Research Article

Evaluation of Electrocardiographic Parameters Predicting Cardiovascular Events in Patients with End-Stage Renal Disease before and after Transplantation

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Keywords

End-stage renal disease · Electrocardiogram · Cardiovascular events · T-wave · T:R ratio

Abstract

Background and Objectives: Cardiovascular (CV) mortality represents the leading cause of death in patients with end-stage renal disease (ESRD). Efficient screening is required to detect CV disease at an early stage, but the best diagnostic work-up is uncertain. The aim of this study was to identify electrocardiographic parameters in dialysis patients associated with an increased frequency of CV events. **Methods:** A 12-lead electrocardiogram was performed in 139 patients who were on the renal transplant waiting list and who subsequently received a kidney transplant. CV events were analyzed from the day of listing for kidney transplantation until 1 year after renal transplantation. **Results:** Multivariate Cox regression analysis showed that an elevated T:R ratio in anterior and inferior leads was independently associated with CV events (T:R ratio of anterior leads hazard ratio [HR] 1.32 [95% CI 1.09–1.59; $p = 0.004$] and inferior leads HR 2.15 [95% CI 1.23–3.77; $p = 0.008$]). In particular, a T:R ratio in inferior leads exceeding 0.6 was associated with CV events in a Kaplan-Meier analysis. **Conclusions:** Taken together, we found an increased T:R ratio in ESRD patients to be a predictive marker for CV events.

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Introduction

Patients with end-stage renal disease (ESRD) exhibit a high risk of cardiovascular (CV) disease (CVD) contributing to increased morbidity and mortality [1, 2]. Arrhythmias and cardiac arrest are among the leading causes of CV mortality in these patients [1]. Especially

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the period patients are treated by dialysis awaiting transplantation until 1 year after transplantation is known to be associated with the highest incidence of CVD [3–6].

Efficient screening including an easily accessible screening tool is required to detect CVD at an early stage in such patients. Electrocardiography (ECG) represents a noninvasive, widely available, easily accessible, and inexpensive test and might thus be a useful tool in predicting CV events [7–9].

Several studies have assessed ECG parameters in hemodialysis patients and their association with CV events. A number of ECG parameter abnormalities have been described including signs of left ventricular hypertrophy, ischemic changes, rhythm disturbances, and repolarization abnormalities [10, 11]. Also, association between various ECG parameter changes with increased CV morbidity and mortality and all-cause mortality has been presented, that is, left ventricular hypertrophy by different scoring systems, increased heart rate, atrial fibrillation, PR-interval and QTc interval prolongation, and T-wave changes [10, 12–20]. However, studies on ECG alterations in dialysis patients found rather poor sensitivity and specificity in predicting coronary artery disease [21]. To further analyze the prognostic value of standard ECG in ESRD patients, we decided to perform a thorough ECG evaluation including all standard ECG parameters, which are evaluated in daily routine. Special emphasis was placed on T-wave changes in this study, since this ECG parameter had received relatively little attention in prior studies despite the fact that T-waves are frequently altered in ESRD patients [20, 22].

Thus, the aim of our study was to identify specific ECG parameters that can serve as predictors of future CV events in dialysis patients on the transplant waiting list.

Materials and Methods

Study Population and Examination

In our retrospective cohort study, we analyzed 196 patients who received a kidney transplant at the RWTH Aachen University Hospital between January 2004 and December 2010. Twenty-one patients were excluded due to missing transplantation files, 27 patients had to be excluded since ECGs were unreadable due to bleaching, eight patients whose ECGs were recorded after transplantation and 1 patient with complete bundle branch block. Finally, 139 patients were included in the final cohort (Fig. 1). All patients were analyzed, regardless of whether they received a deceased or living donor kidney and whether they previously had been treated with hemodialysis or peritoneal dialysis.

Clinical history, such as general patient information consisting of age, gender, body mass index (BMI), and smoking status were collected. In addition, data on previous diagnoses including preexisting CV events, cardiac arrhythmia, and presence of left ventricular hypertrophy and congestive heart failure measured by echocardiography were saved. Also, medication and serum biochemistry obtained at the time of transplant listing, as well as data concerning kidney failure and time on dialysis were analyzed. Subsequently, information about the transplant kidney function and the immunosuppressive regime was collected on the day of discharge after transplantation as well as 1 year thereafter.

Outcomes

CV events included myocardial infarction, coronary bypass surgery, coronary stent implantation, stroke, and interventions in patients with peripheral artery disease. Our period of observation started on the day of listing for renal transplantation and ended 1 year after transplantation, since this period is described as being associated with the highest incidence of CVD [3–6].

ECG Evaluation

Basic ECG Evaluation

Standard 12-lead electrocardiograms had been obtained in all patients at the time of entering the waiting list for transplantation. These ECGs were retrospectively analyzed. The following measurements were taken: heart rate, the PR interval, QRS complex duration, and QTc interval adapted by Bazett's formula. Heart axis, R/S transition,

Fig. 1. Flow chart illustrating reasons for inclusion and exclusion into our study cohort. ESRD, end-stage renal disease; ECG, electrocardiography.

as well as P-wave height and length and T-wave morphology adjusted by the ratio of T-wave to R-wave were also evaluated. In addition, all ECGs were analyzed for atrial fibrillation, AV-block, bundle branch block, ischemic changes, extrasystoles, and evidence of left or right ventricular hypertrophy using the Sokolow-Lyon index.

Analysis of T-Wave Morphology

To identify repolarization abnormalities, manifested by altered T-waves, we created groups representing different regions of the heart. The anterior part of the heart was represented by leads V2–V4; the lateral part by leads V5, V6, I, and aVL; and the inferior section of the heart was represented by leads II, III, and aVF. We calculated the ratio of T-wave to R-wave in order to evaluate the repolarization process without the influence of possible confounders. For this purpose, the height of the T-wave is usually studied in relation to the R-wave amplitude expressed by the T:R ratio [23, 24]. T-wave abnormalities were categorized into a flattened T-wave measuring less than 1/8 of the R-wave, an elevated T-wave measuring more than 2/3 of the R-wave and T-wave inversion, which additionally was divided into preterminal and terminal negative waves.

Statistical Analysis

Data were collected and analyzed using SPSS software for Windows (version 25, SPSS Inc., Chicago, IL, USA). Continuous variables are depicted as mean values and associated standard deviation. Categorical data are presented as relative frequencies and percentages. Comparison between 2 groups was calculated using χ^2 test for categorical data. Continuous data were compared using the *t* test for normally distributed data and the Mann-Whitney U test for skewed data. Correlation with various parameters was performed using Pearson correlation for normally distributed data and rank correlation for skewed data. Cox analysis was used to determine which ECG parameters correlated with CV events with a value of $p < 0.05$ considered to be statistically significant. In order to screen for possible confounders, multivariate statistical analysis with adjustment for age, sex, diabetes, potassium, and additional parameters was performed. To identify a significant threshold of the T:R ratio for predicting CVD, a Kaplan-Meier survival curve was calculated.

Table 1. Baseline demographic and clinical characteristics of our study population with T:R ratio >0.6 versus patients with T:R ratio ≤0.6 in anterior and inferior ECG leads

Variable	All patients (n = 139)	Patients with T:R ratio anterior >0.6 (n = 108)	Patients with T:R ratio anterior ≤0.6 (n = 31)	Patients with T:R ratio inferior >0.6 (n = 21)	Patients with T:R ratio ≤0.6 (n = 118)	p value
Gender, men/women, n (%)	88/51 (63/36)	75/33 (69/31)	13/18 (42/58)	12/9 (57/43)	76/42 (64/36)	0.53
Age, years	46±14	47±14	45±14	52±12	45±14	0.03
BMI, kg/m ²	24±4	25±4	24±5	25±4	24±4	0.46
<i>Smokers, n (%)</i>						
Current smokers	39 (28)	30 (28)	9 (29)	4 (19)	35 (30)	0.32
Previous smokers	50 (36)	41 (38)	9 (29)	10 (48)	40 (34)	0.23
<i>Previous diagnosis, n (%)</i>						
Diabetes mellitus 1 or 2	13 (9)	12 (11)	1 (3)	2 (10)	11 (9)	0.98
CAD	12 (9)	9 (8)	3 (10)	4 (19)	8 (7)	0.07
NSTEMI	5 (4)	5 (5)	0 (0)	0 (0)	5 (4)	0.34
Coronary stent implantation	4 (3)	4 (4)	0 (0)	1 (5)	3 (3)	0.58
Coronary artery bypass	5 (4)	4 (4)	1 (3)	1 (5)	4 (3)	0.76
Peripheral artery occlusive disease	9 (7)	9 (8)	0 (0)	1 (5)	8 (7)	0.73
Prior stroke	3 (2)	3 (3)	0 (0)	0 (0)	3 (3)	0.46
Cardiac defect	63 (45)	49 (45)	14 (45)	8 (38)	55 (47)	0.47
Cardiac arrhythmia	12 (8)	10 (9)	2 (7)	1 (5)	11 (9)	0.49
Congestive heart failure	40 (29)	32 (30)	8 (26)	5 (24)	35 (30)	0.59
Left ventricular hypertrophy	95 (68)	71 (66)	24 (77)	13 (62)	82 (70)	0.49
<i>Cause of ESRD, n (%)</i>						
Diabetic nephropathy	9 (7)	8 (7)	1 (3)	2 (10)	7 (6)	0.54
Hypertensive nephrosclerosis	13 (9)	11 (10)	2 (7)	2 (10)	11 (9)	0.98
Glomerulonephritis	60 (43)	45 (42)	15 (48)	7 (33)	53 (45)	0.32
Interstitial nephritis	4 (3)	3 (3)	1 (3)	0 (0)	4 (3)	0.39
Polycystic kidney disease	22 (16)	16 (15)	6 (19)	7 (33)	15 (13)	0.02
Hereditary	3 (2)	3 (3)	0 (0)	0 (0)	3 (3)	0.46
Unknown	19 (14)	14 (13)	5 (16)	1 (5)	18 (15)	0.20
Others	13 (9)	11 (10)	2 (7)	2 (10)	11 (9)	0.98
<i>Medications, n (%)</i>						
ACE inhibitor	67 (49)	56 (52)	11 (37)	10 (50)	57 (49)	0.92
β-Blocker	92 (66)	72 (67)	20 (65)	14 (67)	78 (66)	0.96
Angiotensin II-receptor antagonist	33 (24)	25 (23)	8 (26)	5 (24)	28 (24)	0.99
Calcium channel blocker	77 (55)	61 (57)	16 (52)	10 (48)	67 (57)	0.44
Sympatholytics	43 (31)	35 (32)	8 (26)	2 (10)	41 (35)	0.02
Diuretic	96 (69)	77 (71)	19 (61)	13 (62)	83 (70)	0.44
Cinacalcet	5 (4)	5 (5)	0 (0)	1 (5)	4 (3)	0.76
Vitamin D	76 (55)	56 (52)	20 (65)	14 (67)	62 (53)	0.23
Phenprocoumon	2 (1)	2 (2)	0 (0)	0 (0)	2 (2)	0.55
ASS	30 (22)	24 (22)	6 (19)	6 (29)	24 (20)	0.40
Erythropoietin	93 (67)	72 (67)	21 (68)	13 (62)	80 (68)	0.60
Statin	24 (17)	18 (17)	6 (19)	2 (10)	22 (19)	0.31
Allopurinol	21 (15)	16 (15)	5 (16)	3 (14)	18 (15)	0.91

Table 1 (continued)

Variable	All patients (n = 139)	Patients with T:R ratio anterior >0.6 (n = 108)	Patients with T:R ratio anterior ≤0.6 (n = 31)	p value	Patients with T:R ratio inferior >0.6 (n = 21)	Patients with T:R ratio ≤0.6 (n = 118)	p value
<i>Laboratory values of the day of listing</i>							
eGFR (CKD-Epi), mL/min	8.0±3.2	7.8±3.3	8.4±3.0	0.23	6.5±3.8	8.2±3.1	0.01
Sodium, mmol/L	137.7±11.1	137.5±12.5	138.4±2.8	0.69	138.9±3.0	137.5±12.0	0.95
Potassium, mmol/L	5.25±0.78	5.32±0.71	5.02±0.94	0.06	5.51±0.46	5.21±0.81	0.02
Calcium, mmol/L	2.44±0.29	2.44±0.31	2.45±0.20	0.49	2.35±0.23	2.46±0.29	0.12
Total protein, g/L	74.4±7.1	74.9±7.1	72.9±7.1	0.20	76.5±7.3	74.0±7.1	0.26
Albumin, %	61.9±7.5	61.5±7.7	63.4±6.9	0.12	63.1±4.5	61.7±8.0	0.51
Phosphorus, mmol/L	1.90±0.62	1.95±0.66	1.73±0.45	0.08	1.89±0.41	1.90±0.65	0.44
Alkaline phosphatase, U/L	92.7±62.5	94.4±68.9	86.7±31.6	0.63	103.1±103.8	90.9±52.4	0.80
Triglycerides, mg/dL	159.2±80.9	154.6±78.1	175.2±89.6	0.20	159.6±99.4	159.2±77.7	0.61
Cholesterol, mg/dL	206±56	201±54	223±59	0.046	229±84	202±48	0.18
HDL, mg/dL	53.8±17.9	53.8±18.2	54.0±17.6	0.93	55.1±20.3	53.6±17.5	0.78
LDL, mg/dL	131.8±50.7	126.7±47.1	146.3±58.1	0.07	128.5±57.2	132.5±49.6	0.76
Glucose, mg/dL	92.2±15.3	92.4±15.8	91.6±13.5	0.97	93.0±17.3	92.1±14.9	0.86
HbA1c, %	5.30±0.70	5.34±0.76	5.18±0.43	0.30	5.48±0.80	5.27±0.68	0.32
Uric acid, mg/dL	4.90±1.50	4.91±1.51	4.88±1.46	0.86	4.72±1.37	4.93±1.52	0.50
Leukocytes, G/L	7.1±2.3	7.1±2.4	7.1±2.2	0.98	6.2±1.7	7.3±2.4	0.07
Hemoglobin, g/dL	12.6±1.5	12.7±1.5	12.3±1.5	0.30	13.1±1.0	12.5±1.6	0.08
Thrombocytes, G/L	259±84	262±86	247±76	0.36	243±66	261±86	0.42
prothrombin time, %	97.1±9.3	96.8±10.3	98.2±4.3	0.47	97.1±7.9	97.1±9.6	1.00
PTT, s	28.2±4.6	28.2±4.9	27.9±3.5	0.97	27.5±4.1	28.3±4.7	0.49
AT, %	87.6±29.5	86.8±30.0	90.8±27.9	0.57	68.8±32.2	90.8±27.9	0.002
Fibrinogen, mg/dL	4.06±1.02	4.01±0.97	4.25±1.19	0.34	4.13±0.95	4.04±1.03	0.68
<i>Further laboratory variables</i>							
eGFR (CKD-Epi) day of discharge after transplantation, mL/min	51.5±25.2	52.1±26.0	49.5±22.7	0.63	41.8±25.4	53.2±24.9	0.06
eGFR (CKD-Epi) 1-year follow-up, mL/min	46.7±22.0	47.3±20.4	44.9±27.1	0.61	41.1±21.6	47.8±22.0	0.21
Previous kidney transplant, n (%)	19 (14)	17 (16)	2 (7)	0.18	4 (19)	15 (13)	0.44
<i>Dialysis-related information</i>							
CAPD, n (%)	21 (14)	15 (13)	6 (15)	0.45	2 (10)	19 (16)	0.46
HD, n (%)	113 (76)	89 (76)	24 (60)	0.53	18 (86)	95 (81)	0.41
Duration of dialysis, h/week	13.5±2.2	13.6±2.2	13.1±2.0	0.39	13.2±1.9	13.5±2.2	0.41
Diuresis on day of listing, mL	1,330±957	1,339±963	1,298±953	0.83	1,110±894	1,369±967	0.32
Frequency of dialysis, day/week	3.05±0.41	3.04±0.45	3.05±0.21	0.46	3.0±0.0	3.1±0.5	0.66
<i>Transplantation-related information</i>							
Time to transplantation, year	3.7±3.3	3.8±3.4	3.6±3.1	0.70	4.4±3.3	3.6±3.4	0.24
Diuresis before transplantation, mL	823±952	876±977	641±849	0.31	692±928	847±958	0.43

Data are presented as mean ± SD or as percentage for categorical data.

BMI, body mass index; CAD, coronary artery disease; NSTEM, non ST elevation myocardial infarction; ACE inhibitor, angiotensin-converting enzyme inhibitor; PTT, partial thromboplastin time; AT, antithrombin; CAPD, continuously ambulatory peritoneal disease; HD, hemodialysis.

Fig. 2. Timeline of the time of observation starting at registration for waiting list and ending on the day of 1-year follow-up after transplantation.

Results

Baseline Characteristics

Patients' characteristics, previous diagnoses, causes of ESRD, medications, and laboratory variables of the day of listing are presented in Table 1. Furthermore, dialysis- and transplantation-related information is demonstrated (Table 1).

Major CV Events

We retrospectively analyzed 139 patients from the time of listing for renal transplantation until 1 year after transplantation as shown in Figure 2. The observation period covered 4.7 ± 3.5 years. During this time, 1 patient developed an ST-elevation myocardial infarction, twelve patients were recorded with non ST-elevation myocardial infarctions, 3 patients received coronary stent implantations, 1 patient underwent coronary bypass surgery, 1 patient presented with a stroke, and 5 patients had to undergo an intervention for peripheral artery disease. In total, 22 patients (16%) thus suffered CV events during our period of observation. CV events occurred at a mean of 4.01 ± 2.96 years after transplant listing.

ECG Evaluation

Basic ECG Parameters

Results of our ECG evaluation are shown in Table 2. Patients who experienced CV events exhibited a significantly higher T:R ratio in anterior leads ($p = 0.03$) and significantly more ECGs with extrasystoles ($p = 0.001$).

Among the ECG parameters evaluated, the T:R ratio showed a significant association with CV events in dialysis patients awaiting a kidney transplant until 1 year after transplantation. To investigate repolarization abnormalities in more detail, we analyzed the T:R ratio in different regions of the heart. An elevated T:R ratio was seen in 76% of anterior leads and 14% of inferior leads.

Second, we correlated T:R values with the patients' clinical characteristics of the day of listing. In anterior leads a significant correlation was detected between T:R ratios and serum values for potassium ($p = 0.006$; correlation coefficient [CC] 0.163), phosphorus ($p = 0.04$; CC 0.118), HbA1C ($p = 0.03$; CC 0.129), and total protein ($p = 0.01$; CC 0.148), the patients' hemoglobin values ($p = 0.003$; CC 0.174) and cinacalcet administration ($p = 0.004$; CC 0.242). Also, a positive correlation between the T:R ratios in anterior leads and the group of patients treated by hemodialysis ($p = 0.02$; CC 0.209) was detected, whereas a negative correlation was found with the group treated by CAPD ($p = 0.02$; CC -0.204). In inferior leads age ($p = 0.04$; CC 0.123) showed a significant correlation with the T:R ratio, whereas a significant negative correlation was detected with ACE inhibitor medication ($p = 0.04$; CC -0.180 ; online suppl. Material Table 1, see www.karger.com/doi/10.1159/000500917).

Univariate Cox Regression

Univariate Cox regression revealed the following parameters to be associated with CV events: age, BMI, serum calcium, serum cholesterol, prothrombin time, duration of dialysis, and time until receiving kidney transplantation (Table 3).

Table 2. ECG parameters of patients with versus without CV events

Parameter	All patients, (n = 139)	Patients with CV events, (n = 22)	Patients without CV events (n = 117)	p value
Heart rate	70±15	69±16	70±15	0.99
<i>Heart axis, n (%)</i>				
Left axis deviation	7 (5)	2 (9)	5 (4)	0.34
Horizontal axis	59 (42)	9 (41)	50 (43)	0.93
Normal axis	44 (32)	9 (41)	35 (30)	0.31
Vertical axis	23 (17)	2 (9)	21 (18)	0.31
Right axis	3 (2)	0 (0)	3 (3)	0.45
Extreme right axis deviation	2 (1)	0 (0)	2 (2)	0.54
SIQIII	1 (1)	0 (0)	1 (1)	0.66
Atrial fibrillation, n (%)	1 (1)	0 (0)	1 (1)	0.66
p-Sinistocardiale, n (%)	37 (27)	6 (27)	31 (27)	0.96
PQ interval, s	0.17±0.04	0.16±0.05	0.17±0.03	0.88
AV-block, n (%)	13 (9)	2 (9)	11 (9)	0.95
QRS interval, s	0.08±0.02	0.07±0.02	0.08±0.01	0.51
Incomplete BBB, n (%)	8 (6)	2 (9)	6 (5)	0.46
Sokolow index left, mV	2.89±1.27	2.39±1.06	2.96±1.25	0.21
Sokolow index right, mV	0.61±0.37	0.49±0.31	0.64±0.37	0.31
<i>R/S turnover, n (%)</i>				
V1/V2	7 (5)	2 (9)	5 (4)	0.34
V2/V3	33 (24)	5 (23)	28 (25)	0.90
V3/V4	69 (50)	9 (41)	60 (51)	0.37
V4/V5	25 (18)	4 (18)	21 (18)	0.98
V5/V6	2 (1)	1 (5)	1 (1)	0.18
No turnover	3 (2)	1 (5)	2 (2)	0.40
ST segment changes, n (%)	22 (16)	5 (23)	17 (15)	0.33
T:R ratio anterior	1.87±1.75	2.91±2.61	1.68±1.47	0.03
T:R ratio lateral	0.007±0.62	0.04±0.46	0.001±0.65	0.80
T:R ratio inferior	0.28±0.82	0.66±1.27	0.21±0.69	0.23
QTc (Bazett's formula), ms	400±47	407±27	399±49	0.42
Extrasystoles, n (%)	4 (3)	3 (14)	1 (1)	0.001
Supraventricular	1 (1)	1 (5)	0 (0)	0.02
Ventricular	3 (2)	2 (9)	1 (1)	0.02

Data are presented as mean ± SD or as percentage for categorical data.

CV, cardiovascular; ECG, electrocardiography; BBB, bundle branch block.

When performing univariate Cox regression analysis concerning ECG parameters an elevated T:R ratio occurring in anterior and inferior leads ($p = 0.001$; 95% CI 1.14–1.64 and $p = 0.001$; 95% CI 1.49–4.57), ECGs containing extrasystoles ($p = 0.005$; 95% CI 1.74–20.93), as well as a decreased left and right Sokolow-Lyon index ($p = 0.02$; 95% CI 0.39–0.91 and $p = 0.03$; 95% CI 0.06–0.90), showed a significant association with CV events (Table 3).

Multivariate Cox Regression

We performed adjustment for several parameters. When adjusting ECG parameters for known potential confounders age, sex, diabetes, and potassium, the T:R ratio in anterior ($p = 0.004$; 95% CI 1.09–1.59) and inferior leads ($p = 0.008$; 95% CI 1.23–3.77) remained significantly associated with future CV events. Further multivariate adjustment also including BMI,

Table 3. Univariate Cox regression analysis on CV events

Parameter	<i>p</i> value	HR (95% CI)
T:R ratio anterior	0.001	1.37 (1.14–1.64)
T:R ratio inferior	0.001	2.61 (1.49–4.57)
Extrasystoles	0.005	6.03 (1.74–20.93)
Sokolow index left	0.02	0.60 (0.39–0.91)
Sokolow index right	0.03	0.23 (0.06–0.90)
Age	<0.001	1.09 (1.04–1.14)
BMI	0.02	1.13 (1.02–1.25)
S-Calcium	0.046	0.14 (0.02–0.97)
S-Cholesterol	0.02	1.01 (1.00–1.01)
Prothrombin time	0.02	0.97 (0.94–1.00)
Duration of dialysis	0.02	1.24 (1.04–1.49)
Days-transplantation	0.02	1.00 (0.99–1.00)

CV, cardiovascular; BMI, body mass index.

serum potassium, calcium, cholesterol, prothrombin time, and estimated glomerular filtration rate (CKD-Epi formula) values at the time of listing and the day of discharge after transplantation as well as duration of dialysis and days to transplantation did not change the observed significance of the T:R ratio (Table 4).

Kaplan-Meier Analysis

To assess whether there is a threshold for predictive T:R ratios, we performed Kaplan-Meier analysis using different cutoff values. Setting the threshold at 0.6, a T:R ratio above 0.6 in inferior leads was significantly associated with future CV events ($p = 0.03$; Fig. 3a). In contrast, a Kaplan-Meier analysis of anterior leads with a T:R ratio >0.6 revealed no significant predictive value ($p = 0.16$; Fig. 3b). Values other than 0.6 resulted in lower predictive power (data not shown).

Discussion

In this study, we evaluated multiple ECG parameters for prediction of CV events in ESRD patients on the kidney transplant waiting list and found an increased T:R ratio as an independent predictor for CV events. Electrocardiographic abnormalities during the process of repolarization, as represented by T-wave changes, correlate with an increased susceptibility for cardiac arrhythmias in the general population [25, 26]. Especially T-wave alternans, that is, a beat-to-beat variation in T-wave amplitude, has been described as being associated with a high risk for sudden cardiac death and CV mortality [27]. In addition, an independent association of T-wave alternans with macrovascular disease has been reported [20]. These observations point to the importance of T-wave abnormalities in predicting CV morbidity and mortality. Furthermore, T-wave changes are common in ESRD patients undergoing dialysis [20, 22].

In our study, we detected a T:R ratio >0.6 in inferior leads as being independently predictive for future CV events. To the best of our knowledge, association of CV morbidity and mortality and T:R ratio has been investigated in ESRD patients in only one previous study [24]. Green et al. [24] described a T:R ratio >0.75 as being independently predictive for sudden death in ESRD patients. In that study, ECGs of 145 ESRD patients were analyzed for T-wave tenting and T:R ratios, their association with serum potassium, and their prognostic value

Table 4. Multivariate Cox regression analysis on CV events

Covariates	T:R ratio anterior <i>p</i> value HR (95% CI)	T:R ratio inferior <i>p</i> value HR (95% CI)	Extrasystoles <i>p</i> value HR (95% CI)	Sokolow index left <i>p</i> value HR (95% CI)	Sokolow index right <i>p</i> value HR (95% CI)
Age (years)	0.01 1.25 (1.06–1.49)	0.006 2.09 (1.23–3.55)	0.048 3.52 (1.01–12.24)	0.29 0.79 (0.51–1.22)	0.07 0.28 (0.07–1.13)
Gender	0.001 1.37 (1.14–1.64)	0.001 2.63 (1.49–4.65)	0.005 6.03 (1.72–21.10)	0.02 0.59 (0.38–0.91)	0.03 0.21 (0.05–0.87)
Diabetes	0.001 1.37 (1.14–1.64)	0.001 2.63 (1.50–4.62)	0.004 6.27 (1.78–22.09)	0.02 0.60 (0.39–0.91)	0.04 0.23 (0.06–0.90)
BMI	0.001 1.36 (1.32–1.62)	0.001 2.54 (1.44–4.47)	0.001 9.64 (2.57–36.17)	0.06 0.66 (0.42–1.02)	0.02 0.17 (0.04–0.71)
S-Potassium	<0.001 1.44 (1.18–1.76)	0.001 2.66 (1.51–4.66)	0.006 5.97 (1.67–21.38)	0.02 0.60 (0.39–0.91)	0.03 0.19 (0.04–0.82)
S-Calcium	0.001 1.36 (1.14–1.63)	0.002 2.36 (1.36–4.12)	0.005 5.93 (1.70–20.73)	0.048 0.65 (0.43–1.00)	0.04 0.22 (0.05–0.91)
S-Cholesterol	0.006 1.31 (1.08–1.60)	0.001 2.62 (1.45–4.74)	0.02 4.48 (1.25–16.08)	0.02 0.59 (0.38–0.91)	0.06 0.26 (0.06–1.04)
Prothrombin time	0.001 1.36 (1.13–1.63)	0.001 2.54 (1.45–4.46)	0.004 6.32 (1.80–22.13)	0.03 0.62 (0.40–0.94)	0.045 0.23 (0.05–0.97)
eGFR, day of listing	0.003 1.33 (1.10–1.60)	0.002 2.61 (1.40–4.85)	0.001 9.53 (2.53–35.86)	0.01 0.58 (0.38–0.88)	0.03 0.23 (0.06–0.88)
eGFR, day of discharge after transplantation	<0.001 1.44 (1.17–1.76)	0.001 2.68 (1.51–4.75)	0.006 5.99 (1.66–21.67)	0.02 0.61 (0.40–0.93)	0.04 0.22 (0.05–0.95)
Duration of dialysis	0.001 1.43 (1.16–1.77)	0.002 3.097 (1.50–6.40)	0.02 6.89 (1.45–32.69)	0.04 0.59 (0.36–0.98)	0.40 0.52 (0.11–2.36)
Days to transplantation	<0.001 1.39 (1.16–1.68)	<0.001 2.72 (1.56–4.75)	0.004 6.25 (1.78–21.92)	0.02 0.61 (0.40–0.94)	0.04 0.22 (0.05–0.90)
Age (years) Gender Diabetes	0.009 1.26 (1.06–1.49)	0.008 2.11 (1.22–3.65)	0.06 3.37 (0.95–11.99)	0.31 0.80 (0.52–1.23)	0.07 0.26 (0.06–1.12)
Age (years) Gender Diabetes S-Potassium	0.004 1.32 (1.09–1.59)	0.008 2.15 (1.23–3.77)	0.08 3.25 (0.89–11.94)	0.31 0.80 (0.52–1.23)	0.06 0.23 (0.05–1.07)
Age (years) Gender Diabetes eGFR, day of discharge after transplantation	0.002 1.35 (1.11–1.64)	0.003 2.40 (1.34–4.31)	0.17 2.61 (0.66–10.42)	0.23 0.76 (0.49–1.19)	0.06 0.22 (0.04–1.07)

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate

concerning CV outcome and sudden death. However, in our study, a threshold of 0.75 carried no significance, but the end point of our study was the occurrence of CV events rather than sudden death.

To the best of our knowledge, percentage data on the prevalence of elevated T-waves in ESRD patients do not exist. Elevated T-waves are often an expression of underlying hyperka-

Fig. 3. Kaplan-Meier analysis of the T:R ratio in inferior (**a**) and anterior (**b**) ECG leads and the occurrence of CV events. A T:R ratio >0.6 in inferior but not anterior leads was significantly related to CV events ($p = 0.03$ and $p = 0.16$, respectively).

lemia, which is common in ESRD patients [24, 28, 29]. This association was confirmed in the present study, given our finding of a significant correlation between the T:R ratio in anterior leads and the serum potassium values. However, additional causes may also lead to elevated T-waves including LVH and the hyperacute phase of myocardial infarction. Furthermore, elevated T-waves can be observed in noninfarction myocardial ischemia and in young, athletic patients [30, 31]. In our study, we failed to observe a correlation between the T:R ratio and ECG signs of LVH. Also, it is unlikely that we recorded ECGs in the hyperacute phase of myocardial infarction, since our ECGs were recorded in a routine outpatient examination setting.

We also found that ECGs containing extrasystoles significantly predicted CV events, however, on univariate analysis only. This is probably due to the low number of cases in our study, since ECGs of only 4 patients contained extrasystoles. Further studies will be needed to confirm this correlation since studies concerning extrasystoles and outcome in ESRD patients are lacking as well.

Left and right Sokolow-Lyon indices in our study predicted outcomes again in univariate analysis only. Multivariate analysis did not show significance. In addition, a negative correlation between the Sokolow-Lyon index and the occurrence of CV events was observed. Our observation supports studies stating that the Sokolow-Lyon index represents a nonreliable parameter in predicting CV events in ESRD patients [19, 32].

In our study, only the T:R ratio was significant for CV events in regression analysis. Other ECG parameters were not significantly related to an increased frequency of CV events. Nevertheless, there was a trend toward a higher occurrence of prolonged QTc interval in ESRD patients developing CV events. In different studies, the QTc interval was reported to increase in dialysis patients [33, 34]. A prolonged QTc interval like T-wave changes is known to be associated with an increased risk of sudden death and total mortality in hemodialysis patients [12].

Other studies found ECG changes like LVH by different scoring systems, increased heart rate, atrial fibrillation, PR-interval prolongation, and T-wave changes as significant parameters related to an increased CV morbidity and mortality and all-cause mortality in ESRD patients [13–20]. However, these were single studies focusing on selected parameters and in part using parameters, which are not measured in routine ECG evaluation. Sharma et al. [10] described an abnormal ECG including signs of LVH, ST depression or elevation, T-wave inversion or bundle branch block as an independent predictor of severe CAD in ESRD patients. These measures were not analyzed as single parameters but rather combined into an “abnormal ECG” if any of the mentioned parameters showed abnormalities. In contrast, our study analyzed all ECG parameters independently and performed a thorough evaluation of parameters, which are evaluated in daily routine.

There are various limitations to this study. Since we applied a retrospective study design, some transplantation files were missing or not usable due to bleaching of ECGs. Also only patients, who received a kidney transplant, were enrolled into the study. This is why patients, who died before kidney transplantation, possibly including sudden death, are not part of the study population. This may have led to a selection bias. Also, our cohort size may have been too small to detect other potentially relevant ECG parameters related to CV outcome or events of sudden death after transplantation. Nevertheless, the strength of our study is the thorough examination of all ECGs.

In conclusion, we present first evidence that an elevated T:R ratio in particular in inferior ECG leads in ESRD patients on the kidney transplant list is predictive for CV events. If confirmed in independent studies, this easily available work-up may identify patients who may benefit from more sophisticated diagnostics to potentially reduce the occurrence of CV events.

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Statement of Ethics

Approval for the usage of transplantation files was confirmed by the respective hospital. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Substantial contributions to the conception or design of the work: L.B., G.S., A.M., and J.F. Acquisition, analysis, or interpretation of data for the work: L.B. and G.S. Drafting the work: L.B. Revising the work critically for important intellectual content: G.S., J.F., and A.M. Final approval of the version to be published: L.B., G.S., J.F., and A.M. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: L.B., G.S., J.F., and A.M.

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