Elevated TG/HDL-C and Non-HDL-C/HDL-C Ratios Predict Mortality in Peritoneal Dialysis Patients

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Abstract
Background and Aims:
Dyslipidemia is common in patients with chronic kidney disease and particular prevalent in patients receiving peritoneal dialysis. However, whether markers of atherogenic dyslipidemia correlate with outcomes in dialysis patients as in the general population is uncertain. Here, we investigated the prognostic value of the serum triglyceride/HDL cholesterol (TG/HDL-C) ratio and non-HDL-C/HDL-C ratio in peritoneal dialysis patients to predict all-cause mortality.

Methods
214 PD patients were retrospectively analyzed from January 2011 to December 2015, with a median follow-up of 59 months. We used receiver operating curves (ROC) to determine the optimal threshold for TG/HDL-C and non-HDL/HDL-C ratios at baseline to predict OS during follow-up. Prognostic values were accessed by univariate and multivariate COX regression analysis and Kaplan-Meier curve. A predictive nomogram was developed to predict prognosis for overall survival, and the predictive accuracy was evaluated by concordance index (c-index).

Results
The optimal cut-off values for TG/HDL-C ratio and non-HDL-C/HDL-C ratio were 1.94 and 2.86, respectively. A high TG/HDL-C ratio and a high non-HDL-C/HDL-C ratio strongly correlated with worse OS in PD patients. Multivariate analysis demonstrated that elevated TG/HDL-C ratio as well as non-HDL/HDL-C ratios were independent markers to predict reduced OS. The TG/HDL-C ratio (HR 2.60, 95% CI 1.40–4.83, P = 0.002) was superior to non-HDL-C/HDL-C ratio based on hazard ratio (HR 2.43, 95% CI 1.09–5.40, P = 0.029).

Conclusion
TG/HDL-C ratio and non-HDL-C/HDL-C were identified as potential prognostic biomarkers in PD patients. The proposed nomograms can be utilized for prediction of OS in PD patients.

Background
The increasing prevalence of chronic kidney disease (CKD) is a worldwide public health issue. Despite dialysis treatment, patients with CKD still have an excessive risk for cardiovascular events, lower quality of life and high mortality\(^1\). Therefore, it is necessary to identify and better manage patients with risk factors for worse outcomes in CKD. Dyslipidemia is a common complication in CKD patients,
especially among those receiving peritoneal dialysis (PD) treatment, which leads to high levels of triglyceride (TG) accompanied by low levels of high-density lipoprotein cholesterol (HDL-C)\textsuperscript{2, 3}. The combination of high TG and low HDL-C has been identified as an independent predictor of cardiovascular disease (CVD) and all-cause mortality in non-CKD patients, with its ratio being of greater predictive value than the individual lipid measures alone\textsuperscript{4-7}. An increased TG/HDL-C ratio\textsuperscript{7-9}, CV death\textsuperscript{10,11}, and all-cause mortality\textsuperscript{12,13} in healthy individuals and patients with increased CVD risk.

Several studies have reported that an elevated TG/HDL-C ratio correlated with the prevalence of CKD\textsuperscript{14,15}. However, conflicting data were reported on the association of high TG/HDL-C ratios with CVD and mortality in dialysis patients. Contrary to non-CKD patients, a large retrospective study in hemodialysis (HD) patients reported that high TG/HDL-C ratios were associated with reduced CV events and improved survival\textsuperscript{16}. In contrast, Chen et al. demonstrated that a higher TG/HDL-C ratio was associated with increased CVD risk and mortality in prevalent dialysis patients including both HD and PD patients\textsuperscript{17}. Indeed, further studies evaluating the prognostic utility of the TG/HDL-C ratio specifically in PD patients found that higher values were significantly associated with CVD mortality in female PD patients\textsuperscript{18}, and with higher all-cause and CVD mortality in older patients on PD\textsuperscript{12}.

In addition, it has been proposed that the non-HDL-C/HDL-C ratio can be utilized as a simple indicator for CVD risk\textsuperscript{19}. Non-HDL-C includes all the atherogenic lipoproteins and is calculated as total cholesterol (TC) minus HDL-C. However, data on the association of the non-HDL-C/HDL-C ratio with prognosis of patients on dialysis is limited.

In this study, we wanted to substantiate the positive association of higher TG/HDL-C ratios with overall survival (OS) in incident PD patients. Furthermore, we compared the prognostic impacts of TG/HDL-C and non-HDL-C/HDL-C ratios in PD patients and established prognostic nomograms to better predict outcomes in PD patients.

Methods
Patients
This was a single-center retrospective observational cohort study. Medical records of 243 incident PD patients were collected between January 2011 and December 2017 at the Affiliated Jiangyin Hospital of Southeast University Medical College. Exclusion criteria were as follows: patients aged < 18 years old and patients receiving less than 3 consecutive months of PD, a history of previous HD or renal transplantation, and patients lost to follow up. Finally, 214 patients were enrolled in this study. The primary endpoint was all-cause mortality. Each patient was followed up until death or censoring on December, 2017. All patients were regularly followed-up with physical examination, and laboratory testing.

Analysis of blood samples
Peripheral blood was obtained for the measurement of laboratory values, including hemoglobin, albumin, serum creatine, blood urea nitrogen, uric acid, calcium, phosphorus, potassium, serum triglyceride, total cholesterol, HDL-C and LDL-C. Intact parathyroid hormone (iPTH) level was measured by immunoassay.

Definition and optimal cutoff values of TG/HDL-C ratio and non-HDL/HDL-C ratio
TG/HDL-C ratio was defined as serum levels of triglyceride (TG) divided by high-density lipoprotein cholesterol (HDL-C). Non-HDL-C was HDL-C subtracted by total cholesterol (TC), and non-HDL/HDL-C ratio was defined as non-HDL-C divided by HDL-C. Receiver operating curve (ROC) analyses was applied to determine the optimal cut-off value of TG/HDL-C ratio and non-HDL/HDL-C ratio. Using OS as endpoint, optimal thresholds of TG/HDL-C ratio and non-HDL/HDL-C ratio were obtained according to the highest Youden’s index. Subsequently, patients were divided into two groups based on the optimal thresholds.

Statistical analysis
Comparison of categorical variables was conducted by the Pearson $X^2$ test. Comparison of continuous variables was analyzed with Mann-Whitney U or Kruskal-Wallis test. Survival rates were evaluated through the Kaplan-Meier method with log-rank test. The predictive accuracy was evaluated using Harrell’s concordance index (c-index). The Cox proportional hazards regression model was performed in univariate analysis and the significant variables of univariate analysis were calculated into the multivariable analysis. All statistical analysis was performed by SPSS 20.0 software (SPSS Inc, IBM,
USA) and R software version 3.2.2 (Institute for Statistics and Mathematics, Vienna, Austria).

Results

Baseline characteristics

A total of 214 incident PD patients were finally enrolled in this study. The clinical and biochemical baseline characteristics of all PD patients according to low versus high serum TG/HDL-C ratio and non-HDL/HDL-C ratio are summarized in Table 1. The mean age of patients was 50 ± 14 years, 59% were men. The median follow-up period was 59 months ranging from 3 to 60 months. 54 patients died from any cause during the follow-up period. The median value of TG/HDL-C ratio and non-TG/HDL-C ratio was 1.33 (range 0.16–9.47) and 2.88 (range 0.56-10.94), respectively.

Table 1

| Variable                  | Cases (n = 214) | TG/HDL-C ratio | P     | Non-HDL/HDL-C ratio | P     |
|---------------------------|-----------------|----------------|-------|---------------------|-------|
| Age, y                    |                 |                |       |                     |       |
|                           | 49 ± 14         | 53 ± 13        | 0.021 | 49 ± 15             | 0.393 |
| Male, (n, %)              | 88 (57.9%)      | 38 (61.3%)     | 0.647 | 69 (63.3%)          | 0.180 |
| BMI                       | 21.8 ± 2.6      | 23.1 ± 3.1     | 0.476 | 22.1 ± 2.7          | 0.519 |
| Laboratory data           |                 |                |       |                     |       |
| Hemoglobin, g/dL          |                 |                |       |                     |       |
|                           | 97.9 (86.3, 108.0) | 98.5 (85.5, 109.2) | 0.772 | 97.7 (84.8, 108.0) | 0.619 |
| Albumin, g/L              |                 |                |       |                     |       |
|                           | 34.5 ± 4.1      | 34.3 ± 4.3     | 0.733 | 34.6 ± 4.2          | 0.580 |
| Creatinine, umol/L        |                 |                |       |                     |       |
|                           | 813.6 (631.8, 1091.1) | 847.6 (738.2, 1047.1) | 0.822 | 871.9 (660.8, 1100.0) | 0.681 |
| BUN, mmol/L               |                 |                |       |                     |       |
|                           | 17.2 (13.5, 20.9) | 16.9 (13.9, 20.4) | 0.569 | 17.2 (14.3, 21.3)  | 0.383 |
| Uric acid, umol/L         |                 |                |       |                     |       |
|                           | 430.6 (378.2, 489.6) | 463.8 (392.8, 546.0) | 0.036 | 426.0 (379.8, 489.3) | 0.017 |
| K, mmol/L                 |                 |                |       |                     |       |
|                           | 3.9 (3.3, 4.5)  | 3.7 (3.3, 4.2) | 0.197 | 3.9 (3.3, 4.5)     | 0.900 |
| Ca, mmol/L                |                 |                |       |                     |       |
|                           | 2.1 (2.0, 2.2)  | 2.1 (1.9, 2.3) | 0.755 | 2.0 (1.9, 2.2)     | 0.047 |
| Na, mmol/L                |                 |                |       |                     |       |
|                           | 140.0 (136.3, 142.6) | 139.0 (134.9, 142.3) | 0.086 | 139.7 (135.9, 142.3) | 0.486 |
| P, mmol/L                 |                 |                |       |                     |       |
|                           | 1.5 (1.2, 1.9)  | 1.7 (1.4, 2.0) | 0.302 | 1.6 (1.3, 1.9)     | 0.631 |
| iPTH, pmol/L              |                 |                |       |                     |       |
|                           | 24.0 (11.9, 64.2) | 24.9 (10.4, 52.9) | 0.805 | 23.0 (13.9, 68.5)  | 0.966 |
| TC, mmol/L                |                 |                |       |                     |       |
|                           | 1.3 ± 0.6       | 4.6 ± 1.3      | 0.770 | 4.1 ± 1.0           | <0.001|
| TG, mmol/L                |                 |                |       |                     |       |
|                           | 1.2 (0.9, 1.5)  | 2.6 (2.2, 3.3) | 0.000 | 1.2 (0.8, 1.5)     | <0.001|
| HDL-C, mmol/L             |                 |                |       |                     |       |
|                           | 1.2 (1.0, 1.5)  | 0.9 (0.8, 1.0) | <0.001| 1.3 (1.1, 1.6)     | <0.001|
| LDL-C, mmol/L             |                 |                |       |                     |       |
|                           | 1.8 (1.3, 2.5)  | 1.8 (1.1, 2.3) | 0.158 | 1.6 (1.2, 2.2)     | 0.002 |
| Non-HDL-C, mmol/L         |                 |                |       |                     |       |
|                           | 3.2 ± 1.2       | 3.6 ± 1.2      | 0.014 | 2.7 ± 0.8          | <0.001|
| Medications, (n, %)       |                 |                |       |                     |       |
| Statin/Fibrate            | 48(31.6%)       | 39(62.9%)      | <0.001| 31(28.4%)          | <0.001|

The optimal cutoff value for TG, HDL-C, TG/HDL-C and non-HDL/HDL-C

The optimal thresholds of TG, HDL-C, TG/HDL-C and non-HDL/HDL-C were determined using receiver operating curve (ROC) analysis (Fig. 1). The optimal cutoff levels of TG, HDL-C, TG/HDL-C and non-HDL/HDL-C based on the highest Youden's index were 1.47 mmol/L (AUC: 0.598, 95%CI: 0.509–0.687, 5

TC, total cholesterol; BUN, blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; iPTH, intact parathyroid hormone.
Associations of TG/HDL-C and non-HDL/HDL-C with patients’ outcomes

Kaplan-Meier survival analysis and log-rank tests were used to determine the association of TG/HDL-C and non-HDL/HDL-C with patients’ survival. Our results demonstrate that TG/HDL-C ≥ 1.94 and non-HDL/HDL-C ≥ 2.86 were significantly associated with decreased OS (Fig. 2, P < 0.001). Furthermore, results from multivariate Cox regression analysis revealed that an elevated TG/HDL-C ratio was independently associated with reduced OS (HR 2.60 P = 0.002). Patients with non-HDL/HDL-C ≥ 2.86 had also an increased risk for all-cause mortality compared to patients with non-HDL/HDL-C < 2.86 (HR 2.43 P = 0.029), suggesting TG/HDL-C was superior to non-HDL/HDL-C to predict reduced OS. In addition, age (HR 1.04 P = 0.001), iPTH (HR 0.99 P = 0.026), TG (HR 1.32 P = 0.002) and HDL-C (HR 0.29 P = 0.009) were independent indicators for OS of PD patients (Table 2).

Table 2

| Variable          | Overall survival | Univariate analysis | Multivariate analysis |
|-------------------|------------------|---------------------|-----------------------|
|                   |                  | HR (95% CI)         | P value               |
|                   |                  |                     | HR (95% CI)           | P value               |
| Age               |                  | 1.05 (1.03, 1.07)   | <0.001                |
| Gender (male)     |                  | 0.83 (0.48, 1.41)   | 0.483                 |
| BMI               |                  | 1.34 (0.79, 2.27)   | 0.286                 |
| Hemoglobin        |                  | 1.00 (0.99, 1.01)   | 0.805                 |
| Albumin           |                  | 0.95 (0.89, 1.02)   | 0.135                 |
| Creatinine        |                  | 1.05 (0.95, 1.16)   | 0.003                 |
|                   |                  | 1.00 (0.99, 1.00)   | 0.144                 |
| BUN               |                  | 0.97 (0.93, 1.02)   | 0.218                 |
| Uric acid         |                  | 1.00 (1.00, 1.00)   | 0.642                 |
| K                 |                  | 1.01 (1.00, 1.02)   | 0.163                 |
| Ca                |                  | 1.31 (0.55, 3.11)   | 0.547                 |
| Na                |                  | 0.99 (0.98, 1.00)   | 0.251                 |
| P                 |                  | 0.86 (0.59, 1.25)   | 0.430                 |
| iPTH              |                  | 0.97 (0.93, 1.05)   | 0.022                 |
|                   |                  | 0.99 (0.98, 1.00)   | 0.026                 |
| TC                |                  | 1.21 (0.99, 1.48)   | 0.066                 |
| TG                |                  | 1.37 (1.21, 1.56)   | <0.001                |
| HDL-C             |                  | 0.42 (0.19, 0.92)   | 0.030                 |
| LDL-C             |                  | 0.9 (0.71, 1.10)    | 0.990                 |
| Non-HDL-C         |                  | 1.35 (1.10, 1.66)   | 0.005                 |
| Non-HDL/HDL-C     |                  | 3.56 (2.08, 6.10)   | <0.001                |
|                   |                  | 2.99 (1.65, 5.44)   | <0.01                 |

TG, triglyceride; TC, total cholesterol; BUN, blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; iPTH, intact parathyroid hormone.

New prognostic model for OS

To predict survival of PD patients, we developed a nomogram by integrating all the independent prognostic factors according to the results from the Cox regression model (Fig. 3). To access the predictive accuracy of the nomogram, we calculated the c-index of the nomogram for OS prediction, which was 0.795. The performance of the nomogram to predict 5-year OS was verified by calibration.
plots (Fig. 4).

Discussion

In this retrospective cohort study, we evaluated the prognostic performance of TG/HDL-C and non-HDL/HDL-C ratios in PD patients to predict OS. An elevated serum TG/HDL-C ratio was most significantly associated with higher all-cause mortality, but also the non-HDL/HDL-C ratio could be identified as an indicator for OS in PD patients. In addition, we developed a novel nomogram incorporating these ratios to improve predictive accuracy.

Dyslipidemia is an important CVD risk factor in the general population and is prevalent in CKD and PD patients\textsuperscript{2,3}. However, in contrast to non-CKD patients serum LDL-C levels have not been identified as a strong risk factor for CVD in end stage renal disease patients undergoing dialysis\textsuperscript{13,20}. Consistently, statin therapy to lower LDL-C did not lead to reduced CVD and mortality in HD patients in respective clinical trials\textsuperscript{21-23}. Independent of LDL-C levels, elevated serum TG and reduced HDL-C have been identified as risk factors for CVD, and the combination of these measures as a TG/HDL-C ratio was found to better predict risk for CVD and mortality than individual markers alone\textsuperscript{5-7}. In CKD, impaired clearance of very low-density lipoproteins (VLDL) and chylomicrons lead to hypertriglyceridemia and deficiency of HDL, with defective HDL antioxidant, anti-inflammatory, and reverse cholesterol transport (RCT) activity\textsuperscript{24}. Consistently, higher TG/HDL-C ratios were associated with the presence of CKD in cross-sectional studies\textsuperscript{14,15}, and predicted the development of CKD in patients with type 2 diabetes\textsuperscript{25}. Prior studies also found a significant association between higher TG/HDL-C ratios and progression of diabetic kidney disease or the risk for CVD events after renal transplantation\textsuperscript{26,27}. Therefore, several studies investigated whether an elevated TG/HDL-C ratio was also a risk factor for the development of CVD and mortality in the dialysis population, but yielded conflicting results. Indeed, a large retrospective study in incident HD patients demonstrated that a higher TG/HDL-C ratio correlated with reduced CVD and better OS\textsuperscript{28}, indicating a complex and even paradoxical relationship of dyslipidemia and clinical risk in this patient population. In contrast, studies enrolling in part or
exclusively PD patients reported a positive association of an increased TG/HDL-C ratio with CVD risk and mortality, particularly in female and older patients\textsuperscript{12,17,29}. Importantly, the results of our study confirm the independent relationship between a high TG/HDL-C ratio and OS in PD patients. We found that an increased TG/HDL-C ratio was independently correlated with all-cause mortality in PD patients, and the optimal threshold of 1.94 for the TG/HDL-C ratio was the best predictor in terms of hazard ratio (HR), and achieved the highest specificity and sensitivity. However, the applicable cut-off value was different from other studies, which may be due to differences in geographic region and race\textsuperscript{11}. Reasons for the opposing relationship of the TG/HDL-C ratio with CVD risk and mortality in PD versus HD patients are not clear. Interestingly, the TG/HDL-C ratio is also a predictor for insulin resistance\textsuperscript{30–35}, which may be particularly prevalent in PD patients and is associated with an increased risk of hyperglycemia, dyslipidemia, and hypertension, all of which drive CVD mortality. Our study extends previous findings by additionally identifying the non-HDL-C/HDL-C ratio as a positive predictor for OS in PD patients. Non-HDL-C/HDL-C may correlate better with CVD risk than LDL-C and non-HLD-C levels\textsuperscript{36}. Similar to the TG/HDL-C ratio associations of high non-HDL-C/HDL-C ratios were reported with CVD in the general population\textsuperscript{19,37}, with insulin resistance\textsuperscript{38}, and with CKD in an adult Chinese population\textsuperscript{15}. To the best of our knowledge, this is the first study to demonstrate that the non-HDL/HDL-C ratio is a potential prognostic marker for OS in PD patients. In the current study, a non-HDL/HDL-C ratio ≥ 2.84 was an independent indicator of overall mortality in PD patients after 5 years of follow-up.

However, based on hazard ratios the TG/HDL-C ratio out-performed non-HDL/HDL-C in predicting OS. Further studies are needed to test whether the non-HDL/HDL-C ratio can predict CV outcomes in CKD patients.

As reported previously\textsuperscript{4–7,39}, low TG/HDL-C and non-HDL-C/HDL-C ratios better predicted OS in this study population than levels of TG, HDL-C and non-HDL-C alone. Indeed, despite the known protective cardiovascular functions of HDL-C, including reverse cholesterol transport, antioxidant, anti-
inflammatory and anti-thrombotic properties\textsuperscript{24}, high HDL-C levels did not associate with all-cause mortality in patients with reduced kidney function in a large cohort study\textsuperscript{40}. These observations were supported by studies investigating HDL-C cholesterol efflux capacity (CEC) as a marker of HDL-C functionality, in which CEC did not predict CV events or mortality in dialysis patients\textsuperscript{41,42}. Although high TG and low HDL-C levels were independently associated with mortality in our cohort after multivariate analysis, LDL-C and non-HDL-C were not, despite the predictive value of a higher non-HDL-C/HDL-C ratio. Together, these results suggest that in CKD and PD patients the TG/HDL-C and non-HDL-C/HDL-C ratios better reflect the balance between pro-atherogenic and protective lipoproteins affecting relevant patient outcomes, i.e. CVD and mortality.

Several nomograms have been used to predict disease prognosis based on clinical characteristic, and nomograms were considered to be more precise than a traditional staging system for predicting prognosis in tumors\textsuperscript{43}. However, few studies have demonstrated whether nomograms can predict outcomes in PD patients. The current study established a prognostic nomogram to predict 5-year mortality in PD patients including the TG/HDL-C and non-HDL-C/HDL-C ratios which we identified as independent prognostic markers. The nomogram performed well for OS, which was supported by the obtained c-index (0.795). Our results demonstrated that the derived nomogram could be a valuable tool to predict prognosis in patients undergoing PD.

This study has potential limitations. First, this was a retrospective study based on a single-center database, which may have resulted in bias for data collection and analysis. In addition, no data are available on the relationship between TG/HDL-C or non-HDL/HDL-C ratios with CVD mortality. The optimal cut-off value of TG/HDL-C ratio and non-HDL/HDL-C ratio to predict long-term CV outcome needs further investigations.

**Conclusion**

In conclusion, our study demonstrated that TG/HDL-C ratio and non-HDL/HDL-C ratio were independent predictors of OS in PD patients. TG/HDL-C ratio was a better predictor of OS than non-HDL/HDL-C ratio. TG/HDL-C and non-HDL/HDL-C ratios and the newly developed predictive nomogram
may be valuable to determine the clinical prognosis and may help to establish optimal therapeutic strategies.

**Abbreviations**

CKD: chronic kidney disease; PD: peritoneal dialysis; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; CVD: cardiovascular disease; HD: hemodialysis; TC: cholesterol; OS: overall survival; iPTH: Intact parathyroid hormone; ROC: receiver operating curve; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; VLDL: very low-density lipoproteins; RCT: reverse cholesterol transport; HR: hazard ratio.

**Declarations**

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**Availability of data and materials**

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

**Ethics approval and consent to participate**

The study was approved by the Medical Ethics Committee of The Affiliated Jiangyin Hospital, School of Medicine, Southeast University, and written informed consent was obtained from all subjects. The number of the ethics certificate is 2011-023.

**Consent for publication**

Not applicable.

**Authors’ contribution**

W.X. and H.H. developed the protocol; X.Y. and Y.C. collected the data; X.Y. and J.L. analyzed the data; W.X. and V.V. reviewed the data and wrote the manuscript; and H.H. supervised the project. All
authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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Figures
Optimal cutoff value for TG, HDL-C, TG/HDL-C ratio and non-TG/HDL-C ratio were applied with ROC curves for survival status.
Figure 2

Kaplan-Meier curves for OS according to TG/HDL-C ratio and non-HDL-C/HDL-C ratio

Figure 3

Nomogram for predicting 5-year survival of PD patients
Figure 4

Calibration plot of the nomogram for 5-year OS. Notes: The 45-degree reference line represents the performance of a perfect nomogram. The red dashed line shows the performance of the observed nomogram. It seems that the nomogram precisely predicts the 5-year OS. n=190; d=50; P=4.5; 50 subjects per group; X-resampling optimism added, B=200; comparison between nomogram-predicted probability of OS (X-axis) and the actual 5-year survival (Y-axis).