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Association of Serum Triglyceride to HDL Cholesterol Ratio with All-Cause and Cardiovascular Mortality in Incident Hemodialysis Patients

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Abstract

Background and objectives Elevated serum triglyceride/HDL cholesterol (TG/HDL-C) ratio has been identified as a risk factor for cardiovascular (CV) disease and mortality in the general population. However, the association of this important clinical index with mortality has not been fully evaluated in patients with ESRD on maintenance hemodialysis (MHD). We hypothesized that the association of serum TG/HDL-C ratio with all-cause and CV mortality in patients with ESRD on MHD is different from the general population.

Design, setting, participants, & measurements We studied the association of serum TG/HDL-C ratio with all-cause and CV mortality in a nationally representative cohort of 50,673 patients on incident hemodialysis between January 1, 2007 and December 31, 2011. Association of baseline and time-varying TG/HDL-C ratios with mortality was assessed using Cox proportional hazard regression models, with adjustment for multiple variables, including statin therapy.

Results During the median follow-up of 19 months (interquartile range, 11–32 months), 12,778 all-cause deaths and 4541 CV deaths occurred, respectively. We found that the 10th decile group (reference: sixth deciles of TG/HDL-C ratios) had significantly lower risk of all-cause mortality (hazard ratio, 0.91 [95% confidence interval, 0.83 to 0.99] in baseline and 0.86 [95% confidence interval, 0.79 to 0.94] in time-varying models) and CV mortality (hazard ratio, 0.83 [95% confidence interval, 0.72 to 0.96] in baseline and 0.77 [95% confidence interval, 0.66 to 0.90] in time-varying models). These associations remained consistent and significant across various subgroups.

Conclusions Contrary to the general population, elevated TG/HDL-C ratio was associated with better CV and overall survival in patients on hemodialysis. Our findings provide further support that the nature of CV disease and mortality in patients with ESRD is unique and distinct from other patient populations. Hence, it is vital that future studies focus on identifying risk factors unique to patients on MHD and decipher the underlying mechanisms responsible for poor outcomes in patients with ESRD.

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Introduction

The number of patients with ESRD requiring maintenance dialysis in the United States currently stands at approximately 460,000 (1). Despite many recent improvements in dialysis treatment, patients with ESRD continue to experience a lower quality of life, high hospitalization rates, and high annual mortality rates of approximately 20%, a rate worse than that of many cancers (1). Although the causes of death are diverse, approximately half are directly attributed to cardiovascular (CV) disease (1). In spite of this enormous CV disease burden and high mortality, the main contributors to mortality risk have not been clearly identified in the ESRD population. In fact, traditional CV risk factors, such as hypercholesterolemia and obesity, have not been found to be reliable predictors of mortality risk in these patients, as previous studies have shown these factors are

paradoxically associated with better survival in the hemodialysis population (2–7). Therefore, it is imperative that the so-called traditional risk factors for CV disease be reassessed in patients with ESRD in order to help improve our ability to identify those patients with the highest risk of mortality who may stand to obtain the most benefit from our interventions.

It is well known that elevated serum triglyceride (TG) and reduced HDL cholesterol (HDL-C) levels are risk factors for CV disease in the general population, independent of LDL cholesterol (LDL-C) levels. This is reflected by the fact that treatment with hydroxymethylglutaryl-CoA reductase inhibitors (statins) only partly reduces the rate of CV disease in high-risk patients, and significant residual risk persists despite achievement of target LDL-C levels. Several observational studies have shown that the

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residual risk, which remains after maximal statin therapy, may be partly attributed to high TG and low HDL-C levels (8–11). More recent studies have found that combination of high TG and low HDL-C in the form of a ratio, and its use as a single marker has greater predictive value for detecting the risk of CV disease when compared with each of those individual markers alone (12–14). Moreover, serum triglyceride/HDL cholesterol (TG/HDL-C) ratio can be a good predictor of risk for the occurrence of nonfatal CV events (14–16), CV death (17,18), and all-cause mortality (19,20) among healthy individuals and those with a wide range of CV risk factors. However, there are significant limitations in the few studies that examine the association between TG/HDL-C ratio and mortality in patients on dialysis given the small sample size, pooling data from patients on prevalent hemodialysis and peritoneal dialysis, and failure to account for changes in TG/HDL-C ratios over time (21,22). It is important to note that the strength of the latter studies is that they were conducted in patients whose lipid levels were measured during a fasting state. However, there is a growing body of evidence indicating that postprandial TG levels are important predictors of CV disease and mortality (23–25). This is in agreement with the Zilversmit hypothesis that atherosclerosis is a postprandial phenomenon and evaluation of plasma lipids (especially TG containing lipoproteins) in a nonfasting state may also provide vital information about an individual's CV risk (26–28). We have previously shown that the association of serum TG and HDL-C levels with outcomes in patients on maintenance hemodialysis (MHD) does not follow the pattern observed in the general population, and in a subset of patients can be paradoxical to what is expected (5,29). Although the information regarding the fasting status of patients in our database is lacking, it is important to note that in the general population, elevated fasting and nonfasting TGs are associated with worse CV outcomes. Hence, regardless of the fasting state, our previous findings are somewhat paradoxical to what is known in the general population (28). Therefore, in this study we set out to examine the association of baseline and

time-varying TG/HDL-C ratio with all-cause and CV mortality among patients on incident hemodialysis.

Materials and Methods

Study Population and Data Source

The study cohort was comprised of all patients with ESRD who were initiated on hemodialysis between January of 2007 and December of 2011 within one of the outpatient facilities of a large dialysis organization, and who were followed over a period of 5 years (30). Patients were included who were ≥ 18 years old, were treated with only in-center hemodialysis for at least 60 days, and had serum TG/HDL-C ratio measured during the first 91-day period of hemodialysis (baseline quarter). The comparison of baseline characteristics between patients in whom baseline TG/HDL-C ratio was missing and those in whom baseline TG/HDL-C ratio was available is summarized in Supplemental Table 1. Patients were further excluded if they had an outlier TG/HDL-C ratio value (below the first percentile or above the 99th percentile of observed values). Therefore, the final study population for all-cause mortality consisted of 50,673 patients (Figure 1).

All data were obtained from electronic records of the dialysis organization. To minimize measurement variability, all repeated measures of every relevant variable within each 3-month period, starting from the date of first dialysis (patient quarters), were averaged to obtain one quarterly mean value. Blood samples were drawn using standardized techniques in all dialysis clinics and were transported to a central laboratory in Deland (Florida), typically within 24 hours. Information regarding the fasting state of the patients was not available in the database; therefore, it is conceivable that this cohort included a mixture of fasting and nonfasting patients. The following 12 preexisting comorbidities were obtained from International Classification of Diseases, Ninth Revision codes from the electronic records database: diabetes mellitus, hypertension, atherosclerotic heart disease (ASHD), congestive heart failure (CHF), other CV disease, cerebrovascular disease, dyslipidemia, HIV, chronic obstructive pulmonary disease, malignancy, alcohol dependence, and substance abuse. The

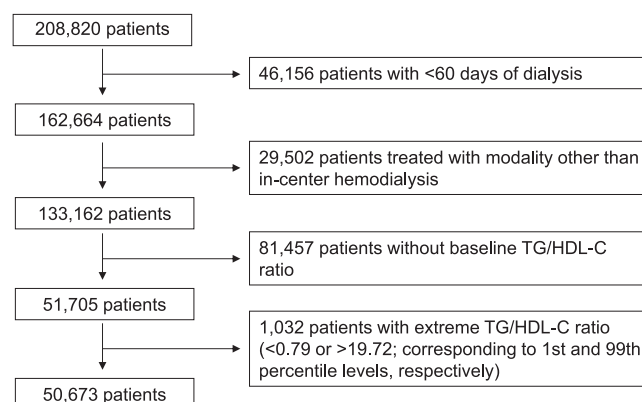


Figure 1. | Among a cohort of 208,820 dialysis patients, 50,673 patients who met the inclusion and exclusion criteria were included in the final analyses. HDL-C, HDL cholesterol; TG, triglyceride.

study was approved by the University of California Irvine Institutional Review Board. Given the large sample size, anonymity of the patients studied, and noninvasive nature of the research, the requirement for written consent was waived.

Exposure and Outcome Ascertainment

The exposures of interest were baseline and time-varying serum TG/HDL-C ratio levels. Given a possible nonlinear relationship with mortality rates, the TG/HDL-C ratio was treated as a categorical variable and divided into deciles (see Tables 1–3 for respective cutoff points). The reference TG/HDL ratio category for all analyses was the sixth decile. This category was chosen as the reference because the median ratio in this study was 3.64, which is similar to the ratio of 3.8 that was used in previous studies and is derived from Adult Treatment Panel recommendations (on the basis of normal fasting TG <150 mg/dl and HDL-C >40 mg/dl) (21,31,32).

The primary and secondary outcomes of interest were time to all-cause and CV death, respectively. For mortality analyses, patients remained at-risk until death, censoring for loss to follow-up, discontinuation of dialysis therapy, kidney transplantation, transfer to a nonaffiliated dialysis clinic, or end of the study period (December 31, 2011).

Statistical Analyses

Data were summarized using proportions, means (\pm SD), or median (interquartile range [IQR]) as appropriate, and were compared using paired *t* test, ANOVA, Kruskal-Wallis, and chi-squared tests, respectively.

Cox proportional hazard regression models were separately performed to study the associations of baseline and time-varying TG/HDL-C ratios with mortality. In baseline models, TG/HDL-C ratio and covariates were determined at baseline and their association with mortality was estimated. In time-varying models, TG/HDL-C ratio and covariates were calculated and updated at each patient quarter over the entire follow-up period to assess short-term associations between TG/HDL-C ratio and risk of death, assuming that TG/HDL-C ratio remained unchanged during the time interval before the next measurement. For each analysis, unadjusted and two additional models were constructed on the basis of the level of multivariate adjustment: (1) case-mix adjusted models, which adjusted for baseline characteristics of age, sex, race/ethnicity (white, black, Hispanic, Asian, or other), primary insurance (Medicare, Medicaid, and others), initial vascular access type (central venous catheter, arteriovenous fistula, arteriovenous graft, or other), 12 comorbid conditions, and dialysis dose as indicated by single-pool Kt/V; and (2) fully adjusted models, which included all covariates in the case-mix model plus malnutrition-inflammation-cachexia syndrome variables, including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL-C, and body mass index (BMI, postdialysis dry body weight in kilograms/height in meters squared). Additional adjustment was also done for statin therapy (*i.e.*, if statin therapy was ever used at any time during the follow-up period) in

addition to the fully adjusted model. All mortality associations are expressed as hazard ratios and 95% confidence intervals.

For sensitivity analyses, we additionally explored the continuous, potentially nonlinear relationship between TG/HDL-C ratio and mortality by using fully adjusted, restricted cubic spline models with four knots. Given that TG and HDL-C metabolism may differ between sexes, we further assessed the association of TG/HDL-C ratio and mortality stratified by sex. To test the robustness of our findings, we also performed subgroup analyses on the basis of *a priori* selected variables; for example, age, sex, race/ethnicity, diabetes, hypertension, ASHD, CHF, statin therapy, serum LDL-C, hemoglobin, ferritin, intact parathyroid hormone, and albumin concentrations.

The frequency of missing data were low (\leq 0.5%, ascertained at baseline) for most covariates in multivariate adjusted models, except for statin therapy (10.2%), for which patients were excluded only from the analysis adjusting for statin therapy. As CV and non-CV death are competing events, sensitivity analyses were done using semiparametric baseline and time-varying competing risk regression evaluating the association of TG/HDL-C ratio, with the two outcomes noted (33). All analyses were implemented using Stata, version 13.1 (StataCorp., College Station, TX).

Results

Study Population

The baseline demographics, clinical, and laboratory characteristics of the patients according to serum TG/HDL-C ratio deciles are summarized in Table 1. The mean age of patients was 62.9 ± 14.9 years, 44% were women, and 63% were diabetic. The mean \pm SD and median (IQR) baseline TG/HDL-C ratio values were 4.51 ± 3.09 and 3.64 (2.33–5.74), respectively. Patients with elevated baseline TG/HDL-C ratios when compared with the reference group tended to be younger men who were more likely to be white and diabetic. They also had lower serum HDL-C and higher BMI, total cholesterol, LDL-C, and TG levels.

During the mean follow-up of 22.7 months, 12,778 deaths occurred, with a crude mortality rate of 133 deaths per 1000 patient-years (95% confidence interval, 131 to 136). Of these, 11,391 individuals had data available on primary cause of death, in which 4541 (39.9%) were attributed to CV mortality. From the lowest (first) to highest (10th) deciles of baseline TG/HDL-C ratio, all-cause and CV mortality rates were 141, 142, 147, 141, 138, 137, 131, 126, 122, and 109, and 55, 51, 49, 55, 48, 52, 48, 44, 43, and 39 deaths per 1000 patient-years, respectively. The most common cause of CV death in this study was sudden cardiac death ($n=2882$, 62.1%), followed by acute myocardial infarction ($n=492$, 10.8%), CHF ($n=296$, 6.5%), cerebrovascular accident ($n=231$, 5.1%), arrhythmia ($n=230$, 5.1%), cardiomyopathy ($n=219$, 4.8%), ASHD ($n=106$, 2.3%), hypoxic brain damage ($n=44$, 1.0%), and pulmonary edema ($n=35$, 0.8%). Although there were some patients whose cause of death was unknown, when compared with patients who had available information about cause of death, their demographic, comorbidity, and laboratory characteristics were mostly similar (Supplemental Table 2).

Table 1. Baseline characteristics of 50,673 patients stratified by serum triglyceride/HDL cholesterol ratio deciles

Characteristics	Serum Triglyceride/HDL Cholesterol Ratio									
	<1.59 (n=5067)	1.59-<2.09 (n=5072)	2.09-<2.57 (n=5062)	2.57-<3.07 (n=5062)	3.07-<3.64 (n=5072)	3.64-<4.30 (n=5071)	4.30-<5.18 (n=5061)	5.18-<6.41 (n=5068)	6.41-<8.63 (n=5070)	≥8.63 (n=5068)
Age, yr	63.9±15.5	64.4±15.4	64.1±15.2	64.1±14.7	63.9±14.9	63.0±14.7	62.8±14.5	62.1±14.2	61.1±14.3	59.2±14.1
Sex, % women	46.7	47.3	45.2	46.9	43.9	43.7	42.6	42.6	39.9	38.0
Race, %										
White	35.4	41.1	43.3	43.9	46.2	48.4	49.9	50.0	52.0	55.3
Black	48.1	40.1	37.8	35.1	32.2	30.1	27.2	26.1	22.2	18.5
Hispanic	10.6	12.5	13.0	14.4	15.1	15.2	16.2	17.2	19.2	19.3
Asian	2.6	3.0	2.8	2.9	2.9	3.0	2.9	3.4	3.2	3.2
Others	3.1	3.4	3.1	3.8	3.7	3.3	3.8	3.3	3.5	3.6
Primary insurance, %										
Medicare	54.8	55.0	55.0	55.0	54.8	53.5	52.9	52.0	50.8	49.8
Medicaid	6.5	6.1	6.4	5.5	6.7	6.3	6.5	6.5	6.8	6.9
Others	38.8	38.9	38.6	39.5	38.5	40.2	40.6	41.4	42.4	43.3
Initial vascular access type, %										
Central venous catheter	70.7	72.4	72.4	74.1	74.8	74.4	75.3	75.6	76.8	76.4
Arteriovenous fistula	17.5	16.8	16.7	14.8	14.6	16.1	15.4	15.4	14.3	14.7
Arteriovenous graft	5.3	4.7	4.9	5.3	4.3	4.1	4.0	3.5	3.4	3.3
Others and unknown	6.5	6.1	6.0	5.8	6.3	5.4	5.3	5.5	5.5	5.6
Comorbidities, %										
Diabetes	60.5	60.6	61.5	61.9	62.5	62.1	64.0	63.6	64.9	66.3
Hypertension	56.8	55.0	52.3	52.5	52.9	51.1	50.6	49.9	49.2	47.3
Congestive heart failure	37.7	36.5	36.4	36.6	35.9	37.3	36.3	35.9	36.0	37.5
Atherosclerotic heart disease	17.6	18.1	19.0	18.0	18.3	19.3	17.9	18.0	18.2	18.2
Other cardiovascular disease	17.3	16.3	16.8	16.7	17.1	16.9	16.2	16.2	17.0	16.7
Cerebrovascular disease	1.9	1.3	1.8	1.6	1.8	1.9	1.7	1.4	2.1	1.9
Dyslipidemia	35.4	33.9	35.0	33.2	34.3	34.7	35.2	33.9	34.8	36.4
HIV	0.4	0.3	0.3	0.4	0.4	0.4	0.6	0.4	0.7	0.8
COPD	5.4	5.3	5.1	5.2	5.6	5.1	5.5	4.5	5.1	4.5

Table 1. (Continued)

Characteristics	Serum Triglyceride/HDL Cholesterol Ratio									
	<1.59 (n=5067)	1.59- 2.09 (n=5072)	2.09- 2.57 (n=5062)	2.57- 3.07 (n=5062)	3.07- 3.64 (n=5072)	3.64- 4.30 (n=5071)	4.30- 5.18 (n=5061)	5.18- 6.41 (n=5068)	6.41- 8.63 (n=5070)	≥8.63 (n=5068)
History of malignancy	2.0	2.1	2.1	2.6	2.3	2.2	2.2	2.3	2.5	2.5
Alcohol dependence, %	0.4	0.3	0.3	0.3	0.2	0.2	0.3	0.3	0.3	0.1
Substance abuse, %	0.5	0.4	0.4	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Statin therapy, %	37.0	40.1	39.2	41.2	41.9	41.6	42.9	42.6	42.8	42.8
Dialysis dose: single pool Kt/V	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.3	1.4±0.3
Body mass index, kg/m ²	25.9±6.5	26.7±7.2	27.2±7.1	27.8±7.3	27.9±7.3	28.5±7.4	29.0±7.5	29.4±7.4	29.8±7.5	30.6±7.4
Lipid parameters										
Total cholesterol, mg/dl	151.9±41.5	146.5±40.9	145.1±41.7	146.4±42.7	145.9±42.5	148.3±43.6	149.8±44.7	152.5±43.7	157.6±46.5	168.0±55.5
LDL-C, mg/dl	78.4±31.9	78.3±31.9	78.1±33.0	80.0±34.2	79.9±34.1	81.0±35.3	81.5±36.8	81.4±36.3	81.9±38.3	78.4±42.2
TG, mg/dl	73.2±18.6	91.8±22.1	106.2±24.9	119.7±28.1	132.7±30.8	148.6±34.7	165.9±38.1	190.3±42.7	225.5±52.1	310.4±91.7
HDL-C, mg/dl	59.0±14.5	49.9±11.9	45.7±10.7	42.6±9.9	39.7±9.2	37.6±8.7	35.2±8.0	33.1±7.4	30.6±6.9	27.0±6.8
TG/HDL-C ratio	1.3±0.2	1.8±0.1	2.3±0.1	2.8±0.1	3.3±0.2	4.0±0.2	4.7±0.2	5.8±0.4	7.4±0.6	11.7±2.6
Other laboratory parameters										
Hemoglobin, g/dl	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2	11.1±1.2
White blood cells, ×10 ³ /μl	7.2±2.3	7.4±2.4	7.6±2.4	7.7±2.7	7.8±2.4	7.8±2.5	7.9±2.5	8.1±2.8	8.1±2.8	8.2±3.0
Albumin, g/dl	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.6±0.5
Calcium, mg/dl	9.1±0.6	9.1±0.5	9.1±0.6	9.1±0.6	9.1±0.6	9.1±0.6	9.1±0.6	9.1±0.5	9.1±0.6	9.1±0.6
Phosphorus, mg/dl	4.9±1.1	4.9±1.1	4.9±1.1	4.9±1.1	4.9±1.2	4.9±1.1	4.9±1.1	4.9±1.1	4.9±1.1	5.0±1.2
Intact PTH, pg/ml	330	317	317	313	313	315	312	316	314	312
Bicarbonate, mEq/L	(202-516)	(201-499)	(198-486)	(199-479)	(196-488)	(201-478)	(198-481)	(196-486)	(196-474)	(196-474)
TiBC, mg/dl	23.9±2.8	24.0±2.8	23.8±2.7	23.8±2.7	23.8±2.7	23.7±2.7	23.6±2.7	23.5±2.6	23.3±2.6	23.0±2.6
Ferritin, ng/ml	224.6±45.4	223.4±46.1	222.3±46.8	222.4±47.6	223.2±47.8	223.9±49.1	226.0±48.7	226.8±48.7	229.1±50.0	234.8±52.7
	253	260	249	280	283	293	296	304	316	312
	(146-429)	(154-438)	(163-465)	(168-482)	(170-469)	(171-508)	(174-496)	(184-506)	(185-535)	(182-535)

Data are presented as means±SD, median (interquartile range), or percentage. COPD, chronic obstructive pulmonary disease; LDL-C, LDL cholesterol; TG, triglyceride; HDL-C, HDL cholesterol; TG/HDL-C, triglyceride/HDL cholesterol ratio; PTH, parathyroid hormone; TiBC, total iron binding capacity.

Table 2. Association of serum triglyceride/HDL cholesterol ratio with all-cause mortality, stratified by decile categories

TG/HDL-C Levels	Unadjusted			Case-Mix			Case-Mix and MICS			Case-Mix, MICS, and Statin		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Baseline model												
<1.59	1.02	(0.95 to 1.10)	0.55	1.06	(0.98 to 1.14)	0.15	1.04	(0.97 to 1.13)	0.29	0.99	(0.91 to 1.08)	0.89
1.59 to <2.09	1.03	(0.95 to 1.11)	0.46	1.02	(0.95 to 1.10)	0.59	1.00	(0.93 to 1.08)	0.99	0.96	(0.89 to 1.05)	0.38
2.09 to <2.57	1.07	(0.99 to 1.16)	0.07	1.04	(0.96 to 1.12)	0.34	1.02	(0.94 to 1.10)	0.67	0.98	(0.90 to 1.07)	0.70
2.57 to <3.07	1.03	(0.96 to 1.11)	0.41	1.01	(0.94 to 1.09)	0.78	1.00	(0.92 to 1.08)	0.99	0.98	(0.90 to 1.07)	0.67
3.07 to <3.64	1.01	(0.93 to 1.09)	0.85	0.97	(0.89 to 1.04)	0.37	0.94	(0.87 to 1.02)	0.14	0.95	(0.87 to 1.03)	0.20
3.64 to <4.30	1.00			1.00			1.00			1.00		
4.30 to <5.18	0.96	(0.88 to 1.03)	0.26	0.94	(0.87 to 1.01)	0.10	0.96	(0.89 to 1.04)	0.35	0.97	(0.89 to 1.05)	0.43
5.18 to <6.41	0.92	(0.85 to 1.00)	0.04	0.92	(0.85 to 0.99)	0.03	0.95	(0.88 to 1.03)	0.21	0.93	(0.86 to 1.02)	0.12
6.41 to <8.63	0.89	(0.82 to 0.96)	0.004	0.90	(0.83 to 0.97)	0.01	0.93	(0.86 to 1.01)	0.07	0.92	(0.84 to 1.00)	0.05
≥8.63	0.79	(0.73 to 0.86)	<0.001	0.85	(0.78 to 0.92)	<0.001	0.91	(0.83 to 0.99)	0.03	0.90	(0.82 to 0.99)	0.02
Time-varying model												
<1.38	1.03	(0.96 to 1.11)	0.43	1.10	(1.02 to 1.19)	0.001	1.12	(1.04 to 1.21)	0.004	1.10	(1.01 to 1.20)	0.03
1.38 to <1.84	1.07	(1.00 to 1.16)	0.06	1.10	(1.02 to 1.19)	0.01	1.09	(1.01 to 1.18)	0.03	1.09	(1.00 to 1.18)	0.05
1.84 to <2.28	1.09	(1.01 to 1.17)	0.03	1.09	(1.01 to 1.17)	0.03	1.06	(0.99 to 1.15)	0.12	1.07	(0.98 to 1.16)	0.12
2.28 to <2.76	1.08	(1.00 to 1.17)	0.04	1.07	(1.00 to 1.16)	0.06	1.03	(0.95 to 1.11)	0.45	1.04	(0.96 to 1.13)	0.36
2.76 to <3.32	1.05	(0.97 to 1.13)	0.20	1.05	(0.97 to 1.13)	0.21	1.04	(0.96 to 1.12)	0.37	1.04	(0.96 to 1.13)	0.32
3.32 to <4.00	1.00			1.00			1.00			1.00		
4.00 to <4.88	0.91	(0.84 to 0.98)	0.01	0.92	(0.85 to 0.99)	0.03	0.95	(0.88 to 1.03)	0.23	0.91	(0.84 to 1.00)	0.04
4.88 to <6.17	0.85	(0.79 to 0.92)	<0.001	0.86	(0.80 to 0.93)	<0.001	0.89	(0.82 to 0.97)	0.01	0.89	(0.82 to 0.98)	0.01
6.17 to <8.57	0.79	(0.73 to 0.86)	<0.001	0.83	(0.76 to 0.90)	<0.001	0.89	(0.82 to 0.97)	0.01	0.88	(0.81 to 0.97)	0.01
≥8.57	0.71	(0.65 to 0.77)	<0.001	0.78	(0.71 to 0.85)	<0.001	0.86	(0.79 to 0.94)	0.001	0.86	(0.78 to 0.94)	0.002

Adjustments in case-mix model ($n=50,105$): age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V. Adjustments in case-mix plus MICS model ($n=48,527$): case-mix adjusted model plus laboratory parameters including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL cholesterol, and body mass index. Adjustments in case-mix plus MICS plus statin model ($n=43,742$): statin therapy on the fully adjusted models. TG/HDL-C, triglyceride/HDL cholesterol ratio; MICS, malnutrition-inflammation-cachexia syndrome; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 3. Association of serum triglyceride/HDL cholesterol ratio with cardiovascular mortality, stratified by decile categories

TG/HDL-C Levels	Unadjusted			Case-Mix			Case-Mix and MICS			Case-Mix, MICS, and Statin		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Baseline model												
<1.59	1.06	(0.94 to 1.20)	0.32	1.12	(0.99 to 1.27)	0.07	1.09	(0.96 to 1.24)	0.17	1.07	(0.93 to 1.23)	0.33
1.59 to <2.10	0.98	(0.86 to 1.11)	0.74	0.99	(0.87 to 1.12)	0.86	0.95	(0.84 to 1.08)	0.45	0.90	(0.78 to 1.03)	0.13
2.10 to <2.57	0.95	(0.84 to 1.08)	0.48	0.94	(0.82 to 1.06)	0.32	0.92	(0.81 to 1.05)	0.21	0.87	(0.75 to 1.00)	0.05
2.57 to <3.08	1.07	(0.95 to 1.21)	0.28	1.06	(0.93 to 1.20)	0.40	1.04	(0.91 to 1.17)	0.59	1.06	(0.92 to 1.21)	0.44
3.08 to <3.65	0.94	(0.82 to 1.06)	0.31	0.90	(0.79 to 1.03)	0.12	0.88	(0.77 to 1.00)	0.06	0.90	(0.78 to 1.03)	0.13
3.65 to <4.32	1.00			1.00			1.00			1.00		
4.32 to <5.19	0.94	(0.83 to 1.07)	0.35	0.91	(0.80 to 1.04)	0.16	0.92	(0.81 to 1.05)	0.24	0.93	(0.80 to 1.07)	0.29
5.19 to <6.43	0.85	(0.74 to 0.97)	0.01	0.84	(0.74 to 0.96)	0.01	0.87	(0.76 to 0.99)	0.04	0.84	(0.73 to 0.98)	0.02
6.43 to <8.64	0.83	(0.73 to 0.95)	0.01	0.82	(0.72 to 0.94)	0.003	0.84	(0.73 to 0.96)	0.01	0.85	(0.73 to 0.98)	0.03
≥8.64	0.76	(0.67 to 0.87)	<0.001	0.79	(0.69 to 0.91)	0.001	0.83	(0.72 to 0.96)	0.01	0.84	(0.72 to 0.98)	0.03
Time-varying model												
<1.38	1.10	(0.97 to 1.25)	0.12	1.21	(1.07 to 1.37)	0.003	1.21	(1.06 to 1.38)	0.004	1.19	(1.03 to 1.37)	0.02
1.38 to <1.84	1.09	(0.97 to 1.24)	0.16	1.14	(1.00 to 1.29)	0.04	1.11	(0.98 to 1.26)	0.11	1.11	(0.96 to 1.27)	0.16
1.84 to <2.29	1.13	(1.00 to 1.28)	0.06	1.15	(1.01 to 1.30)	0.03	1.10	(0.96 to 1.24)	0.16	1.08	(0.94 to 1.24)	0.30
2.29 to <2.77	1.05	(0.93 to 1.19)	0.42	1.06	(0.93 to 1.20)	0.40	1.02	(0.89 to 1.16)	0.80	1.03	(0.89 to 1.18)	0.71
2.77 to <3.33	1.00	(0.88 to 1.14)	0.97	1.01	(0.88 to 1.14)	0.94	0.98	(0.86 to 1.11)	0.74	0.97	(0.84 to 1.12)	0.70
3.33 to <4.00	1.00			1.00			1.00			1.00		
4.00 to <4.89	0.92	(0.81 to 1.05)	0.23	0.93	(0.82 to 1.06)	0.29	0.96	(0.84 to 1.09)	0.52	0.88	(0.76 to 1.02)	0.10
4.89 to <6.19	0.81	(0.71 to 0.93)	0.002	0.82	(0.72 to 0.94)	0.004	0.84	(0.74 to 0.97)	0.02	0.84	(0.72 to 0.98)	0.02
6.19 to <8.59	0.81	(0.71 to 0.93)	0.002	0.83	(0.73 to 0.95)	0.01	0.88	(0.77 to 1.01)	0.07	0.88	(0.76 to 1.03)	0.11
≥8.59	0.66	(0.57 to 0.76)	<0.001	0.70	(0.61 to 0.81)	<0.001	0.77	(0.66 to 0.90)	0.001	0.78	(0.66 to 0.92)	0.004

Adjustments in case-mix model (n=48,728): age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V. Case-mix plus MICS model (n=47,185): case-mix adjusted model plus laboratory parameters including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL cholesterol, and body mass index. Case-mix plus MICS plus statin model (n=42,605): statin therapy on the fully adjusted models. TG/HDL-C, triglyceride/HDL cholesterol ratio; MICS, malnutrition-inflammation-cachexia syndrome; HR, hazard ratio; 95% CI, 95% confidence interval.

All-Cause and CV Mortality

In contrast to the association between TG/HDL-C ratio and mortality that is seen in the general population, higher TG/HDL-C ratio was associated with better survival in patients on incident hemodialysis. The highest decile group on the basis of baseline TG/HDL-C ratio was associated with the lowest all-cause and CV mortality at all four levels of adjustment (Supplemental Figure 1, Tables 2 and 3). To account for changes in serum TG/HDL-C ratios over time and to examine short-term TG/HDL-C ratio and mortality associations, we used time-varying Cox regression models as shown in Figure 2. The median number of TG/HDL-C ratio that contributed to each quarterly-averaged metric per patient was three (IQR, 1–5 measurements). In the fully adjusted model, there was a graded inverse association between serum TG/HDL-C ratio and all-cause and CV mortality from the lowest to highest deciles, with significantly higher mortality in deciles 1–2 and lower mortality in deciles 8–10. It should be noted that these associations remained largely unchanged despite additional adjustment for statin therapy (Tables 2 and 3).

In sensitivity analyses using competing risk regression models in which non-CV death was assigned as a competing event, higher TG/HDL-C ratio was similarly associated with better survival and reduced CV mortality (Supplemental Table 3). In addition, a similar trend was observed for both all-cause and CV mortality in fully adjusted cubic spine models using baseline (Supplemental Figure 2) and time-varying (Figure 3) TG/HDL-C levels in which incrementally higher TG/HDL-C ratios were associated with lower risk of death. Although extreme TG/HDL-C levels tended to trend toward higher all-cause mortality risk, the small sample size in these categories makes these associations less reliable. Given the role of sex on lipids profile and metabolism, we also compared these

association on the basis of patients' sex. Although the overall trend remained similar between the two groups, there were small differences between men and women, as the association between higher TG/HDL-C ratio and better survival appeared to be stronger in men (Supplemental Figures 3 and 4). Further subgroup analyses confirmed the strong and consistent association between high TG/HDL-C ratio (median TG/HDL-C ≥ 3.64 versus < 3.64) and lower all-cause and CV mortality across all prespecified subgroups (Figure 4).

Discussion

In a large contemporary cohort of 50,673 patients treated with thrice-weekly hemodialysis and followed for up to 5 years, we found that higher TG/HDL-C ratios were associated with better survival and reduced CV mortality. To the best of our knowledge, this is the first published study to demonstrate an inverse association between TG/HDL-C ratio and mortality in the dialysis population. These findings are in contrast to the associations seen in the general population, in whom higher TG/HDL-C ratio are associated with increased risk of mortality. The large sample size, consideration of changes in TG/HDL-C ratios over time, and extensive adjustment and subgroup analyses are strengths of this study. These results are important in that they provide additional information about the unique and paradoxical associations between lipid levels and mortality in patients with ESRD on MHD. Furthermore, these findings highlight the distinct nature of hemodialysis- and ESRD-associated dyslipidemia, which is marked by abnormal TG production and metabolism and HDL-C deficiency and dysfunction.

Dyslipidemia is a well established traditional risk factor for CV disease in the general population. However, we

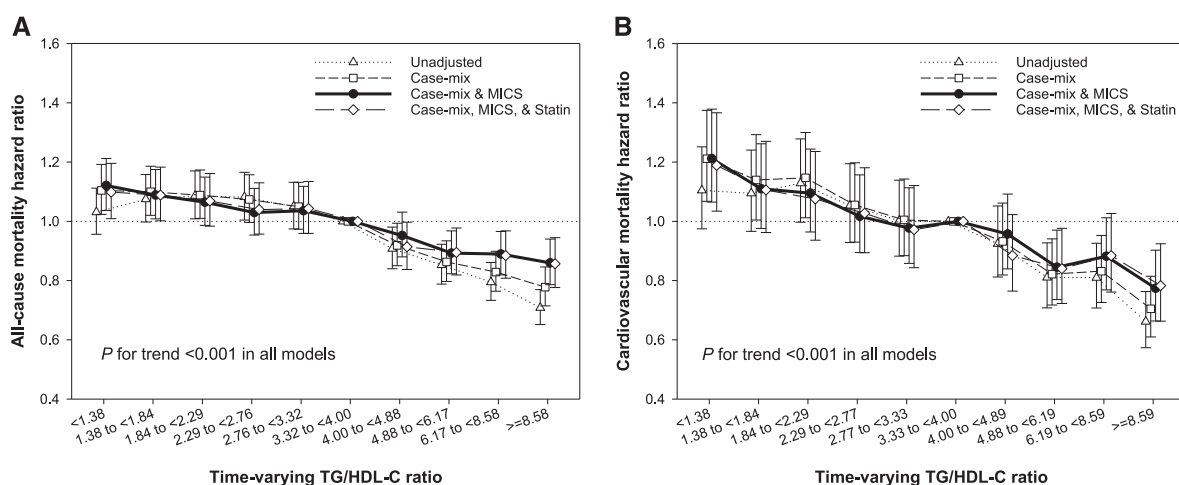


Figure 2. | Higher TG/HDL-C ratio was associated with improved survival in incident hemodialysis patients. Time-varying all-cause (A) and cardiovascular (B) mortality hazard ratios (and 95% confidence interval error bars) by serum triglyceride/HDL cholesterol (TG/HDL-C) ratio. Adjustments in case-mix model: age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V; case-mix plus malnutrition-inflammation-cachexia syndrome (MICS) models: case-mix adjusted model plus laboratory parameters, including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL cholesterol, and body mass index; case-mix plus MICS plus statin models: statin therapy on the fully adjusted models. Higher TG/HDL-C ratio was associated with improved survival in incident hemodialysis patients.

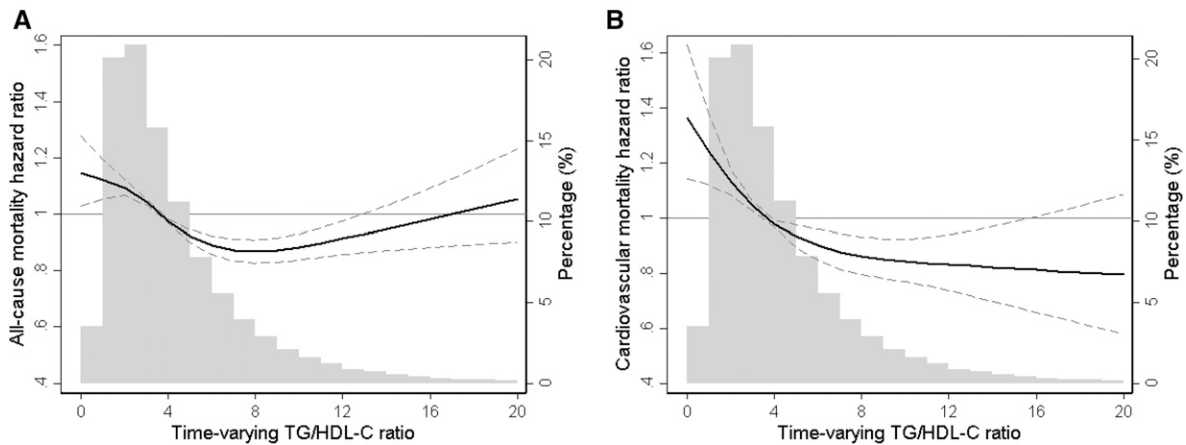


Figure 3. | The data demonstrate that incrementally higher TG/HDL-C ratios were associated with lower risk of death. Multivariate adjusted hazard ratios of all-cause (A) and cardiovascular (B) mortality associated with time-varying triglyceride/HDL cholesterol (TG/HDL-C) ratios in a Cox model using restricted cubic splines, adjusted for age, sex, race/ethnicity, primary insurance, vascular access type, comorbidities, alcohol dependence, substance abuse, single-pool Kt/V, hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL cholesterol, and bodymass index. A histogram of observed time-varying TG/HDL-C ratio values and a hazard reference ratio of 1 (solid line) is overlaid.

have found that this relationship is much more complex and can even be paradoxical in some patients with ESRD on MHD (34,35). For instance, in contrast to the general population, serum LDL-C level has not been found to be a reliable indicator of CV risk in patients with ESRD (36,37). These epidemiologic observations are further supported by the recent randomized clinical trials that show that lowering serum LDL-C levels using statin therapy does not lead to reduction in CV events or mortality in patients on hemodialysis (38–40). Indeed, it is important to note that the hallmarks of dyslipidemia in CKD are impaired clearance of VLDL and chylomicrons, leading to hypertriglyceridemia, accumulation of intermediate-density lipoprotein and chylomicron remnants, and deficiency and impaired maturation of HDL, in addition to defective HDL antioxidant, anti-inflammatory, and reverse cholesterol transport activities (41). Clinically these molecular mechanisms manifest as high serum TG and low HDL-C levels, whereas serum total cholesterol and LDL-C concentrations are typically within the normal or reduced range (42). Previously, we found that increasing serum concentrations of TG are not associated with adverse outcomes in the hemodialysis population (5). Furthermore, in a more recent study we found that elevated serum levels of HDL-C can be associated with worse CV and all-cause mortality in a cohort of patients with prevalent ESRD on MHD (29). However, in both studies the associations mentioned were J-shaped, and the lowest and highest levels were associated with increased mortality. This is in contrast to the association between TG/HDL-C ratio and outcomes, which follows a more linear pattern in most of our analyses, as increasing ratios are mostly associated with improvement in survival. However, there does seem to be some difference in the association of this ratio and outcomes, depending on the patients' sex: higher ratio seems to be more strongly associated with better outcome in men. Furthermore, as noted earlier, information regarding the fasting state of the patients in these cohorts is

not available, and therefore one can argue that those with elevated TG levels may have been in a postprandial state.

Although the underlying mechanisms responsible for these observations are not clear at this time, these findings further demonstrate the limitations of serum lipid profile in predicting outcomes in patients on MHD. In this regard, paradoxical associations between high TG/HDL-C ratio and better survival can be explained by a growing body of evidence that indicates that nontraditional risk factors, such as oxidative stress and inflammation, may play a more critical role in ESRD-associated mortality than conventional indices, such as dyslipidemia. It is now becoming clear that in the setting of uremia, oxidative stress, and inflammation, HDL can be transformed from an antioxidant and anti-inflammatory lipoprotein to a pro-oxidant, proinflammatory particle, known as acute-phase HDL (43–46). Therefore, measurement of serum HDL-C concentrations does not provide any information regarding the nature of the HDL structure present in a given patient, or its function or properties (47,48). In fact, a study in a cohort of Japanese patients on MHD found that higher HDL-C concentrations were associated with higher levels of oxidized HDL-C, which were also associated with increased CV mortality (49). The same concept can be applied to TG and TG-rich lipoproteins because serum TG levels do not reflect the qualitative characteristics of the TG-carrying lipoproteins. Therefore, it is possible that the make-up or nature of a particular lipoprotein is much more important than its quantity in determining its effect on CV disease and mortality. Another important potential explanation for these seemingly paradoxical associations is the time-dependency of adverse effects imparted by dyslipidemia. Because the deleterious effects of dyslipidemia in atherogenesis typically take effect over a longer time period, it is possible that serum lipid levels in the short term are reflective of other factors (*i.e.*, those with elevated serum TGs have a better nutritional status). This is also in line with so-called “reverse causation,” meaning it is also possible that lower

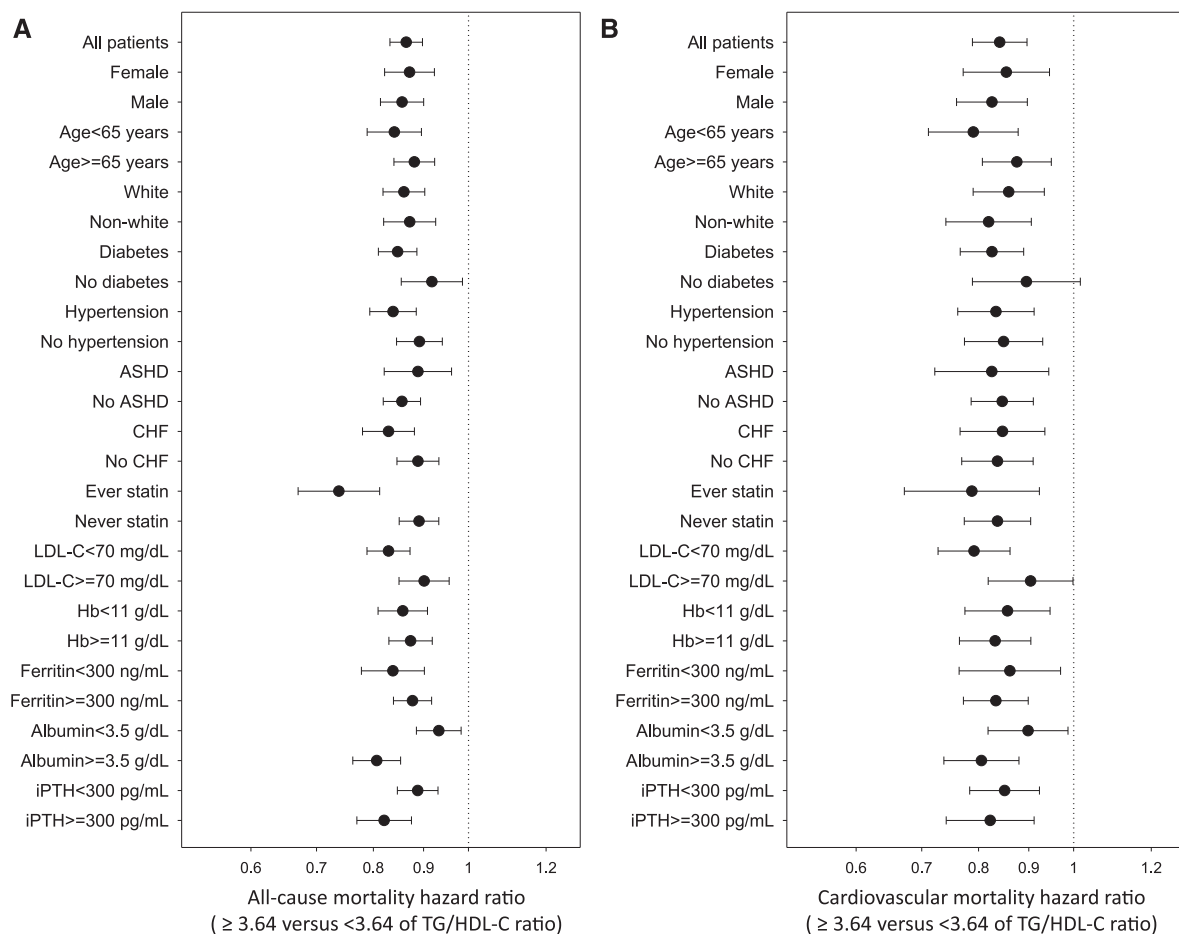


Figure 4. | There is significant association between high TG/HDL-C ratio (≥ 3.64 versus <3.64 of median TG/HDL-C value) and lower all-cause and CV mortality across all prespecified subgroups. Time-varying hazard ratios of the level of or above median (≥ 3.64) versus the level below median (<3.64) of triglyceride/HDL cholesterol (TG/HDL-C) ratios for all-cause (A) and cardiovascular (B) mortality, adjusted for age, sex, race/ethnicity, primary insurance, vascular access type, comorbidities, alcohol dependence, substance abuse, single-pool Kt/V, hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL cholesterol, and body mass index. ASHD, atherosclerotic heart disease; CHF, congestive heart failure; Hb, hemoglobin; iPTH, intact parathyroid hormone; LDL-C, LDL cholesterol.

TG/HDL-C ratio is not a cause but a consequence of underlying conditions, such as malnutrition, that concurrently lead to poor outcomes in this population (50). In fact, the role of malnutrition and protein energy wasting deserve close attention because our subgroup analyses revealed that the association of higher TG levels with improved outcomes may play a major role in the findings of this study. Although our findings remain significant despite adjustment for BMI, in order to better assess the role of malnutrition, future studies need to examine more objective nutritional assessments and their effect on the association of serum TG levels and outcomes in patients with ESRD. Regardless of the underlying mechanism, the interplay between these lipid abnormalities and their association with CV disease and mortality in patients on hemodialysis presents a unique challenge in clinical practice, as their effect on outcomes still remains to be fully clarified.

Several limitations of our study should be mentioned. First, the present findings should be qualified, given the

observational nature of our study design, which precludes conclusions about causality. In addition, it should be mentioned that not all of the patients in our database had baseline TG/HDL-C ratio and 11% of patients did not have data available on CV mortality, which raises concern for selection bias. However, we did compare all baseline characteristics between the participants included and excluded in the cohort or those with and without data on cause of death, and found no meaningful differences between the two groups (Supplemental Tables 1 and 2). Furthermore, given that we did not have complete data on all lipid-modifying medications and traditional and non-traditional CV disease risk factors (such as serum high sensitivity C-reactive protein and other nutritional parameters, such as subjective global assessment or lean body mass), our studies may have been limited by residual confounding. Nonetheless we did try to address this shortcoming, at least in part, by vigorous adjustment for measured covariates such as demographic, clinical, and laboratory parameters including BMI.

In conclusion, elevated baseline and time-varying TG/HDL-C ratios were associated with reduced CV mortality and better survival in patients treated with hemodialysis. This relationship remained significant even after extensive adjustment for relevant clinical and laboratory covariates and subgroup analyses. These observations further highlight the need for a more in-depth and qualitative, in addition to quantitative, evaluation of lipids and lipoproteins and their outcomes in patients with ESRD, given the unique nature of dyslipidemia and CV disease in this population.

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