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journal or publication title	Renal Replacement Therapy
volume	2
page range	60
year	2016-11-10
URL	http://doi.org/10.20780/00031633

doi: https://doi.org/10.1186/s41100-016-0069-4

Hasegawa et al. Renal Replacement Therapy (2016) 2:60
DOI 10.1186/s41100-016-0069-4

Renal Replacement Therapy

RESEARCH Open Access

Triglyceride to high-density lipoprotein cholesterol ratio predicts cardiovascular events in maintenance hemodialysis patients

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Abstract

Background: The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio has been shown to be a predictor of cardiovascular (CV) outcomes in the general population. The aim of this study was to determine whether the TG/HDL-C ratio is a predictor of CV events and all-cause mortality in maintenance hemodialysis (MHD) patients.

Methods: We performed a retrospective, observational cohort study in which we enrolled 193 MHD patients from a single center in Japan who had been followed up for a median of 3.9 years. The outcomes were the occurrence of a CV event and all-cause mortality during the follow-up period. Baseline TG/HDL-C ratios were investigated for associations with outcomes by using Cox regression models adjusted for demographic parameters.

Results: Overall, 88 of the subjects experienced a CV event, and 32 patients had died, of whom 4 died due to CV events. Patients with higher TG/HDL-C levels (tertile 3) had a higher incidence of CV events (adjusted hazard ratio [HR] 1.82, 95 % confidence interval [CI] 1.01–3.35) and higher all-cause mortality (adjusted HR 6.13, 95 % CI 2.13–20.22) than the patients in tertile 1. Kaplan–Meier analyses by the log-rank test showed that the TG/HDL-C ratio had significant predictive power for detecting a CV event.

Conclusions: The TG/HDL-C ratio is a reliable and easily accessible marker for predicting CV events and mortality in MHD patients.

Keywords: Triglyceride to HDL cholesterol ratio, Cardiovascular events, Hemodialysis, Survival

Background

Chronic kidney disease (CKD) is one of the major causes of dyslipidemia [1], and an elevated serum triglyceride (TG) level is a common feature of CKD [2]. The serum concentrations of TG-rich lipoproteins, including very-low-density lipoprotein, start to increase in the early stages of CKD. The predominant mechanism responsible for the increased concentration of TG-rich lipoproteins in CKD is a low catabolic rate [3]. By contrast, several epidemiological studies have demonstrated that high-density lipoprotein cholesterol (HDL-C) is a negative risk factor for atherosclerosis [4].

Dyslipidemia in which there is a combination of a high TG level and low HDL-C level has been reported to strongly predict cardiovascular (CV) morbidity, and coronary artery disease, in particular, in the general population [5, 6]. Several studies have demonstrated a correlation between the TG to HDL-C (TG/HDL-C) ratios and both the severity of insulin resistance and presence of coronary atherosclerotic lesions in the general population [7, 8]. The TG/HDL-C ratio has been shown to predict the occurrence of myocardial infarction, ischemic heart disease [9, 10], and CV mortality, both in women with coronary artery disease and in the general population [11, 12].

Low-density lipoprotein cholesterol (LDL-C) has been found to be a non-sensitive marker for risk of CV events because of its weak association with coronary events in CKD patients who have a low estimated glomerular

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filtration rate [13, 14], and no CV benefit in HD patients has been clearly demonstrated in response to aggressive LDL-C reduction strategies [15, 16]. Hypertriglyceridemia has been reported to have a U-shaped relationship with mortality in HD patients [17, 18], whereas HDL-C has been reported to have a discordant association with all-cause or CV mortality in HD patients [19, 20].

The aim of this study was to determine if the TG/HDL-C ratio is a predictor of CV events and all-cause mortality in maintenance HD (MHD) patients.

Methods

Subjects

This was a retrospective cohort study conducted at a single center in Japan. The subjects were recruited from among patients who had been routinely dialyzed via an arteriovenous fistula in the dialysis unit of the Shinjuku Ishikawa Clinic for at least 6 months by the procedure [21].

MHD patients with malignancy, active inflammation, liver cirrhosis, gastrointestinal bleeding, or severe illness were excluded from participation as subjects. The patients who were enrolled as subjects ($n = 193$) had been undergoing stable regular HD with a bicarbonate dialysate. The underlying disease was chronic glomerulonephritis in 85 cases, diabetic nephropathy in 68 cases, hypertensive nephrosclerosis in 30 cases, polycystic kidney disease in 8 cases, and chronic pyelonephritis in 2 cases.

Evaluation of demographic and laboratory parameters

All patients were on thrice-weekly HD therapy. Blood pressure (BP) was measured with a mercury sphygmomanometer with the patient in the supine position after resting for 10 to 15 min, and mean values for the 1-month period preceding enrollment were used in the statistical analysis. Dry weight was targeted to achieve a normotensive edema-free state. Information regarding previous CV disease was collected from the patient's medical records. Diabetes mellitus (DM) was recorded as present if the patient had been diagnosed with DM and/or had a fasting plasma glucose concentration >126 mg/dl or HbA1c value >6.5 % or prescription of glucose-lowering agent.

A past history of CV disease was recorded as positive if the patient had a history of stroke, coronary artery disease (including myocardial infarction and unstable angina), or history of decompensated heart failure. Body mass index (BMI) was calculated by dividing body weight in kilograms by body height in meters squared and is expressed in kg/m^2.

Blood samples were collected before dialysis sessions after an overnight fast. Whole blood samples were used to measure hemoglobin, and serum samples were used to measure creatinine, albumin, calcium, phosphorus, TG, total cholesterol (T-Chol), LDL-C, HDL-C levels, and C-reactive protein (CRP) levels with an autoanalyzer (Hitachi Co., Tokyo, Japan) that uses standard laboratory methods. Whole parathyroid hormone (PTH) levels were determined by immunoassay [22].

Outcomes

Primary outcomes were a CV event, which was recorded as having occurred when a new CV event, including a coronary event (nonfatal myocardial infarction, unstable angina, and coronary revascularization) was diagnosed, a patient was hospitalized for heart failure, a patient was hospitalized for incident stroke (either ischemic or hemorrhagic stroke), or an incident peripheral arterial disease requiring surgical intervention was diagnosed. The secondary outcome was all-cause mortality. The outcome information was centrally adjudicated by trained nephrologists based on the above prespecified criteria.

Statistical analysis

Continuous data are reported as the mean value ± SD, and categorical data are reported as percentages. Differences in baseline characteristics and biochemical parameters were assessed using Student's t test and the Mann–Whitney U test. Groups of patients in different TG/HDL-C ratio tertiles were compared in regard to continuous variables by analysis of variance, and in regard to nonnormally distributed continuous variables by the nonparametric Kruskal–Wallis test, and the χ^2 test was used for categorical variables. To evaluate and compare the predictive performance of the TG/HDL-C ratio and non-HDL-C levels, we used receiver operating characteristic (ROC) curves for censored data and the area under the ROC curve (AUC) as the criterion.

We stratified the patients into three groups according to their TG/HDL-C ratio. The primary predictor variable was the TG/HDL-C ratio in each tertile. The outcome analysis was performed by using Cox proportional hazard models. We considered some variables whose P value was <0.10 according to the results of the univariate logistic regression analyses in the multivariate analysis. The adjusted covariates included age, gender, dialysis vintage, presence of DM, previous CV disease, CRP, creatinine, statin use and hemoglobin levels in the analysis of a CV event, and all-cause mortality. The results are expressed as hazard ratios (HRs) and 95 % confidence intervals (CIs). The age- and gender-related odds ratios (ORs) for CV events and all-cause mortality were calculated using logistic regression models. We also selected the non-HDL-C value (calculated by subtracting the HDL-C value from the T-Chol value) [23] and stratified the patients into tertiles accordingly for analysis. We tested for heterogeneity in the relationship between

Table 1 Baseline characteristics of the study subjects according to the TG/HDL-C ratio

	All patients	TG/HDL-C tertile 1 (0.35–1.60) $n = 64$	TG/HDL-C tertile 2 (1.61–3.00) $n = 65$	TG/HDL-C tertile 3 (3.01–64.05) $n = 64$	*P* value
Age, years	60 (50–69)	59 (51–68)	61 (51–70)	57 (49–65)	0.3249
Female sex, %	26.8	28.2	28.2	24.1	0.7819
DM, %	32.3	28.2	31.8	36.8	0.4837
Dialysis vintage, years	9.4 (4.7–15.8)	11.1 (5.7–16.3)	10.8 (4.4–16.9)	8.0 (4.6–13.8)	0.2608
History of hypertension, %	79.7	80.0	76.5	82.6	0.6107
History of previous CVD, %	29.2	23.5	35.3	28.7	0.2394
Systolic BP, mmHg	153 (139–165)	154 (142–165)	152 (138–166)	153 (136–163)	0.7112
Diastolic BP, mmHg	82 (73–91)	83 (76–91)	81 (72–90)	82 (70–93)	0.4152
BMI, kg/m^2	21.8 (19.7–24.4)	20.5 (19.0–22.6)	21.8 (19.7–24.0)	23.2 (21.1–25.7)	<0.0001
Laboratory data					
Hemoglobin, g/dL	10.7 (10.2–11.2)	10.7 (10.2–11.1)	10.6 (10.1–11.2)	10.8 (10.1–11.4)	0.2499
Creatinine, mg/dL	11.8 (10.3–13.5)	11.4 (10.15–12.75)	12.0 (10.15–13.65)	12.3 (10.4–13.9)	0.1032
Calcium (Ca), mg/dL; corrected	9.0 (8.6–9.4)	9.0 (8.6–9.4)	9.1 (8.45–9.4)	9.0 (8.6–9.4)	0.9831
Phosphorus (P), mg/dL	5.4 (4.6–6.1)	5.5 (4.8–6.2)	5.1 (4.4–5.9)	5.5 (4.5–6.1)	0.0967
Ca x P, (mg/dL)^2	48.1 (40.9–55.2)	51.4 (42.1–55.7)	45.6 (40–54.1)	47.8 (41.2–57)	0.0554
Whole PTH, pg/mL	63 (31–103)	68 (28–95)	53 (27–110)	64 (34–114)	0.5728
CRP, mg/L	0.1 (0.1–0.3)	0.1 (0.1–0.2)	0.1 (0.1–0.3)	0.1 (0.1–0.4)	0.1403
Albumin, g/L	3.9 (3.7–4.1)	3.9 (3.7–4.1)	3.9 (3.7–4.1)	3.9 (3.7–4.1)	0.9530
T-CHO, mg/dL	157 (137–178)	156 (136–177)	150 (133–170)	162 (142–188)	0.0341
TG, mg/dL	98 (70–144)	60 (47–73)	98 (83–112)	172 (138–229)	<0.0001
HDL-C, md/dL	44 (37–55)	59 (51–72)	43 (40–49)	37 (31–41)	<0.0001
LDL-C, mg/dL	77 (62–94)	69 (54–86)	79 (65–103)	86 (64–105)	0.0001
TG/HDL-C ratio	2.28 (1.29–3.66)	1.03 (0.76–1.29)	2.27 (1.84–2.61)	4.63 (3.62–6.57)	<0.0001
Medications, %					
ESA	92.5	91.5	90.5	95.4	0.4447
HMG-CoA reductase inhibitors	29.4	22.9	24.7	40.5	0.0228
Antihypertensive agents	79.0	77.7	78.8	80.5	0.9017

DM diabetes mellitus, *CVD* cardiovascular disease, *BP* blood pressure, *BMI* body mass index, *PTH* parathyroid hormone, *CRP* C-reactive protein, *T-Chol* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density cholesterol, *ESAs* erythropoiesis-stimulating agents

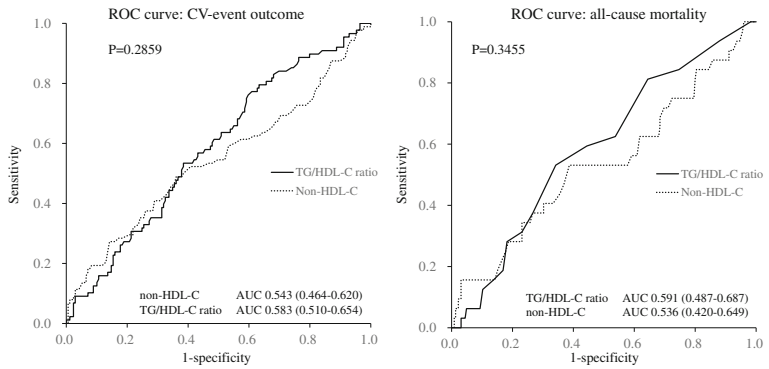

Fig. 1 ROC curve of the TG/HDL-C ratios and non-HDL-C levels as predictors of the outcomes. The TG/HDL-C ratio exhibited a similar predictive performance for cardiovascular events and all-cause mortality

Table 2 Hazard ratios (HRs) of dyslipidemia in predicting the outcomes using Cox proportional hazards regression models with multivariate adjustments

	CV event Adjusted HR (95 % CI)	All-cause mortality Adjusted HR (95 % CI)
TG/HDL-C ratio		
TG/HDL-C ratio tertile		
(Third vs first tertile)	1.82 (1.01–3.35)	6.13 (2.13–20.22)
TG/HDL-C ratio tertile		
(Second vs first tertile)	1.84 (1.05–3.31)	2.64 (0.92–8.38)
TG/HDL-C ratio >1.64 (yes vs no)	1.81 (1.11–3.06)	3.12 (1.30–8.54)
Non-HDL-C		
Non-HDL-C tertile		
(Third vs first tertile)	1.19 (0.71–2.01)	1.32 (0.55–3.20)
Non-HDL-C quartile		
(Second vs first tertile)	0.90 (0.32–2.37)	1.47 (0.49–4.29)
Non-HDL-C >140 mg/dL (yes vs no)	1.51 (0.88–2.51)	1.56 (0.53–4.09)

Adjusted for age, sex, dialysis vintage, presence of DM, concurrent CV disease, CRP, creatinine, statin use, and hemoglobin levels

subgroups by adding a multiplicative interaction term in our statistical model as previously described [24]. The survival analysis was based on the Kaplan–Meier curve with subjects censored for death. A log-rank test was used to compare the survival rates of two groups. *P* values <0.05 were considered evidence of statistical significance. All statistical analyses were performed by using the SAS version 9.2 software program (SAS Institute Inc., Cary, NC, USA) for Windows.

Results

The baseline characteristics of the subjects according to TG/HDL-C tertiles are summarized in Table 1. The study cohort consisted of 193 subjects, 52 females, and 141 males, and their mean age was 59.3 ± 12.7 years. Their mean dialysis vintage was 11.0 ± 7.7 years, and their mean BMI was 22.3 ± 3.7 kg/m^2. All of the subjects had an arteriovenous fistula. None of the subjects had residual renal function (urine volume >100 mL/day). DM was present in 32.3 %. A history of CVD was present in 29.2 %.

The patients in the TG/HDL-C tertiles had different levels of BMI and lipid profiles. There was no significant difference between the median values of TG/HDL-C ratio were 2.28 at the time of entry and 2.31 after 1 month and 2.22 after 2 months. The TG/HDL-

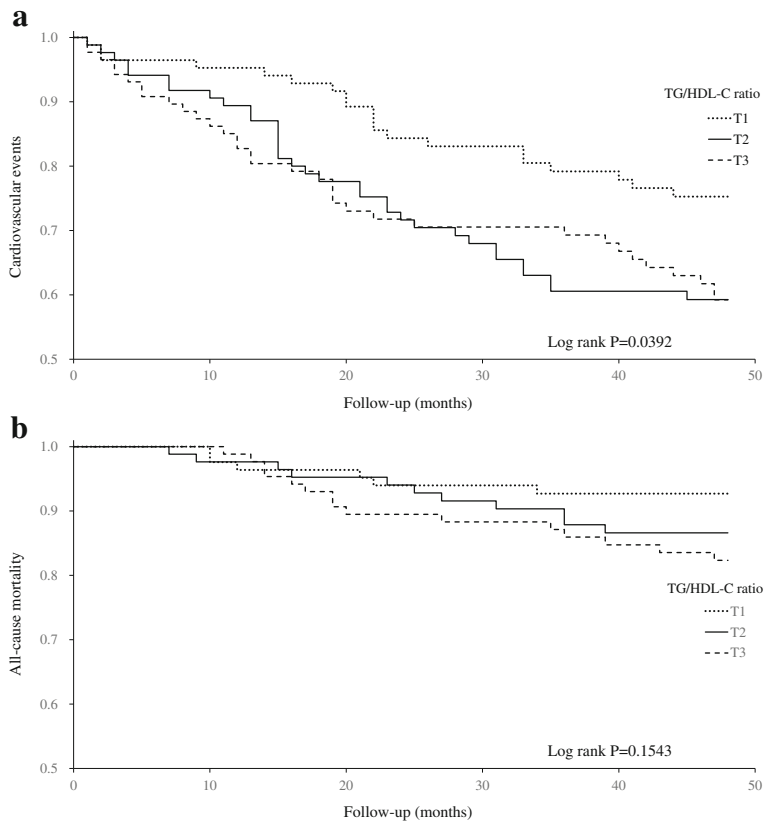

Fig. 2 Kaplan–Meier curves for patients with different TG/HDL-C ratio levels. **a** Cardiovascular events. **b** All-cause mortality

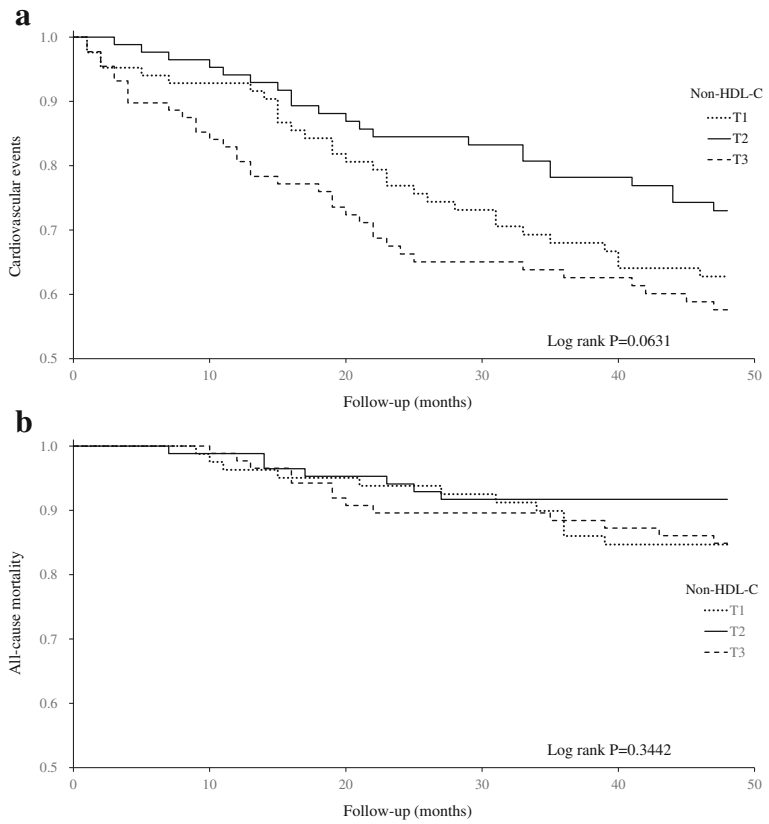

Fig. 3 Kaplan–Meier curves of patients with different non-HDL-C levels. **a** Cardiovascular events. **b** All-cause mortality

C ratio (5.02 ± 8.57) in subjects with statin treatment (29.4 %) was significantly higher than those (2.83 ± 3.09) in subjects without statin treatment (70.6 %) ($P = 0.0028$).

During the mean follow-up period of 43.3 ± 11.0 months, 88 of the subjects experienced a CV event, and 32 patients died, 4 of a CV event. Among the 88 patients who experienced a CV event, 17 had an intracranial hemorrhage or ischemic stroke, 33 had coronary artery disease (either nonfatal acute myocardial infarction or coronary revascularization or coronary bypass surgery), 11 had peripheral arterial disease, 16 were hospitalized for heart failure, and the CV events in the other subjects were unknown. Of the 32 patients who died of any cause, 11 died of an infectious disease, 6 of a sudden cardiac death, 5 of malignancy, and 4 of a cerebrovascular event, and the causes of other death were unknown.

The AUCs for the TG/HDL-C ratio and non-HDL-C level vs. outcomes are shown in Fig. 1. The TG/HDL-C ratio and non-HDL-C levels exhibited similar predictive performance for CV event outcome (AUC 0.583 vs. AUC 0.543, $P = 0.2859$) and all-cause mortality outcome (AUC 0.591 vs. AUC 0.536, $P = 0.3455$).

In the multivariate Cox regression model, the MHD patients with a higher TG/HDL-C level (tertile 3; T3) had a higher incidence of CV events (adjusted HR 1.82, 95 % CI 1.01–3.35) and higher all-cause mortality (adjusted HR 6.13, 95 % CI 2.13–20.22) than the patients in tertile 1 (T1, Table 2). When the TG/HDL-C ratio was used as a dichotomous variable, the group with a TG/HDL-C ratio >1.64 was found to have a higher incidence of CV events (adjusted HR 1.81, 95 % CI 1.11–3.06). Similarly, the group in non-HDL-C tertile 3 also had a higher incidence of CV events and all-cause mortality than the group in non-HDL-C tertile 1. In addition, the group with a TG/HDL-C ratio >1.64 was found to have a higher incidence of cerebrovascular events, although not significant (adjusted HR 2.66, 95 % CI 0.85–3.14).

The Kaplan–Meier survival estimates of CV events and all-cause mortality at different TG/HDL-C ratios are shown in Figs. 2 and 3. The results of the log-rank test showed that the TG/HDL-C ratio had significant predictive power for detecting the CV events (Fig. 2a, $P = 0.0392$). However, the TG/HDL-C ratio did not significantly significant contribute to predicting all-cause mortality (Fig. 2b, $P = 0.1543$). As shown in Fig. 3a, b, there was no significant

difference in non-HDL-C level tertiles for predicting CV events ($P = 0.0631$) and all-cause mortality ($P = 0.3442$).

Stratified analyses to detect associations between TG/HDL-C ratios and CV events and all-cause mortality according to gender and presence of DM revealed that the risk of a CV event gradually increased with greater TG-HDL-C ratios ($P = 0.0076$ for interaction, Fig. 4a). However, the risk of all-cause mortality was not associated with greater TG-HDL-C ratios (Fig. 4b).

Discussion

The results of this study showed that the baseline TG/HDL-C ratio was predictive of CV events and all-cause mortality in MHD patients. Dyslipidemia in MHD patients with the TG/HDL-C ratio for stratification of its severity should be recognized as a reliable and readily available tool for predicting long-term CV outcomes and survival.

HD patients have unique lipid profiles, and the associations between their lipid profiles and CV outcomes and mortality are different from the associations in the general population [17]. Several clinical studies of dialysis patients have reported finding unique correlations between the levels of T-CHO and LDL-C levels and CV outcomes, the so-called "cholesterol paradox" [25, 26]. In addition, recent data have shown the absence of a significant association between the HDL-C levels and their risk of CV events of diabetic HD patients [20], and HDL-C and TG did not to predict CV or all-cause mortality in a large HD cohort who were followed up for 3 years [17]. The non-HDL-C level is also easily calculated by subtracting the HDL-C from TC, and non-HDL levels have been found to be a predictor of CV outcomes in MHD patients [27, 28]. The TG/HDL ratio was superior to the non-HDL-C as a predictor of CV event in the present study (Table 2).

We used the TG/HDL-C ratio to predict CV events and all-cause mortality in MHD patients in the present

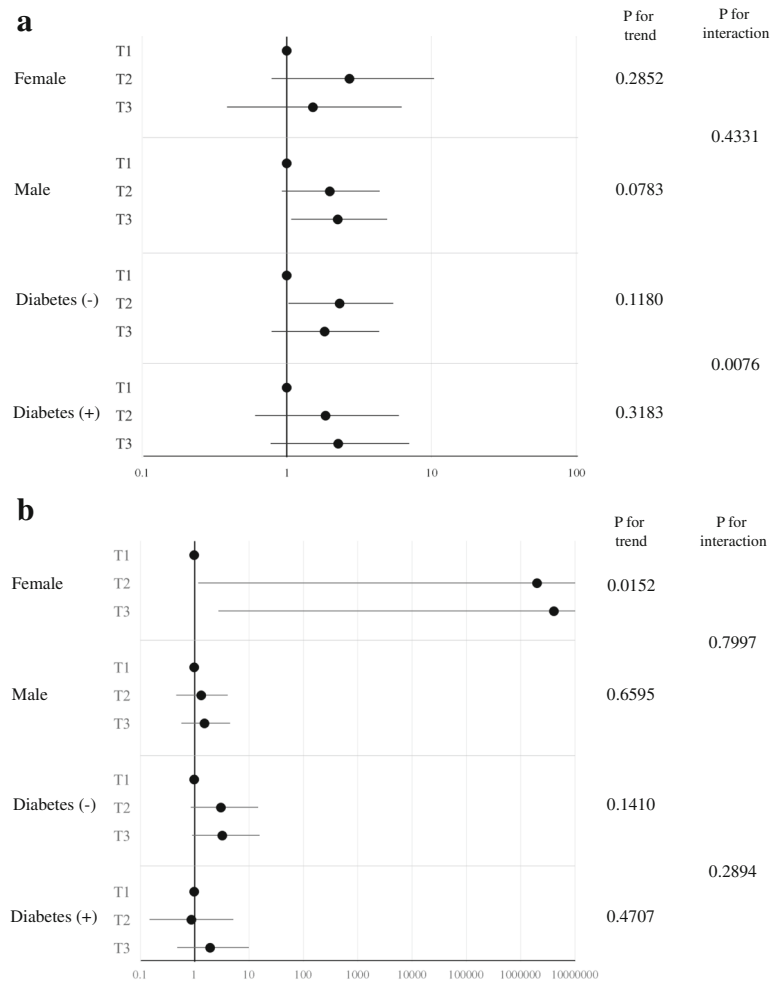

Fig. 4 Odds ratio for CV events (**a**) and all-cause mortality (**b**) according to tertile (T) of TG/HDL-C ratio stratified by gender and presence of diabetes mellitus

study, and the results clearly demonstrated the predictive power of the TG/HDL-C ratio. Chen et al. have recently shown the predictive ability of the TG/HDL-C ratio for CV outcomes and survival in patients undergoing prevalent dialysis [29]. The TG/HDL-C ratio may therefore be the optimal marker for predicting CV outcomes in MHD patients. Moreover, a higher TG/HDL-C ratio including atherogenic lipoprotein particles results in consequent CV events in MHD patients [30].

The cut-off value of TG/HDL-C ratio in prediction of CV event in our study was much lower than that in the previous studies [29, 31]. One of the reasons for lower TG/HDL-C ratio of our patients seems to be based on the good management of food intake by dietitian. In addition, most of the patients came to our dialysis clinic without assistance on foot. Moreover, we could not rule out the effects of statin treatment. The TG/HDL-C ratio (5.02 ± 8.57) in subjects with statin was significantly higher than those (2.83 ± 3.09) in subjects without statin ($P = 0.0028$), suggesting that statin had been administered to patients with increased serum TG.

The mechanisms underlying the association between TG/HDL-C ratios and CV event and all-cause mortality in MHD patients are still unknown. A previous study showed significant associations between increases in TG/HDL ratio and both decreases in LDL particle size and increases in fractional esterification rates of cholesterol in plasma depleted of apoB lipoproteins [32]. Moreover, the TG/HDL-C ratio is already been used as a predictor of insulin resistance [33] and DM [34]. Insulin resistance has been found to increase the serum concentrations of TGs and HDL-C, and the TG/HDL-C ratio was involved in decreased insulin secretion and poor glycemic control among subjects with type 2 DM [35].

We found an interaction between the TG/HDL-C ratio and DM in the prediction of CV events (Fig. 4a). This finding is consistent with the interaction between them in predicting events in the general population, and patients with a high TG/HDL-C ratio have been reported to be predisposed to DM [36]. The diabetic status of patients with both DM and dyslipidemia is crucial when assessing CV outcomes compared with non-diabetic patients with dyslipidemia. As shown in a clinical study [37], manipulation of high TG and low HDL-C levels in DM patients by medical interventions does not reduce their risk of CV outcomes. Consequently, the utility of the TG/HDL-C ratio for predicting long-term CV outcomes in diabetic MHD patients should be carefully assessed in further large-scale investigations.

The present study had several limitations. First, the observational nature of the study precludes drawing conclusions about causal relationships. Second, we did not measure the specific lipoproteins related to atherogenic dyslipidemia, such as apolipoprotein B, which may be more specific to LDL particles, and the relationship between TG/HDL-C ratios and apolipoproteins in MHD patients needs to be validated further. Third, the AUC for TG/HDL-C ratio was 0.583, implying a low accuracy (<0.7). Fourth, this was a single-center study; all of the participants were Japanese and treated by the same physicians, and the same uniform laboratory tests were performed during the observation period, which guaranteed the accuracy of our results, but our conclusions cannot be generalized to other ethnicities.

Conclusions

The results of this study suggest that the TG/HDL-C ratio can independently predict CV events and mortality in MHD patients, especially in diabetic MHD patients.

Abbreviations

BP: Blood pressure; CKD: Chronic kidney disease; DM: Diabetes mellitus; HDL-C: High-density lipoprotein cholesterol; MHD: Maintenance hemodialysis; TG: Triglyceride

Acknowledgements

The authors thank all the participants and medical staff at Shinjuku Ishikawa Clinic.

Funding

This study was supported in part by a Grant-in-Aid from the Japan Promotion Society for Cardiovascular Diseases.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

AH planned the study, searched the literature, assessed the study protocols, extracted the data, analyzed the data, and prepared the article. YT, FK, and UM searched the literature, assessed the study results, and assisted in the preparation of article. KN planned the study, analyzed the data, and assisted in the preparation of article. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from every subject.

Ethics approval and consent to participate

The Institutional Review Board of the Shinjuku Ishikawa Clinic approved the study protocols (I-01-2016), and the study was performed in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. Informed consent was obtained from every subject at the time of entry.

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Received: 16 April 2016 Accepted: 18 October 2016
Published online: 10 November 2016

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