in this time. The changes in CV risk and mortality that develop with increasing kidney function after successful KT were not considered [22]. Kasiske *et al.* [23] showed in 1124 KT recipients that the FRAMINGHAM score is able to predict the risk of ischaemic heart disease, but underestimates it, especially in the presence of diabetes mellitus. Here, we performed a retrospective cohort analysis of 389 KT candidates, scoring them at the time of entering the waiting list to compare the performances of the FRAMINGHAM, ESC-SCORE, PROCAM and ASSIGN algorithms after KT, and analysed survival and the incidence of CVE after transplantation. Since graft function and graft survival are both strongly related to arteriosclerotic vascular disease manifested as PAD and CAD [24, 25], we also hypothesized that there might be a correlation between the CV risk and chronic allograft dysfunction, and that a careful risk profile assessment might lead to reduced graft loss.

MATERIALS AND METHODS

Chart review, data collection and ethics statement

We enrolled adult patients undergoing KT between February 1996 and November 2016 at our tertiary referral centre. Inclusion criteria for the study were ESKD for >12 months, haemodialysis as RRT and induction therapy with either thymoglobulin or basiliximab. Since there is indication for higher low-density lipoprotein (LDL) cholesterol, fibrinogen and homocysteine levels in patients on peritoneal dialysis, we excluded these factors [26]. From charts, we assessed the age, gender, body mass index (BMI), diabetes, smoking status, history of CVD or events, family history of CAD, atrial fibrillation, latest or average systolic blood pressure before transplantation, LDL and high-density lipoprotein (HDL) cholesterol, total serum cholesterol, triglycerides, time of ESKD, follow-up time, dialysis modality and cause of ESKD for every participant. Diabetes was defined according to the PROCAM (pre-existing when on waiting list or occasional repeated fasting glucose >120 mg/dL). All laboratory parameters for scoring, vital parameters, general information and information about the patient's history were collected during the 3–6 months evaluation period before waiting list registration. Outcome parameters were recorded during outpatient long-term surveillance after KT. To avoid selection bias by immunologic parameters and diverging maintenance immunosuppression, we only included patients who received induction therapy either with interleukin-2 antibody or thymoglobulin. Due to missing data, we did not consider oral anticoagulation. Types of thromboembolic scoring algorithms have changes significantly during the long-ranged data collection period, so we also did not perform thromboembolic risk scoring. We identified a cohort of 389 patients fulfilling these criteria (Table 1). All participants signed informed consent for data usage at the time of entering the waiting list. All the findings, data acquisition and processing in this study comply with the ethical standards laid down in the latest Declarations of Helsinki and Amsterdam as well as within the statutes of the Ethics Committee of the University of Würzburg concerning anonymized retrospective medical studies.

Table 1. Patients' characteristics and demographics for the scored waiting list patients

Demographic parameter	$n = 389$
Age, years	
Mean ± SD	53.67 ± 11
Range	23–77
Follow-up, years	
Mean ± SD	8 ± 5.8
Range	0.5–20.3
Induction, *n* (%)	
Anti-thymocyte globulin	156 (40.1)
Interleukin-2, *n* (%)	233 (59.9)
Male, *n* (%)	254 (65)
ESKD, years	
Mean ± SD	6.1 ± 2.8
Range	1–14.5
BMI	26.10 ± 11.5
Smoking, *n* (%)	
Never	256 (66)
Former	78 (20)
Active	53 (14)
Hypertension	373 (96)
Systolic blood pressure, *n* (%)	
≤120 mmHg	63 (16)
121–140 mmHg	145 (38)
141–160 mmHg	134 (34)
>161 mmHg	47 (12)
CAD, *n* (%)	68 (17)
Family history of CVD, *n* (%)	49 (12)
Atrial fibrillation, *n* (%)	57 (15)
Diabetes mellitus, *n* (%)	100 (26)
Eurotransplant Senior Programme, *n* (%)	86 (22)
Hypercholesterolaemia, *n* (%)	205 (52)
Renal disease, *n* (%)	
Diabetes	32 (8.2)
Hypertension	24 (6.2)
Focal segmental sclerosis	13 (3.3)
Glomerulonephritis	58 (15)
Immunoglobulin A nephropathy	78 (20)
Interstitial	19 (4.9)
Polycystic kidney disease	53 (13.6)
Rapid progressive	8 (2.0)
Other urological condition	42 (10.8)
Reflux	19 (4.9)
Vasculitis	8 (2.0)
Unknown	35 (9%)

BMI, body mass index; CAD, coronary artery disease; ESKD, end stage kidney disease; SD, standard deviation.

Table 2. Patients' distribution by scoring according to their estimated 10-year risk

Risk model	*n* (%)
ESC-SCORE	
<1	117 (30)
1–4	193 (50)
5–9	61 (16)
10–14	14 (3.7)
>15	3 (0.9)
ESC-SCORE by risk class	
<5	220 (56.5)
>5	169 (43.5)
FRAMINGHAM (%)	
0–4	27 (6.9)
5–9	42 (11)
10–19	90 (23)
20–29	95 (24)
>30	133 (34)
ASSIGN (%)	
0–4	86 (22.1)
5–9	86 (22.1)
10–19	111 (28.5)
20–29	57 (14.6)
>30	49 (12.5)
PROCAM (%)	
0–4	106 (27)
5–9	40 (10)
10–19	36 (9)
20–29	36 (8.8)
>30	171 (45)
PROCAM Stroke (%)	
<1	62 (15.9)
1–4	175 (44.7)
5–9	99 (25.4)
10–14	29 (7.4)
>15	24 (6.1)

Statistical analysis

Statistical analysis was performed using R 3.10 (URL: https://www.r-project.org). The frequencies of metric variables were expressed by arithmetic mean and standard deviation. New onset of CAD, non-fatal myocardial infarction, new onset of non-valvular atrial fibrillation or higher heart rhythm disorder (other than ventricular or non-ventricular extrasystoles), interventions for PAD and fatal or non-fatal stroke were considered as CVE. Pearson's Chi-square test was used to make comparisons between groups. If two means of normally distributed data were compared, then a two-sided unpaired Student's *t*-test was used. Means from more than two groups were evaluated using the analysis of variance with *post hoc* testing (Tukey's test) if significant differences occurred. Cox regression models and survival estimates were evaluated using the R package 'survival' and 'survminer', and receiver-operating characteristic (ROC) curves and Youden Index were computed using the R package 'pROC'. Graft loss was estimated with Cox regression and censored for death. Variables found to be statistically significant at 10% level in the univariate analysis were included in the multivariate model. Significant associations were set at $P \leq 0.05$.

RESULTS

There were 389 patients with a mean age of 53 years (range 23–77 years) included, transplanted and followed for an average of 8 years (range 0.5–20.3 years). To achieve homogeneity, only patients treated with RRT for >12 months were enrolled. CV risk factors were as follows: the average BMI was 26.1 (±11.5) kg/m^2, 26% of patients were diagnosed with diabetes or repeatedly had elevated serum glucose, 34% were former or active smokers (20% and 14%, respectively), 52% suffered from hypercholesterolaemia, 17% had known CAD, 12% had a familial history of heart disease, 15% reported episodes or permanent atrial fibrillation and almost all patients (95.9%) used medication for hypertension. Eighty-six patients underwent KT through the Eurotransplant Senior Programme. Of these, 65% were male and the average time on the waiting list was 6.1 years (interquartile range 1–14.5 years). The clinical demographics of the patient

Table 3. CV and overall outcome after transplantation in our study population

Event	*n* (%)
Death overall	
CV	30 (7.7)
Non-CV	66 (17.0)
3-year mortality	36 (9.37)
CVE, non-fatal	54 (13.9)
Stroke	6 (1.5)
Graft loss	84 (21. 6)

Table 4. Cox regression analysis of potential risk factors for CVE, cardiac death (CD), stroke and 3 year-mortality in our 389 study patients with risk association and P-values

Risk factor	CVE	CD	Stroke	CD 3 years
Age	<0.001	0.002	0.02	0.12
BMI	0.76	0.69	0.66	0.82
CAD	0.28	0.88	0.41	0.46
Diabetes	0.62	0.17	0.42	0.47
ESKD	0.08	0.04	0.02	0.12
Family history	0.61	0.52	0.28	0.92
High LDL cholesterol	0.58	0.55	0.07	0.24
Low HDL cholesterol	0.15	0.10	0.45	0.22
Male	0.04	0.12	0.99	0.04
Smoking	0.26	0.42	0.29	0.42
Systolic blood pressure	0.79	0.67	0.08	0.09

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; ESKD, end stage kidney disease; HDL, high density lipoprotein; LDL, low density lipoprotein.

cohort as well as the scoring distribution are presented in Tables 1 and 2.

CV outcome

All 389 patients had successful KTs. Ninety patients (24.6%) died after transplantation during follow-up, 36 (9.2%) during the first 3 years with 7 (1.7%) of those deaths due to major cardiac adverse events. In total, 30 patients (7.7%) died of cardiac causes and 81 patients (20.8%) suffered CVE during the observation period, and 6 patients (1.5%) experienced a stroke. Fifty-four patients (13.9%) suffered non-fatal cardiac events during the follow-up period (excluding stroke and sudden cardiac death) (Table 3).

To robustly identify risk factors for CVE, cardiac death, EFS and stroke, we performed univariate and multivariate Cox regression analyses (Tables 4 and 5). We found that higher age was significantly related to shorter EFS [hazard ratio (HR) = 1.05; $P < 0.001$] and cardiac death ($P = 0.003$). Age had no influence on 3-year mortality in this KT population ($P = 0.13$). A longer transplant waiting time was associated with shorter EFS (HR = 1.01; $P = 0.04$) and CVE ($P = 0.08$), including cardiac death ($P = 0.04$) and stroke (HR = 1.03; $P = 0.02$), but was not associated with short-term survival ($P = 0.13$). Male sex was predictive of CVE, a higher 3-year mortality ($P = 0.04$) and EFS ($P = 0.05$). In our cohort, pre-existing CAD had no influence on EFS ($P = 0.31$), CVE ($P = 0.28$), stroke ($P = 0.41$) and long- or short-term cardiac mortality ($P = 0.88$ and $P = 0.46$, respectively). For stroke, high systolic blood pressure and serum cholesterol (HR = 0.95; $P = 0.07$ and HR 0.41; $P = 0.08$, respectively) were predictive, while smoking, pre-existing CAD and male sex had no influence ($P = 0.29$; $P = 0.41$; $P = 0.99$).

Table 5. Cox regression analysis of EFS after transplantation in our 389 study patients with risk association and P-values

Risk factor	HR (95% CI)	P-value
Age	1.05 (1.03–1.07)	<0.01
BMI	1.00 (0.97–1.02)	0.86
CAD	0.71 (0.37–1.38)	0.31
Diabetes	1.09 (0.65–1.81)	0.75
ESKD	1.01 (1.00–1.01)	0.04
Family history	1.29 (0.67–2.49)	0.44
HDL cholesterol	0.90 (0.55–1.46)	0.67
Male sex	1.75 (1.00–3.04)	0.05
Smoking	1.10 (0.68–1.78)	0.69
Systolic blood pressure	1.00 (0.99–1.01)	0.98
Total cholesterol	0.97 (0.81–1.17)	0.79

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; ESKD, end stage kidney disease; HDL, high density lipoprotein.

The univariate Cox regression model showed that all five scores properly estimated EFS and overall survival (ESC-SCORE, FRAMINGHAM, PROCAM, PROCAM Stroke and ASSIGN, $P < 0.01$) in our cohort of CKD and KT patients. The ESC-SCORE, FRAMINGHAM, PROCAM and ASSIGN were all suitable to predict cardiac mortality. The modified variants of PROCAM for stroke (PROCAM Stroke), and all other tested scores, were not predictive for cerebrovascular events in this cohort (HR = 1.41; $P = 0.35$), when considering the low number of events (6/389, i.e. 1.5%). We also performed an analysis for short-term 3-year mortality since almost 40% of KT recipients experience a CVE within the first 3 years after KT [27]. The FRAMINGHAM, ESC-SCORE, PROCAM and ASSIGN scores were not predictive for the 3-year mortality ($P = 0.09$; $P = 0.02$; $P = 0.02$ and $P = 0.04$), whereas the PROCAM Stroke had predictive potential ($P < 0.001$).

All scores rely on common CV risk factors such as the lipid profile, blood pressure, age, smoking and reasons for poor graft function and survival. We performed a Cox regression analysis to determine whether one of these scores might also be suitable for predicting graft outcome. We found that the FRAMINGHAM, PROCAM, PROCAM Stroke and ASSIGN could predict a higher risk of graft loss ($P < 0.001$), whereas the ESC-SCORE was slightly less predictive, but still reliable ($P = 0.04$) (Table 6). To visualize and apply these findings, we used the ESC-SCORE as an example to estimate survival times with cumulative hazard plots since it performed robustly for nearly all examined endpoints. We next computed an ROC curve and the Youden Index and found an ideal threshold of 1.0, which was further used for dichotomization. As expected, patients with an ESC-SCORE that showed >5% risk had a significantly worse outcome regarding overall mortality, cardiac mortality and death censored graft loss (Figures 1–4).

DISCUSSION

Risk assessment of potential KT recipients is mandatory since their medical condition can rapidly deteriorate on haemodialysis as waiting times increase. Due to a higher incidence of cardiomyopathy, hypertension and calcifying CAD, non-invasive strategies are often not reliable for an exact assessment of CV risk in CKD patients. The incidence of CVE in high-risk candidates remains 5-fold higher than in non-CKD patients even

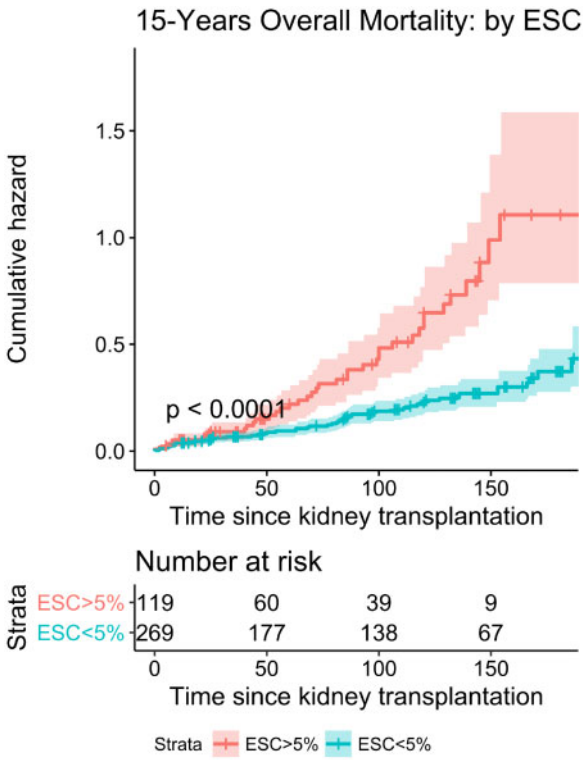

FIGURE 1: Overall mortality by Cox regression analysis.

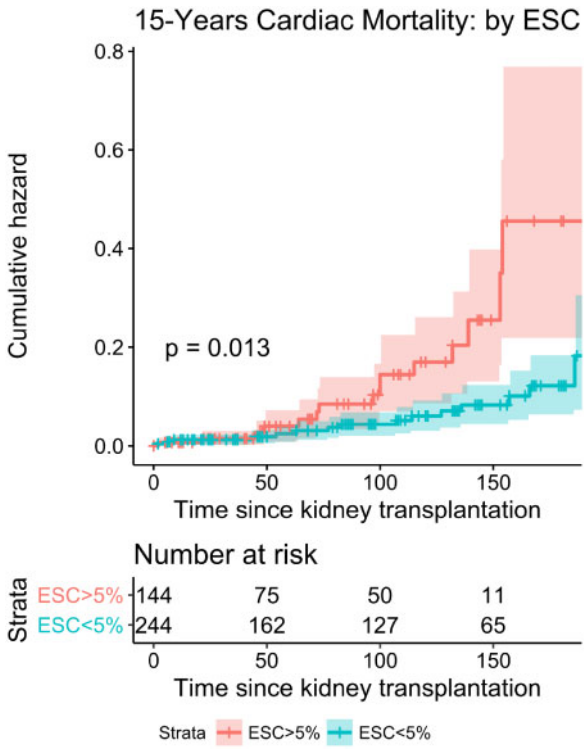

FIGURE 2: Cardiac mortality by Cox regression analysis.

after KT [28]. Additionally, with an incidence of 16–25%, CVEs represent the most common cause of death in KT recipients [29, 30]. In these subjects, metabolic disorders such as diabetes, hypercholesterolaemia and arterial hypertension are influenced by immunosuppressive medication and lead to an increased risk of CVE [31–33]. Finally, CKD itself triggers non-traditional risk factors such as inflammation, oxidative stress and endothelial dysfunction, which all lead to an elevated coronary artery calcium score, an independent predictor of cardiac events [34].

Current guidelines for transplant candidates by the AST and the Kidney Disease Outcomes Quality Initiative workgroup [35] recommend stress testing in high-risk candidates, followed by angiography and revascularization. There is not much evidence to support this testing and the recommendation is in contrast to those of the ACC and AHA guidelines, which do not generally recommend screening of asymptomatic patients before non-cardiac surgery [36]. European guidelines only include recommendations for symptomatic patients, which are based on the pretest probability of existing CAD and are not suitable for routine testing [37]. Strong recommendations for KT candidates are still missing and implementation of different guidelines leads to differences in the pre-transplantation preparation and risk management between centres [36]. A standardized assessment is needed to delineate a high-risk cohort and estimate the need for aggressive diagnostic testing and revascularization while improving the cost effectiveness and patient safety by avoiding over-interventions [28].

The FRAMINGHAM score was established to assess CV risk in the general population [17]. The KT candidates often have non-obstructive CAD, which is poorly predicted by usual risk factors [38]. The assumed pathogenesis with differing mechanisms for CV morbidity and mortality in these patients impedes the applicability of common risk scores. Oxidative stress, plasma levels of inflammatory cytokines, hyperphosphataemia and other uraemia-specific metabolites rise with deteriorating kidney function and are strongly associated with accelerated atherogenesis. The incidence of sudden cardiac death and arrhythmia is also higher in patients with CKD than non-CKD patients, and this additively diminishes the reliability of common scores [39, 40]. Furthermore, the impact of these factors increases with the waiting time before KT. It remains unclear how the risk of CVE changes after restoration of kidney function. The aim of our study was to compare different scoring systems in our KT recipient cohort time to improve risk assessment during waiting and to enhance outcome after KT. Additionally, we assessed which classical CVD risk factors were predictive for CVE in our study population.

Reuter *et al.* performed a retrospective analysis of 347 KT candidates regarding their risk of CVE and CV death during the transplant waiting time and, if transplanted, after KT and found the ESC-SCORE most predictive for EFS and overall survival. In our study, we found that all five scores were predictive for all-cause mortality and the incidence of CVE [23]. Though all scores reflect the common changes in risk profiles after KT, which may be caused by side effects of immunosuppressive agents (such as hyperlipidaemia, elevated blood pressure, elevated serum glucose and changes in kidney function), some scores are more precise. The PROCAM, FRAMINGHAM and ASSIGN rely on parameters that reflect the changes due to immunosuppression and in kidney function; thus, these scores are more appropriate for evaluating these characteristics. The Munster group found smoking and age at the start of RRT to be confounders for CVE in their population, while BMI, lipids and blood pressure profile played a minor role. In our study, age, time of ESKD and male sex contributed to reduced EFS. One Scandinavian group could predict major cardiac events in kidney transplant recipients

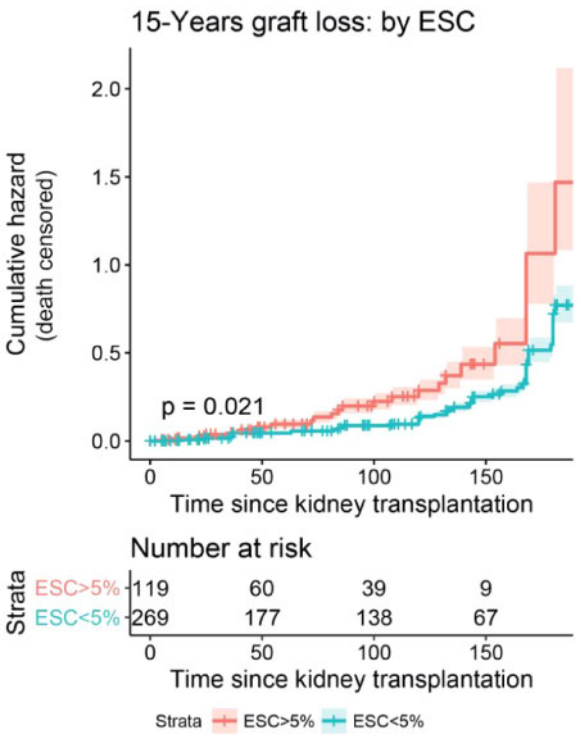

FIGURE 3: Risk of graft loss by Cox regression analysis.

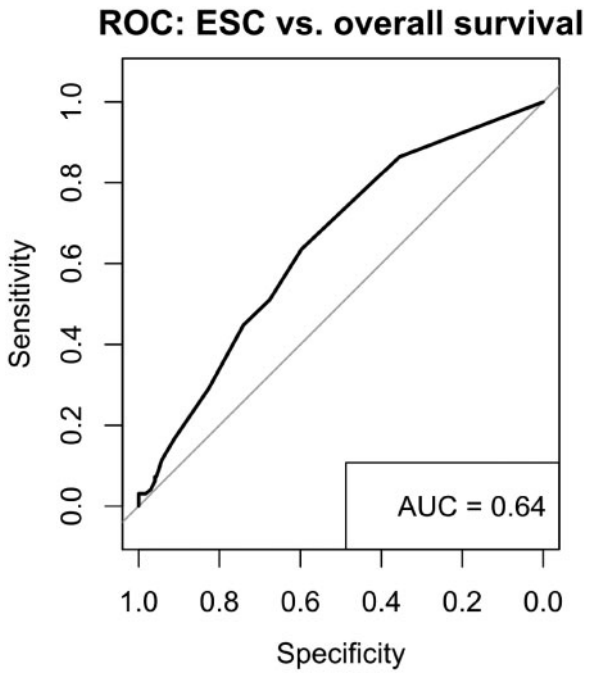

FIGURE 4: Exemplary ROC analysis of the ESC-SCORE. AUC, area under the ROC curve.

Table 6. Cox regression analysis of potential risk factors for graft loss with risk association and P-values in this study population

Risk factor	HR (95% CI)	P-value
Age	1.06 (1.03–1.08)	<0.001
BMI	0.99 (0.96–1.03)	0.77
CAD	1.43 (1.00–2.06)	0.04
Diabetes	1.23 (0.79–1.90)	0.34
ESKD	1.00 (0.99–1.00)	0.57
Family history	1.17 (0.61–2.21)	0.62
HDL cholesterol	0.68 (0.43–1.08)	0.10
Male sex	1.09 (0.67–1.76)	0.73
Smoking	1.26 (0.81–1.96)	0.28
Systolic blood pressure	1.00 (0.99–1.01)	0.11
Total cholesterol	1.01 (0.83–1.19)	0.85

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; ESKD, end stage kidney disease; HDL, high density lipoprotein.

using a seven-variable model similar to our tested scores after successful transplantation. Besides age, previous coronary heart disease, diabetes, LDL and smoking, they also included kidney function and number of transplants to develop a valid scoring system based on the ALERT-Trial population [41, 42]. Our aim was to find a reliable equation by the time before waiting list acceptance to find out which CKD patient should undergo invasive risk assessment before waiting list acceptance. Though graft function has shown to be an important outcome parameter, we could not consider this for the scoring of these pre-transplant CKD patients, which might be one limitation to this study.

We also assessed whether the same scores were able to estimate the risk of death-censored graft loss in this population. CV risk factors such as diabetes, hypertension, obesity, smoking and hyperlipidemia contribute most to the development of chronic loss of function and graft loss in addition to immunological problems [43, 44]. Immunosuppressive agents *per se* may lead to chronic allograft dysfunction, but also increase the classic risk factors with their side effects. Though the FRAMINGHAM, PROCAM, ASSIGN and ESC-SCORE only consider non-immunological risk parameters, we found them all able to predict graft loss in this population. Pre-existing CAD and age were independent risk factors for shorter graft survival. This might suggest that traditional and non-traditional CV risk factors contribute more to graft survival than immunological issues, probably since they promote comorbidities and deteriorate the patient's overall condition.

For the risk of suffering a stroke, the FRAMINGHAM and PROCAM provide slightly modified scores (such as the PROCAM Stroke) where the primary age, sex, smoking, diabetes and systolic blood pressure are considered. In the present cohort, none of these variables was able to predict the risk for cerebral insult. However, only six patients experienced a stroke, accounting for 1.5% of the study population. This small incidence of stroke was most likely responsible for these observed results. Not surprisingly, age and systolic blood pressure were confounders for the risk of stroke in our multivariate analysis. Remarkably, the PROCAM Stroke score, which does not consider the patient's lipid profile and weight, was able to estimate the short-term (3 year) mortality in our cohort (see Appendix Table A2).

The central question remains whether one of these scoring systems can help determine which KT candidates should undergo invasive or non-invasive screening methods before entering the waiting list or should be rejected from transplantation due to unaccountable risk. The ESC only lists recommendations for symptomatic patients with typical or atypical chest pain that are identified by the pretest probability [37]. Screening of non-symptomatic patients only obtains data on clinical investigations and early lifestyle factors or drug interventions. Recommendations for asymptomatic patients, for example before planned surgery, do not exist for those with CKD. The

pretest probability indicates cut-off points for three risk classes for developing CAD: low (1–15%), intermediate (15–85%) and high (>85%) risk of suffering chest pain due to CVD [39].

One study with 1296 stable chest pain patients, without CKD, compared the FRAMINGHAM, PROCAM, ESC-SCORE and the pretest probability by their ability to predict CAD [45]. The group found all scores were suitable for their non-symptomatic study population. Since all scores led to almost identical results, the pretest probability derived recommendations should also be applicable for our non-symptomatic CKD population. The pretest probability was not designed to predict CVE, only CAD, but our results and prior findings suggest a very strong association between CVE and CAD in this special population. Therefore, we suggest an ESC-SCORE cut-off of 5% to separate the low-risk (LR) and high-risk groups. This seems relatively low and assigns almost half of our cohort to the higher risk group, which might limit the clinical value. The other scores should be adapted for LR, intermediate-risk (IR) and high-risk profiles. These should be <10% (LR), 10–29% (IR) and >30% (high-risk) for the FRAMINGHAM, ASSIGN and PROCAM and <4% (LR), 5–14% (IR) and >15% (high-risk) for the PROCAM Stroke analogous to the correlating pretest probability, where cut-offs of 15 and 85% separate LR, IR and high-risk. Diagnostic procedures should then be executed as suggested by the ESC guidelines or the Nationale Versorgungs-Leitlinie by Bundesärztekammer in Germany [46]. According to these guidelines, all candidates should receive basic diagnostics with 12-channel electrocardiography and echocardiography. Patients with LR do not require further investigation, while patients with IR should undergo non-invasive diagnostic procedures, such as pharmacological stress echocardiography, myocardial scintigraphy or magnetic resonance tomography. Physical stress electrocardiography should only be performed in case of a marginal IR affiliation, not as a routine practice in LR patients. The high-risk patients, especially those who showed symptoms in the past, should undergo early invasive strategies and therapies. Patients with an ESC-SCORE estimated risk <5% need no further investigation after the basic diagnostic routine, while patients with >5% risk should be assessed for an IR and receive early coronary arteriography when symptoms occur. From a clinical aspect, the ESC guidelines result in an earlier invasive strategy in the high-risk group and reduce undirected and repeated non-invasive diagnostics. After implementation of such a strategy, further testing must show that routine scoring in a greater population is superior to former evaluation standards for decreasing CVE, invasive testing and costs. Another interesting approach might be a correlation between routine echocardiographic findings before KT and the development of CVE afterwards in the LR group. Prior data showed that echocardiographic imaging could predict adverse CV outcome in CKD patients [47, 48]. The parameters relevant for the evaluation were collected by the maintenance dialysis unit and transferred to the transplantation centre, where the results were sighted but not filed. In addition to that, data were collected by different examiners. In our retrospective study, we could not rely on this imaging in all patients. Since there is also a strong examiner dependence in all ultrasound-based imaging procedures, we did not yet illuminate this approach in this study due to missing or unreliable data.

CONCLUSION

In our pre-KT CKD population, we found all five scores were reliable for CV assessment. The FRAMINGHAM, PROCAM and ASSIGN were appropriate for predicting cardiac mortality, CVE, overall survival and graft loss after successful KT in CKD patients, even if the functional outcome cannot be considered yet. We suggest including one of these scoring systems in the risk assessment of potential KT recipients, as this might lead to a more specific diagnostic strategy and avoid over-assessments.

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AUTHORS' CONTRIBUTIONS

A.L.H. collected data, performed research, analysed data, was involved in in-hospital and outpatient treatment of the patients and wrote the article. C.K. performed statistical analyses and was involved in in-hospital and outpatient treatment of the patients. C.W. contributed important information and revised the manuscript draft. K.L. collected data, performed research and revised the manuscript draft.

CONFLICT OF INTEREST STATEMENT

None declared.

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