

Original Paper

Usefulness of an Upright T-Wave in Lead aVR for Predicting the Short-Term Prognosis of Incident Hemodialysis Patients: A Potential Tool for Screening High-Risk Hemodialysis Patients

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Key Words

Lead aVR · T-wave · Cardiovascular disease · End-stage kidney disease · Hemodialysis · Mortality

Abstract

Background/Aims: An upright T-wave in lead aVR (aVRT) has recently been reported to be associated with cardiovascular death and mortality among the general population and patients with prior cardiovascular disease (CVD). However, evidence for the predictive ability of aVRT in patients with chronic kidney disease is lacking. Therefore, a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of an upright aVRT for the short-term prognosis in incident hemodialysis patients. **Methods:** Among 208 patients who started maintenance hemodialysis, 79 with preexisting CVD (CVD cohort) and 129 with no history of CVD (non-CVD cohort), were studied. An upright and non-upright aVRT were defined as a wave with a positive deflection in amplitude of ≥ 0 mV and a negative deflection in amplitude of < 0 mV, respectively. The endpoint was all-cause death. **Results:** Overall, the prevalence of an upright aVRT was 22.6% at baseline. During the mean follow-up period of 2.1 ± 1.0 years, 33 deaths occurred. Cumulative survival rates at 3 years after starting dialysis in patients with an upright and non-upright aVRT were 50.0 and 80.7%, respectively, in the CVD cohort and 92.0 and 91.3%, respectively, in the non-CVD cohort. In the CVD cohort, mul-

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tivariate Cox regression analysis showed that an upright aVRT was an independent predictor of death after adjusting for confounding variables. **Conclusion:** Among Japanese hemodialysis patients at high risk for CVD, an upright aVRT seems to be useful for predicting death.

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Introduction

Although the mechanism of cardiorenal syndrome has been elucidated in considerable detail over the past decade [1], atherosclerotic cardiovascular disease (CVD) remains a leading cause of death among hemodialysis patients [2], and their cardiovascular mortality is greater than in the general population [3]. It should be noted that the prevalence of atherosclerotic vascular disease at the start of renal replacement therapy is already high. For instance, angiographic assessment has shown that more than half of the patients with new end-stage kidney disease (ESKD) have significant coronary artery disease (CAD) [4, 5]. Based on this background, the K/DOQI guideline has recommended that nephrologists screen for cardiac disease at the beginning of maintenance dialysis therapy [6, 7]. Because the majority of hemodialysis patients are taken care of in small facilities, simple, easy, and universal surrogate tools for identifying CVD and for the assessment of its severity and prognosis are needed for these patients.

The 12-lead electrocardiogram (ECG) is the gold standard procedure in the diagnosis of ischemic heart disease, and a high frequency of ECG abnormalities is observed in dialysis patients [8, 9]. Lead aVR, an augmented and unipolar limb lead, was constructed to obtain specific information from the right upper position of the heart, including the outflow tract of the right ventricle and the basal portion of the interventricular septum. Although numerous studies have examined the association of T-wave abnormalities with cardiovascular events [10–13], the significance of an abnormality of T-wave in lead aVR (aVRT) has not been fully explored. Recently, a retrospective cohort study including 24,270 male veterans whose ECGs were obtained for any clinical reasons evaluated the diagnostic value of an upright aVRT and showed an association between the T-wave amplitude in lead aVR and cardiovascular mortality during a mean follow-up period of 4 years [14].

However, evidence for its use in chronic kidney disease (CKD) patients has been lacking, and the association between upright aVRT and mortality in CKD patients is unknown. We hypothesized that upright aVRT might be observed with high frequency in ESKD patients at high risk for CVD and that patients with an upright aVRT would have a higher incidence of death, including cardiovascular death. Therefore, this study was conducted to evaluate the predictive ability of an upright aVRT for mortality in ESKD patients.

Materials and Methods

Subjects and Study Design

This was a hospital-based, prospective cohort study involving 308 consecutively hospitalized ESKD patients who started maintenance hemodialysis at Toho University Ohashi Medical Center, Tokyo, Japan, between April 2004 and December 2013. A total of 100 patients were excluded according to the following criteria: (1) patients who died during hospitalization; (2) patients who had a past history of dialysis; (3) the cause of ESKD was acute kidney injury; (4) the cause of ESKD was rapidly progressive glomerulonephritis; (5) the cause of ESKD was nonrenal parenchymal disease; (6) the cause of ESKD was congenital kidney disease; (7) patients who were changed to peritoneal dialysis; (8) patients who discontinued dialysis; (9) patients who received renal transplantation after starting dialysis; (10) patients who moved away just after discharge; (11) patients for whom ECGs were not available; (12) patients with chronic atrial fibrillation; (13)



Fig. 1. Representative aVR lead with an upright T-wave (a) and a non-upright T-wave (b).

patients with right or left bundle branch block; (14) patients with sick sinus syndrome, and (15) patients who had cardiac pacing or a defibrillator (fig. 1).

The subjects were followed up until December 31, 2013. This study adhered to the Declaration of Helsinki. The Ethics Committee for Clinical Research at Toho University Ohashi Medical Center approved the study protocol (permission No. 13-52 and 13-61). We did not have to obtain consent from the individual patients; however, we posted a note when starting this study, and the patients could express their objections to using their data.

Electrocardiography

At the initial dialysis, standard 12-lead resting ECGs were taken in the resting supine position soon after admission to the hospital, and all ECGs were evaluated before undergoing maintenance hemodialysis. Upright aVRT was defined as a wave with a positive deflection of ≥ 0 mV, and non-upright aVRT was defined as aVRT of < 0 mV (fig. 1). The durations of the QRS complex and QT interval were recorded automatically by the ECG machine. The corrected QT (QTc) was adjusted for the RR interval using the Bazett formula ($QTc = QT / \sqrt{RR}$).

Other Variables

The clinical diagnosis of the underlying kidney disease (not necessarily biopsy proven), the presence of diabetes, preexisting CVD and malignancy, and medications used at the time of discharge were recorded. In the present study, CVD included ischemic heart disease that had been diagnosed as acute myocardial infarction (MI), coronary stenosis detected by coronary angiography and treated by percutaneous coronary revascularization (PCI) and/or coronary artery bypass grafting, ischemic stroke, hemorrhagic stroke, peripheral artery disease, and history of macrovascular surgery. Blood pressure was recorded in the supine position, and a blood sample was collected just before the first hemodialysis session. Whole blood was used for measuring hemoglobin, and other biochemical assays were performed using serum samples. Serum albumin, calcium, phosphate, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) levels were measured by routine laboratory methods in our hospital. The non-high-density lipoprotein cholesterol (non-HDL-C) level was calculated by subtracting the HDL-C level from the TC level [$\text{non-HDL-C (mg/dl)} = \text{TC (mg/dl)} - \text{HDL-C (mg/dl)}$], and serum total calcium was adjusted for albumin using the formula proposed by the Japanese Society for Dialysis Therapy guideline (Payne's formula) if there was hypoalbuminemia (serum albumin < 4.0 g/dl): corrected calcium (mg/dl) = total serum calcium (mg/dl) + $[4 - \text{serum albumin (mg/dl)}]$ [15].

Outcome Data Collection

The outcome of this study was defined as all-cause death. Information about death was obtained from a questionnaire survey of the maintenance hemodialysis facilities or the hospital medical records. The cohort was followed until the end of 2013, and the 3-year survival rate after starting dialysis was evaluated.

Statistical Methods

Data are summarized as numbers, prevalences, arithmetic means \pm standard deviation, or medians (interquartile range), as appropriate. Comparisons of prevalence and values between groups were performed by Student's *t* test and the χ^2 test. In the prospective analysis, the Kaplan-Meier method was used with the

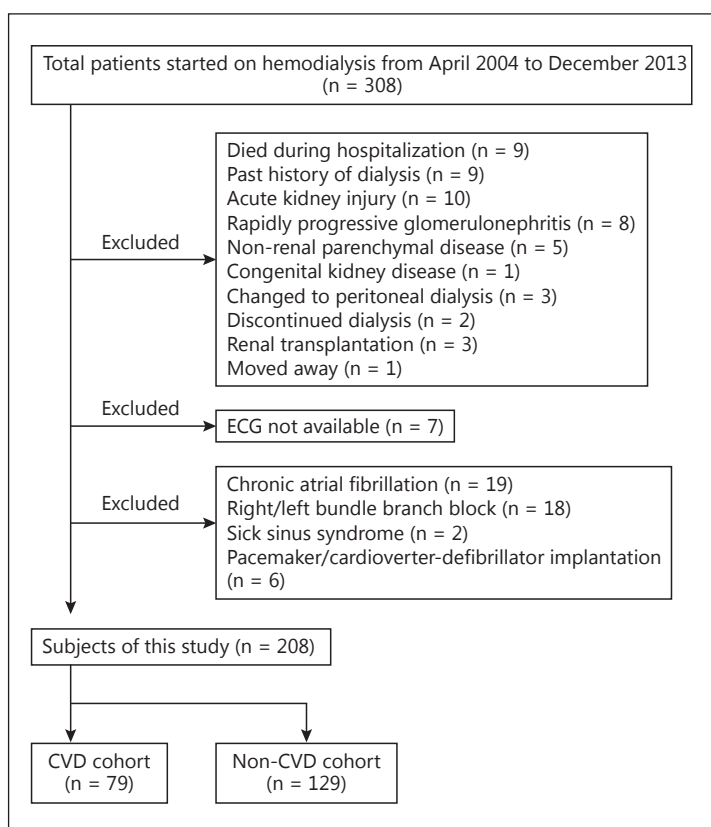


Fig. 2. Subject flow diagram.

log-rank test. Prognostic variables were examined by the Cox proportional hazard models, and hazard ratios and 95% confidence intervals are reported. *p* values <0.05 were considered significant. The nonlinear effects of continuous independent variables were evaluated using quadratic and log transformations. Separate analyses were conducted for patients with preexisting CVD (CVD cohort) and patients with no history of CVD (non-CVD cohort). All statistical analyses were performed using SPSS for Windows version 20 (IBM, New York, N.Y., USA).

Results

Patients' Characteristics at Baseline

Among the 308 consecutively hospitalized patients who started maintenance hemodialysis, a total of 208 patients were studied, i.e. 79 in the CVD cohort and 129 in the non-CVD cohort (fig. 2). Overall, the prevalence of an upright aVRT was 22.6% at baseline (table 1). Although the aVRT amplitude was significantly higher in the CVD cohort, the prevalence of an upright aVRT was not different between the CVD and non-CVD cohorts. Table 2 gives both cohorts' characteristics according to the presence of an upright aVRT at baseline, and shows the comparison among the 4 groups. Significant differences among the 4 groups were noted in age, percentage of males and malignancy, serum phosphate and CRP levels, the use of β -blockers, aspirin, and erythropoiesis-stimulating agents, aVR amplitude, heart rate, and QRS duration. Patients with an upright aVRT in the CVD cohort showed the oldest age, the highest percentage of males, the highest CRP level, the highest aVRT amplitude, and the widest QRS complex. In the CVD cohort, the prevalence of patients with preexisting CVD, including CAD, cerebrovascular disease, peripheral artery disease, and a history of macrovascular surgery, was not different between the upright and the non-upright aVRT groups.

Table 1. Patients' characteristics at baseline

Variable	Total cohort (n = 208)	CVD cohort (n = 79)	Non-CVD cohort (n = 129)	p value
Age, years	66 (57–75)	71 (61–78)	64 (55–73)	0.006
Male, %	64.9	72.2	60.5	0.058
Diabetes, %	61.5	65.8	58.9	0.199
Malignancy, %	11.5	6.3	14.7	0.050
CAD, %	21.6	57.0	–	–
Cerebrovascular disease, %	15.9	41.8	–	–
Peripheral artery disease, %	10.1	26.6	–	–
History of macrovascular surgery, %	3.8	10.1	–	–
Upright aVRT, %	22.6	27.8	19.4	0.107
aVRT amplitude, mV	–1 (–2 to –1)	–1 (–1 to 0)	–1 (–2 to –1)	<0.001
Heart rate, bpm	76 (68–88)	73 (66–82)	79 (69–90)	0.059
QRS duration, ms	98 (92–103)	99 (93–106)	96 (92–102)	0.048
QTc interval, ms	458 (441–476)	459 (440–477)	458 (442–475)	0.532

Values for continuous variables are given as medians (interquartile range). Upright and non-upright aVRT were defined as a wave with a positive deflection in amplitude ≥ 0 mV and a negative deflection in amplitude < 0 mV, respectively. p values between the CVD and non-CVD cohorts.

Follow-Up

At the end of follow-up, 166 patients were alive on maintenance hemodialysis, and the remaining 33 patients died from various causes, i.e. 22 (27.8%) in the CVD cohort and 11 (8.5%) in the non-CVD cohort. The mean follow-up period (mean \pm standard deviation) was 2.1 ± 1.0 years in both cohorts.

As seen in figure 3, the Kaplan-Meier curves showed that patients with an upright aVRT had a higher death rate in the CVD cohort (log-rank test, $p = 0.005$), but in the non-CVD cohort, cumulative survival was not different between patients with upright and non-upright aVRT (log-rank test, $p = 0.857$). The cumulative survival rates at 3 years after starting dialysis of patients with upright and non-upright aVRT were 50.0 and 80.7%, respectively, in the CVD cohort and 92.0 and 91.3%, respectively, in the non-CVD cohort.

Association between an Upright aVRT and Death

Table 3 summarizes the results of univariate Cox analysis of factors predicting death in the cohorts. Age in the CVD and non-CVD cohorts, the presence of peripheral artery disease and an upright aVRT in the CVD cohort, and the presence of malignancy and serum CRP level in the non-CVD cohort were identified as significant predictors of death. In the non-CVD cohort, an upright aVRT was not associated with death, unlike in the CVD cohort.

Independent Association of an Upright aVRT with Death

Overall, in the CVD cohort, multivariate Cox regression analyses showed that an upright aVRT remained an independent predictor of death after adjusting for confounding variables (table 4). The variables for adjustment in the analysis were age, sex, diabetes, malignancy, and pre-existing CVD, including CAD, cerebrovascular disease, peripheral artery disease, and history of macrovascular surgery. In the non-CVD cohort, as in the univariate model, an upright aVRT was not associated with death in the multivariate model.

Table 2. Characteristics of the CVD and non-CVD cohorts according to the presence of an upright aVRT at baseline

Variable	CVD cohort		Non-CVD cohort		p value
	upright aVRT (n = 22)	non-upright aVRT (n = 57)	upright aVRT (n = 25)	non-upright aVRT (n = 104)	
Age, years	72 (57–76)	70 (61–79)	64 (59–70)	64 (54–73)	0.047
Male, %	86.4	66.7	76.0	56.7	0.030
Diabetes, %	77.2	61.4	72.0	55.8	0.178
Malignancy, %	18.2	1.6	20.0	13.5	0.038
CAD, %	72.7	50.9	–	–	0.127*
Cerebrovascular disease, %	40.9	42.1	–	–	1.000*
Peripheral artery disease, %	36.4	22.8	–	–	0.261*
History of macrovascular surgery, %	9.1	10.5	–	–	1.000*
BMI	19.9 (18.7–22.1)	20.5 (18.5–23.2)	22.0 (18.9–24.1)	20.8 (19.0–23.3)	0.567
SBP, mm Hg	151 (132–158)	150 (134–161)	162 (154–181)	160 (142–177)	0.064
DBP, mm Hg	74 (61–89)	72 (68–83)	83 (79–95)	78 (70–98)	0.175
Alb, g/dl	3.2 (2.8–3.5)	3.4 (3.1–3.6)	3.2 (3.0–3.7)	3.5 (3.1–3.8)	0.197
Corrected Ca, mg/dl	8.7 (8.2–8.9)	8.5 (7.9–8.9)	8.1 (7.5–8.9)	8.4 (7.9–8.9)	0.640
P, mg/dl	5.9 (4.9–7.4)	5.7 (5.0–6.7)	6.8 (6.0–8.5)	6.2 (5.2–7.3)	0.007
Intact PTH, pmol/l	220 (175–336)	268 (166–407)	274 (190–366)	308 (191–425)	0.329
HDL-C, mg/dl	45 (37–54)	45 (38–55)	50 (40–68)	47 (40–59)	0.706
Non-HDL-C, mg/dl	102 (91–140)	120 (89–153)	108 (96–165)	114 (86–143)	0.183
CRP, mg/dl	0.10 (0.01–0.20)	0.10 (0.00–0.10)	0.02 (0.00–0.11)	0.02 (0.00–0.10)	0.017
Hb, g/dl	8.9 (8.5–10.2)	8.7 (7.7–9.7)	9.0 (7.2–9.5)	8.5 (7.5–9.6)	0.166
Use of RAS inhibitors, %	72.7	68.4	76.0	74.0	0.860
Use of β -blockers, %	36.4	31.6	16.0	13.5	0.013
Use of statins, %	45.5	35.1	32.0	31.7	0.661
Use of aspirin, %	72.7	59.6	8.0	15.4	<0.001
Use of ESAs, %	81.8	78.9	64.0	86.5	0.042
aVRT amplitude, mV	0 (0–1)	–1 (–1 to –1)	0 (0–0)	–1 (–2 to –1)	<0.001
Heart rate, bpm	73 (62–90)	73 (67–82)	87 (68–100)	78 (69–88)	0.014
QRS duration, ms	103 (99–107)	98 (90–105)	96 (94–99)	96 (91–102)	0.004
QTc interval, ms	473 (442–492)	458 (439–471)	468 (455–475)	454 (441–475)	0.157

Values for continuous variables are given as medians (interquartile range). Upright and non-upright aVRT were defined as a wave with a positive deflection in amplitude ≥ 0 mV and a negative deflection in amplitude < 0 mV, respectively. p values across four groups in the CVD and non-CVD cohorts. * p values between two groups in the CVD cohort. SBP = Systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; Alb = albumin; Ca = calcium; P = phosphate, PTH = parathyroid hormone; Hb = hemoglobin; RAS = renin-angiotensin-aldosterone system; ESA = erythropoiesis-stimulating agent.

Discussion

In this study, it was found for the first time that an upright aVRT on ECG was associated with short-term mortality in incident hemodialysis patients with prior CVD; Kaplan-Meier analysis showed a lower cumulative survival rate in patients with an upright aVRT than in those with a non-upright aVRT, and this association remained significant after adjusting for other variables that are well-known risk factors for mortality. These results imply that an upright aVRT on the standard resting ECG, which can be evaluated by a nurse or clinical engineer even in small facilities, may be a useful procedure for predicting mortality in ESKD patients.

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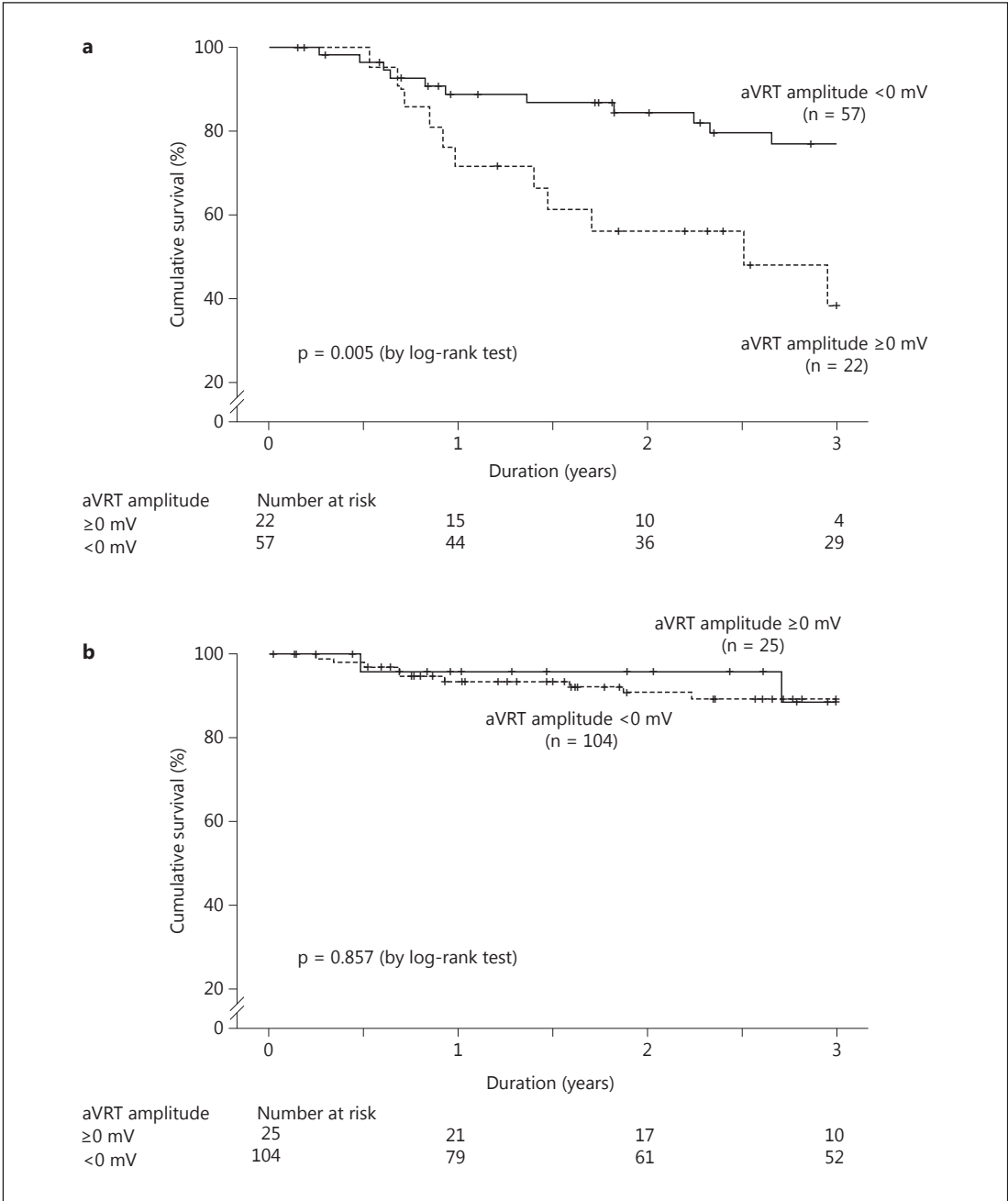


Fig. 3. Cumulative survival of the two cohorts. **a** Cumulative survival of the CVD cohort (n = 79) with an upright aVRT (aVRT amplitude ≥0 mV) or a non-upright aVRT (aVRT amplitude <0 mV). **b** Cumulative survival in the non-CVD cohort (n = 129) with an upright aVRT (aVRT amplitude ≥0 mV) or a non-upright aVRT (aVRT amplitude <0 mV).

At baseline, the prevalence of an upright aVRT in the total and CVD cohorts was 22.6 and 27.8%, respectively, which was higher than in previous studies. In the general population, an upright aVRT was observed in 2.2% of people [16], and other studies showed that the prevalence of an upright aVRT was 16.2% in patients with a prior MI [17] and 17.5% in patients with heart failure [18]. We have thought that the prevalence of an upright aVRT would

Table 3. Univariate Cox analysis of predictors for death

Variable	CVD cohort		Non-CVD cohort	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per year)	1.052 (1.012–1.093)	0.009	1.046 (1.004–1.089)	0.031
Male (vs. female)	0.690 (0.281–1.695)	0.491	3.207 (0.693–14.846)	0.136
Diabetes (vs. non-diabetes)	1.486 (0.581–3.797)	0.409	1.850 (0.491–6.973)	0.364
Malignancy (vs. absence)	0.661 (0.089–4.941)	0.687	7.586 (2.309–24.917)	0.001
CAD (vs. absence)	2.242 (0.877–5.732)	0.092	–	–
Cerebrovascular disease (vs. absence)	2.192 (0.936–5.130)	0.071	–	–
Peripheral artery disease (vs. absence)	3.052 (1.322–7.046)	0.009	–	–
History of macrovascular surgery (vs. absence)	0.467 (0.062–3.498)	0.459	–	–
BMI	0.914 (0.766–1.090)	0.319	0.828 (0.671–1.022)	0.079
SBP (per mm Hg)	1.010 (0.985–1.019)	0.872	0.990 (0.968–1.012)	0.373
DBP (per mm Hg)	1.008 (0.979–1.037)	0.610	0.981 (0.943–1.020)	0.328
Alb (per g/dl)	0.681 (0.255–1.823)	0.455	0.555 (0.168–1.840)	0.336
Corrected Ca (per mg/dl)	1.138 (0.721–1.796)	0.579	1.518 (0.816–2.822)	0.187
P (per mg/dl)	1.017 (0.738–1.402)	0.919	0.836 (0.582–1.201)	0.334
log-intact PTH (per log unit)	0.667 (0.346–1.288)	0.228	0.623 (0.312–1.246)	0.181
HDL-C (per mg/dl)	0.995 (0.965–1.026)	0.741	0.982 (0.939–1.028)	0.445
Non-HDL-C (per mg/dl)	1.005 (0.996–1.014)	0.246	1.001 (0.991–1.011)	0.898
log-CRP (per log unit)	1.042 (0.685–1.584)	0.847	3.034 (1.437–6.405)	0.004
Hb (per g/dl)	1.100 (0.858–1.411)	0.452	1.085 (0.749–1.571)	0.665
Upright aVRT (vs. non-upright aVRT)	3.161 (1.361–7.342)	0.007	0.868 (0.188–4.021)	0.857
Heart rate (per bpm)	1.013 (0.988–1.038)	0.324	0.985 (0.942–1.030)	0.508
QRS duration (per ms)	0.997 (0.982–1.013)	0.723	0.987 (0.915–1.064)	0.728
QTc interval (per log ms)	1.007 (0.994–1.020)	0.281	0.988 (0.964–1.012)	0.308

Data for death events in the CVD (n = 79) and non-CVD (n = 129) cohorts. Upright and non-upright aVRT were defined as a wave with a positive deflection in amplitude ≥ 0 mV and a negative deflection in amplitude < 0 mV, respectively. HR = Hazard ratio; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; Alb = albumin; Ca = calcium; P = phosphate, PTH = parathyroid hormone; Hb = hemoglobin.

Table 4. Multivariate Cox proportional hazards model analysis

Variable	CVD cohort		Non-CVD cohort	
	HR (95% CI)	p value	HR (95% CI)	p value
Upright aVRT (vs. non-upright aVRT)	3.838 (1.227–12.004)	0.021	0.622 (0.132–2.921)	0.547
Age (per year)	1.072 (1.012–1.136)	0.017	1.040 (0.989–1.095)	0.128
Male (vs. female)	0.868 (0.270–2.784)	0.812	3.774 (0.713–19.984)	0.118
Diabetes (vs. non-diabetes)	1.291 (0.354–4.712)	0.699	2.006 (0.457–8.809)	0.357
Malignancy (vs. absence)	0.423 (0.037–4.788)	0.487	7.115 (2.032–24.909)	0.002
CAD (vs. absence)	1.961 (0.527–7.295)	0.315	–	–
Cerebrovascular disease (vs. absence)	4.316 (1.554–11.992)	0.005	–	–
Peripheral artery disease (vs. absence)	1.276 (0.447–3.642)	0.648	–	–
History of macrovascular surgery (vs. absence)	1.081 (0.117–9.966)	0.945	–	–

Data for death events in the CVD (n = 79) and non-CVD (n = 129) cohorts. Upright and non-upright aVRT were defined as a wave with a positive deflection in amplitude ≥ 0 mV and a negative deflection in amplitude < 0 mV, respectively. HR = Hazard ratio; CI = confidence interval.

increase with aging, with an underlying high risk for arteriosclerotic disease, and ESKD patients with older age and a higher incidence of CAD [4, 5] might be no exception. There is some research showing that the prevalence of T-wave abnormalities in general increases with age, being 5.9% at 50 years of age and 16.0% at 70 years of age [16]. Although patients with an upright aVRT in the CVD cohort had the highest age and aVRT amplitude, the prevalence of patients with a history of CAD was not significantly different between the upright and non-upright aVRT groups, and this was thought to be due to the existence of undetected CAD at the start of dialysis, the change of myocardial blood flow after therapeutic procedures including PCI and coronary artery bypass grafting, and the small sample size. Badheka et al. [19] reported that the general population with a higher aVRT amplitude had a higher prevalence of not only preexisting CAD but also heart failure, stroke, hypertension, diabetes, and renal dysfunction. These findings suggest that ESKD patients with an upright aVRT are expected to need further screening for CVD in the prehospital phase.

Lead aVR, which gives information from the right upper side of the heart, has been considered to provide reciprocal information from the apical, inferior, and lower lateral regions of the heart. Although the underlying mechanisms explaining why an upright aVRT occurs on the ECG are not identified, it has been suggested that a long left anterior descending artery and multivessel disease, in both cases, along with an ischemically injured myocardium in these areas of the heart, would be expected to make a normally negative T-wave inverted and lead to a flat or positive T-wave [20–23]. Ayhan et al. [22] suggested that a positive T-wave in lead aVR in patients with anterior ST segment elevation myocardial infarction undergoing primary PCI may be caused by multivessel disease, and Joki et al. [4] evaluated coronary angiography in incident hemodialysis patients and showed that more than half of the patients had significant CAD; it should be noted that >70% of CAD patients had multivessel disease. Therefore, it is possible that an upright aVRT would be associated with multivessel coronary disease in ESKD patients, as shown in previous research.

This study indicated that an upright aVRT would be useful as a predictor of death, especially cardiovascular death, in ESKD patients with CAD. Unfortunately, the information about the cause of death was not available in this study; however, about 36.8% of Japanese dialysis patients die from CVD [2]. Our hypothesis is supported by recent studies that suggested an association between upright aVRT and cardiovascular mortality [14, 16, 17, 19], especially one study that examined the prognostic significance of an upright aVRT in patients with a prior MI and demonstrated that an upright aVRT was independently associated with increased cardiac death during the follow-up period [17]. Although the reasons why an upright aVRT was not associated with mortality in the non-CVD cohort were not clarified in this observational study, several explanations can be considered. During the 3 years after starting maintenance hemodialysis, a total of 11 (8.5%) patients, of whom only 2 (1.6 %) had an upright aVRT, died from various causes in the non-CVD cohort, and the number reaching the primary endpoint during the short follow-up duration was very small, yielding less statistical power to evaluate the association between upright aVRT and death. Furthermore, in the multivariate Cox proportional hazard model, only a history of malignancy was associated with death, and it was possible that this cohort had a high prevalence of death from other causes not associated with ECG abnormalities.

The limitations of the current study may include an ethnically and socially homogeneous population since the study was hospital-based; therefore, the generalization of our findings and theories might be limited. Second, time-dependent changes in the ECGs, including other lead information, and the risk factors for mortality during the follow-up period were not evaluated. Third, the cause of death was not confirmed, and data of cardiac function were not collected in order to sufficiently evaluate the association between an upright aVRT and cardiovascular death. Therefore, it was unclear at present if an upright aVRT was associated

with cardiovascular mortality in this study. Finally, the number of patients both at baseline and those reaching the endpoint was small, yielding less statistical power to see an association between upright aVRT and the outcome.

In conclusion, this single-center, observational cohort study provided evidence that an upright aVRT seems to be useful to predict the short-term prognosis in incident hemodialysis patients with prior CVD. The ECG might be a simple and useful surrogate tool for identifying CVD and for the assessment of its severity and prognosis in ESKD patients, even in small facilities. These findings need to be confirmed in studies with a larger sample size and in a multi-center design. In addition, further investigations are needed to clarify the underlying mechanism for increased cardiovascular mortality in CKD patients with an upright aVRT.

Disclosure Statement

All authors have no conflicts of interest to declare in connection with this paper.

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