

The Association Between Diabetes Coexisting With Low Levels of High-density Lipoprotein Cholesterol and Peritoneal Dialysis-related Peritonitis

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Research Article

Keywords: peritoneal dialysis, high density lipoprotein cholesterol, diabetes, peritonitis, infection

Posted Date: January 5th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1215683/v1>

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Abstract

Background

Low levels of high-density lipoprotein-cholesterol (HDL-C) and diabetes are common in patients undergoing peritoneal dialysis (PD). The aim of this study was to investigate the association between diabetes coexisting with a low level of HDL-C and the first episode of peritoneal dialysis-related peritonitis (PDRP) in patients with PD.

Methods

We retrospectively investigated patients with PD from January 1, 2003, to May 31, 2020 in four PD centers. Patients with PD were divided into four groups: no comorbidity, low HDL-C only, diabetes only, and diabetes plus low HDL-C. The clinical and laboratory baseline data of the four groups were collected and compared. The association between diabetes coexisting with low HDL-C levels and the first episode of PDRP was analysed by multivariate Cox regression analysis.

Results

A total of 1013 patients with PD were recorded in our study. The mean age was 49.94 ± 14.32 years, and 597 (58.99%) were males. A total of 301 (29.7%) patients had their first episodes of PDRP, and low HDL-C levels existed with diabetes in 72 patients with PD. After adjusting for confounding factors, a low level of HDL-C coexisting with diabetes was significantly associated with the first episode of PDRP in our study (hazard ratio: 1.93, 95% CI: 1.03-3.61, $p < 0.05$). The associations between HDL-C, diabetes and PDRP were consistent in the following subgroups: sex, age, pre-existing CVD (all P interaction > 0.05).

Conclusions

Low levels of HDL-C alone or diabetes alone were not independent risk factors for PDRP. Patients with both diabetes and low HDL-C levels were at high risk for PDRP.

Background

Peritoneal dialysis (PD) is an important renal replacement therapy. Peritoneal dialysis-related peritonitis (PDRP) is associated with mortality and technical failure in patients with PD. Diabetes is now increasingly common in patients with PD as diabetic nephropathy and has risen in recent years in China¹. Patients with diabetes are at increased risk for bacterial infection². Whether diabetes is associated with PDRP in patients with PD is controversial. It is reported that diabetes was not an independent risk factor for PDRP³. Dyslipidaemia is common in patients with diabetes. It has been reported that a low high-density lipoprotein-cholesterol (HDL-C) level is a risk factor for infection in diabetic patients⁴.

Low levels of HDL-C are a manifestation of dyslipidaemia in patients with PD and has been associated with mortality and cardiovascular disease (CVD) in patients with PD in many reports^{5,6}. HDL-C protected

patients form serious infection and low levels of HDL-C are also a risk factor for adverse outcomes in sepsis ⁷. It has been reported that 50% of people with type 2 diabetes have low HDL-C concentrations ⁸. Since diabetes was not necessarily an independent risk factor for PDRP, we presumed that diabetes coexisting with low HDL-C might be associated with PDRP in patients with PD. In this study, we investigated whether diabetes coexisting with low HDL-C level was associated with the first episode of PDRP in patients with PD.

Methods

Patients

Patients were recruited from four peritoneal dialysis centres in three provinces in China in this retrospective multiple-centre study. Our study included adult patients aged ≥ 18 with PD, recruited from January 1, 2003 to May 31, 2020. These patients received continuous ambulatory peritoneal dialysis (CAPD) with standard glucose solution. Patients were excluded if they were on PD for < 3 months or had no lipid testing.

Data collection and Clinical definitions

Demographic and clinical characteristics, including age, sex, weight, height, blood pressure, history of smoking and alcohol use, pre-existing CVD, pre-existing stroke, residual urinary volume, use of statins, and laboratory test results, were recorded at baseline by at least two trained nurses. Laboratory characteristics included routine blood tests, biochemical tests, kidney and liver function tests, and lipid levels. These records were rechecked by at least two trained doctors.

Diabetes was defined as follows: (1) Fasting plasma glucose ≥ 7.0 mmol/L. or (2) 2 h plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test (OGTT). Or (3) glycated haemoglobin (HbA1c) $\geq 6.5\%$. or (4) diabetes symptoms plus random plasma glucose ≥ 11.1 mmol/L. or (5) use of glucose-lowering drugs. If patients had no diabetes symptoms and only once had hyperglycaemia, criteria 1 to 3 were confirmed by repeated testing ⁹. A low level of HDL-C was defined as < 1.0 mmol/L according to Chinese guidelines on the prevention and treatment of dyslipidaemia in adults ¹⁰.

A diagnosis of the first episode of PDRP was made if the patient had at least two of the following criteria according to the 2017 ISPD guidelines ¹¹: 1) abdominal pain with or without cloudy peritoneal dialysis effluent, and with or without fever. 2) dialysis effluent total leukocyte count $\geq 100 \times 10^6$ cells/L, with more than 50% polymorphonuclear cells in the differential count. 3) Positive gram staining or culture of peritoneal dialysis effluent.

Outcomes and follow up

The outcome of our study was the first episode of PDRP. Patients with PD routinely returned to each centre and were tested every three months in each centre. If patients did not return, they received telephone interviews. September 1, 2020, was the end of the follow-up date in this study. Patients without

PDRP were followed up until death or PD cessation. Time when patients received haemodialysis, kidney transplantation, transferred care to another dialysis centre, or were lost to follow-up were also recorded.

Statistical analysis

Quantitative data are presented as the mean \pm standard deviation (SD) or median (interquartile range [IQR]) after testing for normality. Nominal data were described as percentages. Baseline patient characteristics were compared for each group by chi-squared, one-way ANOVA, or Kruskal-Wallis tests. Univariate Cox regression analysis was used for the preliminary exploration of variables to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) for the first episode of PDRP.

Survival curves and the time to peritonitis were calculated using the Kaplan-Meier method. Multivariate Cox regression analysis was conducted to examine the association between diabetes coexisting with low HDL-C levels and the first episode of PDRP: model 1, unadjusted; model 2, plus demographic and clinical characteristics; and model 3, model 2 plus laboratory variables and medications. Subgroups of sex, age, and history of pre-existing CVD were also analysed. A p value across groups and the interactions between sex, age, and history of pre-existing CVD, and PDRP was examined. The results are presented as HRs and 95% confidence intervals (95% CI). P values were two-sided, and $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS statistical software (version 21.0; Chicago, IL, USA) and R (<http://www.R-project.org>) and EmpowerStats software (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA).

Results

Clinical baseline data of enrolled patients

A total of 1307 patients were included in our study from four peritoneal dialysis centres from January 1, 2003 to May 31, 2020. A total of 145 patients were excluded due to no available lipid level results. Twenty-two patients were excluded because they were younger than 18 years. A total of 127 patients were excluded due to the duration of follow-up < 3 months. The remaining 1013 patients were analysed in our study (Figure 1).

Patients were divided into four groups according to HDL-C levels and presence of diabetes, that is, group 0 (no comorbidity), group 1 (low HDL-C only), group 2 (DM only), and group 3 (both DM and low HDL-C). The baseline demographics, clinical and laboratory characteristics, and medications are summarized in Table 1. The mean age was 49.94 ± 14.32 years old, and 597 (58.99%) were male. A total of 193 (19.05%) had a history of current smoking, 71 (7.01%) had a history of current alcohol consumption, and 39 (3.85%) had pre-existing stroke. A total of 104 (10.27%) had pre-existing CVD, and 145 (14.31%) received statin therapy prior to PD. There were no differences in serum calcium and 24-h urine volume among the four groups. Age and BMI were higher in the DM plus low HDL-C level group. The incidence of pre-existing stroke and pre-existing CVD was also higher in the DM plus low HDL-C level group. WBC and triglyceride

were higher in the DM plus low HDL-C level group. Serum potassium was lower in the DM plus low HDL-C level group.

Table 1
Baseline demographic characteristics, medications, and laboratory parameters

Variables*	TOTAL (n=1013)	No comorbidity (n=472)	Low HDL-C (n=374)	DM (n=75)	DM plus Low HDL- C (n=72)	P- value
Age (years)†	49.94 ± 14.32	47.89 ± 14.04	47.98 ± 14.20	59.67 ± 9.93	60.74 ± 11.56	<0.001
Male [n (%)]	597 (58.99%)	241(51.06%)	267 (71.39%)	51 (53.68%)	38 (53.52%)	<0.001
Body mass index (kg/m ²)†	22.81 ± 3.23	22.04 ± 2.98	23.34 ± 3.36	23.76 ± 3.14	23.91 ± 3.10	<0.001
Residual urine volume (mL)‡	800.00 (400.00- 1245.00)	750.00 (400.00- 1200.00)	810.00 (450.00- 1338.75)	700.00 (487.50- 1200.00)	800.00 (325.00- 1045.00)	0.245
Current smoking [n (%)]	193 (19.05%)	72 (15.25%)	89 (23.80%)	19 (20.00%)	13 (18.06%)	0.019
Current alcohol consumption [n (%)]	71 (7.01%)	21 (4.45%)	39 (10.43%)	7 (7.37%)	4 (5.56%)	0.002
Pre-existing stroke [n (%)]	39 (3.85%)	6 (1.27%)	15 (4.01%)	9 (9.47%)	9 (12.50%)	<0.001
Pre-existing CVD [n (%)]	104 (10.27%)	21 (4.45%)	24 (6.42%)	30 (31.58%)	29 (40.28%)	<0.001
WBC (10 ⁹ /L)†	6.37 ± 2.30	5.95 ± 2.10	6.53 ± 2.53	6.80 ± 2.09	7.57 ± 2.04	<0.001
Hemoglobin (g/L)†	97.07 ± 23.36	97.83 ± 24.26	93.05 ± 22.67	105.35 ± 22.32	101.85 ± 17.59	<0.001
Serum albumin (g/L)†	34.49 ± 5.65	34.83 ± 5.38	35.06 ± 5.97	31.81 ± 4.72	32.80 ± 5.66	<0.001
AST (U/L)‡	17.00(13.00- 22.00)	17.00 (13.00- 22.00)	16.00 (12.00- 22.00)	19.00 (15.50- 24.50)	18.50 (14.00- 24.25)	<0.001

Statistically significant results are indicated in bold.

HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; WBC, white blood cell; CVD, cardiovascular disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; iPTH, intact parathyroid hormone.

*Data are expressed as number (%) unless otherwise indicated.

†Data are expressed as mean ± standard deviation.

‡Data are expressed as median (interquar the range).

Variables*	TOTAL (n=1013)	No comorbidity (n=472)	Low HDL-C (n=374)	DM (n=75)	DM plus Low HDL- C (n=72)	P- value
ALT (U/L)‡	13.00 (9.00- 20.00)	13.00 (9.00- 20.00)	14.00 (8.00- 20.00)	15.00 (11.00- 21.00)	12.00 (8.00- 16.25)	0.024
Cholesterol (mmol/L)†	4.42 ± 1.31	4.63 ± 1.25	3.92 ± 1.09	5.00 ± 1.41	4.90 ± 1.73	<0.001
Triglyceride (mmol/L)‡	1.30 (0.94- 1.88)	1.13 (0.82- 1.51)	1.53 (1.11- 2.17)	1.20 (0.91- 1.79)	1.92 (1.24- 2.79)	<0.001
Low-density lipoprotein cholesterol (mmol/L)†	2.67 ± 0.97	2.76 ± 0.98	2.47± 0.87	2.91 ± 1.17	2.74 ± 0.95	<0.001
Serum calcium (mmol/L)†	2.12 ± 0.28	2.13 ± 0.28	2.09 ± 0.31	2.11 ± 0.23	2.16 ± 0.24	0.077
Serum phosphorus (mmol/L)†	1.66 ± 0.67	1.65 ± 0.59	1.77 ± 0.70	1.50 ± 0.48	1.43 ± 1.04	<0.001
Serum potassium (mmol/L)†	4.11 ± 0.85	4.12 ± 0.83	4.16 ± 0.81	4.12 ± 0.96	3.82 ± 0.97	0.019
iPTH (pg/mL)‡	31.40 (12.25- 93.56)	32.45 (12.05- 106.45)	32.90 (14.50- 98.00)	31.40 (14.20- 97.35)	17.10 (5.98- 63.10)	0.073
Statins [n (%)]	145 (14.31%)	56 (11.86%)	39 (10.43%)	33 (34.74%)	17 (23.61%)	<0.001
Statistically significant results are indicated in bold.						
HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; WBC, white blood cell; CVD, cardiovascular disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; iPTH, intact parathyroid hormone.						
*Data are expressed as number (%) unless otherwise indicated.						
†Data are expressed as mean ± standard deviation.						
‡Data are expressed as median (interquartile range).						

Risk factors for the first episode of PDRP in patients with PD

As shown in Table 2, after univariate Cox regression, diabetes, pre-existing stroke, pre-existing CVD, statins, haemoglobin, serum albumin, HDL-C, low HDL-C group, and diabetes plus low HDL-C group were

associated with the first episode of PDRP in patients with PD.

Table 2
Risk factor associated with the first episode of peritonitis

Variables	HR (95% CI)	P-Value
Age (years)	1.0 (1.0, 1.0)	0.991
Gender		
Male	1.0	
Female	1.1 (0.9, 1.4)	0.417
BMI	1.0 (1.0, 1.0)	0.953
Residual urine volume	1.0 (1.0, 1.0)	0.189
Current smoking	1.3 (1.0, 1.8)	0.066
Current alcohol consumption	1.2 (0.8, 2.0)	0.338
DM	1.8 (1.4, 2.4)	<0.001
Pre-existing stroke	2.0 (1.2, 3.3)	0.009
Pre-existing CVD	1.8 (1.3, 2.5)	<0.001
Statins	1.9 (1.4, 2.6)	<0.001
WBC	1.1 (1.0, 1.1)	0.130
Hemoglobin	1.0 (1.0, 1.0)	0.023
Serum albumin	1.0 (1.0, 1.0)	0.007
AST	1.0 (1.0, 1.0)	0.495
ALT	1.0 (1.0, 1.0)	0.578
Cholesterol	0.9 (0.9, 1.0)	0.253
Triglyceride	0.9 (0.8, 1.1)	0.301
High-density lipoprotein cholesterol	1.3 (1.1, 1.6)	0.002
Low-density lipoprotein cholesterol	0.9 (0.8, 1.0)	0.180
Serum calcium	0.9 (0.6, 1.4)	0.747
Serum phosphorus	0.8 (0.7, 1.0)	0.081
IPTH	1.2 (1.0, 1.4)	0.017

Statistically significant results are indicated in bold.

HR, hazard ratio; CI, confidence interval; WBC, white blood cell; CVD, cardiovascular disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; iPTH, intact parathyroid hormone; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.

Variables	HR (95% CI)	P-Value
Serum potassium	1.1 (1.0, 1.3)	0.088
GROUP		
No comorbidity	1.0	
Low HDL-C	0.8 (0.6, 1.0)	0.037
DM	1.4 (1.0, 2.1)	0.072
DM plus Low HDL-C	1.9 (1.3, 2.8)	0.002
Statistically significant results are indicated in bold.		
HR, hazard ratio; CI, confidence interval; WBC, white blood cell; CVD, cardiovascular disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; iPTH, intact parathyroid hormone; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.		

Observational period and outcome

The overall follow-up period was 43213 patient-months, with a median period of 32.0 (4.0-211.0) months per patient. At the end of the study, 194 (19.15%) patients had died, 74 (7.31%) patients were transferred to hemodialysis, 42 (4.15%) patients received renal transplantation, 14 (1.38%) patients were transferred to other centers, and 10 (0.99%) patients were lost to follow-up. A total of 301 (29.7%) patients had their first episode of PDRP, and the incidences of their first episode of PDRP were 15.1%, 8.6%, 3.1%, and 3.0% in groups 0, 1, 2, and 3, respectively.

Associations of low HDL-C level and diabetes and the first episode of PDRP in patients with PD

In survival analyses, the overall peritonitis-free survival of patients in the DM plus low HDL group declined significantly faster than that in the other groups ($p < 0.0001$, Figure 2). The associations between low HDL-C levels and diabetes and PDRP were presented in Table 3. After adjusting for sex, age, BMI, current smoking, pre-existing CVD, pre-existing stroke, statins, and laboratory tests (Table 3), compared to group 0, groups 1, 2, and 3 had a 0.91 (95% CI 0.54~1.55), 1.39 (95% CI 0.75~2.55), and 1.93 (95% CI 1.03~3.61) higher risk for PDRP, respectively (using model 3). Diabetes plus a low level of HDL was significantly associated with a higher risk (HR=1.93, 95% CI 1.03~3.61, $p=0.0404$) for the first episode of PDRP. The subgroups of sex, age, and pre-existing CVD are shown in Figure 3. P values for the interactions were >0.05 for subgroups by gender ($p=0.0716$), age ($p=0.0599$) and pre-existing CVD ($p=0.9279$).

Table 3
Association among DM and Low HDL-C and the first episode of peritonitis

	Model 1*		Model 2†		Model 3‡	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
No comorbidity	1.0(ref.)		1.0		1.0	
Low HDL-C	0.76 (0.58, 0.98)	0.0374	0.74 (0.56, 0.97)	0.0318	0.91 (0.54, 1.55)	0.7303
DM	1.43 (0.97, 2.11)	0.0724	1.32 (0.86, 2.01)	0.2023	1.39 (0.75, 2.55)	0.2939
DM plus Low HDL-C	1.86 (1.25, 2.76)	0.0021	1.69 (1.09, 2.62)	0.0201	1.93 (1.03, 3.61)	0.0404
HR, hazard ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.						
*Unadjusted.						
†Model 1 plus age, sex, body mass index, current smoking, Pre-existing stroke, Pre-existing cardiovascular disease.						
‡model 2 plus hemoglobin, serum albumin, cholesterol, triglyceride, low-density lipoprotein, aspartate aminotransferase, aspartate aminotransferase, intact parathyroid hormone, Statins and Serum potassium.						

Discussion

The rate of diabetes in patients with PD was 16.5% in our study. It is similar to previous literature reports. The cause of ESRD was diabetic nephropathy in 16.4% of patients in China ¹². We found that in 44.03% of patients, serum HDL-C levels decreased during the course of our study. A total of 7.1% of diabetic patients also had low HDL-C levels in our study. We found that low HDL-C levels alone or diabetes alone were not independently associated with the first episode of PDRP in patients. Diabetes and concurrent Low HDL-C levels were associated with the first episode of PDRP in patients with PD in our study.

It is reported that the PDRP rate was higher in DM patients than in non-DM patients ¹³. Diabetes alters the immunity of peritoneal defences, such as leukocyte adherence, chemotaxis, and phagocytosis. Diabetes also interferes with the migration of phagocytic cells into the peritoneum and suppresses the phagocytic activity of resident peritoneal macrophages ¹⁴. Not all study supported the conclusion. Some studies found that diabetes was not an independent risk factor for PDRP ^{15 16}. Hyperglycaemia was reported to be a predictor of risk for tunnelled catheters and existing infections but not for peritoneal infections ¹⁷. Diabetes was not an independent risk factor for PDRP in our study. Low HDL-C levels were seen in diabetes patients. Lack of apo AI and apo AII and increased clearance of HDL are the main reasons for low HDL-C levels in diabetes. HDL plays an important role in fighting infection in many ways. HDL binds

and neutralizes gram-negative bacterial lipopolysaccharide (LPS) and gram-positive bacterial lipoteichoic acid (LTA). HDL inhibits adhesion molecule expression induced by proinflammatory cytokines after inflammation, such as V-CAM-1, ICAM-1, and E-selectin. HDL may also prevent monocyte activation and recruitment. As a result, the inflammatory response decreases after sepsis. HDL limits oxidation by decreasing ROS production and inhibiting LDL oxidation. Low HDL levels lead to a decrease in antioxidation and exacerbate damage from infection¹⁸. Low HDL levels are a risk factor for foot infection in diabetic foot osteomyelitis¹⁹. Low HDL levels were also associated with parasitic disease and Mycobacterium tuberculosis infection in diabetic patients^{20 21}. Finally, low HDL levels were seen in periodontal infection in diabetic patients²². All these reports demonstrated that diabetes coexisting with low HDL-C levels were associated with infection. HDL-C binds to pathogenic microorganisms and reduces inflammatory damage in diabetes. PDRP is a typical bacterial infection in patients with PD. Diabetes plus low HDL-C levels increased the risk for PDRP in patients with PD in our study. The K-M curves confirmed the result. It is therefore important to maintain normal serum HDL levels in diabetic patients with PD.

PD patients usually show increased levels of triglycerides (TGs), cholesterol (CHOL), and low-density lipoprotein - cholesterol (LDL-C) and decreased levels of HDL -C²³. Since disorders of HDL-C are associated with severe infection and exaggerate the systemic inflammatory response^{24 25 26}, we analysed the association between HDL-C level and PDRP in patients with PD. We found low HDL-C levels were not independently associated with PDRP in PD patients in our study. The reason might be that dyslipidaemia is a complicated process in patients with PD. Disorders of TG, CHOL and LDL-C also participate in the pathological process of PDRP. Low HDL-C levels alone were not enough to be an independent risk factor for PDRP in our study.

In previous studies, dyslipidaemia and poor glycaemic control were reported to be risk factors for ESRD and mortality in young patients and women²⁷⁻²⁹. HDL-C was inversely associated with left ventricular mass index in patients with PD³⁰. Subgroups of age, sex, and history of cardiovascular disease were analysed in our study. We found that the association between DM plus low HDL-C levels and PDRP was not affected by age, sex, or history of cardiovascular disease after adjusting for age, sex, body mass index, current smoking, Pre-existing stroke, Pre-existing CVD, Statins and laboratory tests except the subgroup variable. We confirmed that DM plus low HDL levels is an independent risk factor for PDRP in patients with PD.

Our study has several limitations: 1. our study is a retrospective, multicentre study that possible had selection bias; 2. our study only looked at the association between DM plus a low level of HDL-C and PDRP. We could not determine the causality relationship between DM plus low HDL-C and PDRP; 3. TG, CHOL, and LDL-C levels were associated with HDL-C levels, and we should detect the detailed relationship between TGs, CHOL, LDL-C, and HDL-C in patients with PD and evaluate the effect of the interaction between HDL-C and other lipids on PDRP.

Conclusions

This study showed that either a low HDL-C level or diabetes was not an independent risk factor for the first episode of PDRP in patients with PD. However, diabetes concurrent with low HDL-C levels were associated with the first episode of PDRP in patients with PD. It is important to maintain normalization of HDL-C levels in diabetic patients with PD to avoid PDRP.

Abbreviations

ALT: alanine aminotransferase

ANOVA: analysis of variance

AST: aspartate transaminase

CHOL: cholesterol

CI: confidence intervals

CVD: cardiovascular disease

DM: diabetes mellitus

ESRD: end-stage renal disease

HbA1c: glycosylated hemoglobin, type A1C

HDL: high-density lipoprotein

HDL-C: high-density lipoprotein-cholesterol

HR: hazard ratio

IQR: interquartile range

K-M: Kaplan-Meier

LDL: low-density lipoprotein

LDL-C: low-density lipoprotein-cholesterol

OGTT: oral glucose tolerance test

PD: peritoneal dialysis

PDRP: peritoneal dialysis-related peritonitis

SD: standard deviation

TG: triglyceride

WBC: white blood cell

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines detailed in the Declaration of Helsinki, and all procedures involving patients were approved by The Sixth Affiliated Hospital of Sun Yat-sen University (No. 2021ZSLYEC-177). Written informed consent was not required for this article because we retrospectively collected medical records available in the hospital, also approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-Sen University.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Dongguan Science and Technology Major Project, 201950715046196.

Authors' contributions

Ya-Juan Huang and Rui Zhang designed of the entire study. Xing Zhang summarized and analyzed the data. Ning Su provided guidance on this study. Xing-ming Tang, Li-wen Tang, Si-jia Shang, Xiao yang Wang, Yue-qiang Wen, Xiao-ran Feng, and Qian Zhou were responsible for data acquisition.

Acknowledgements

We thank all the doctors and nurses at the peritoneal dialysis centers. We thank all patients with PD who participated and provided data for the study.

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Figures

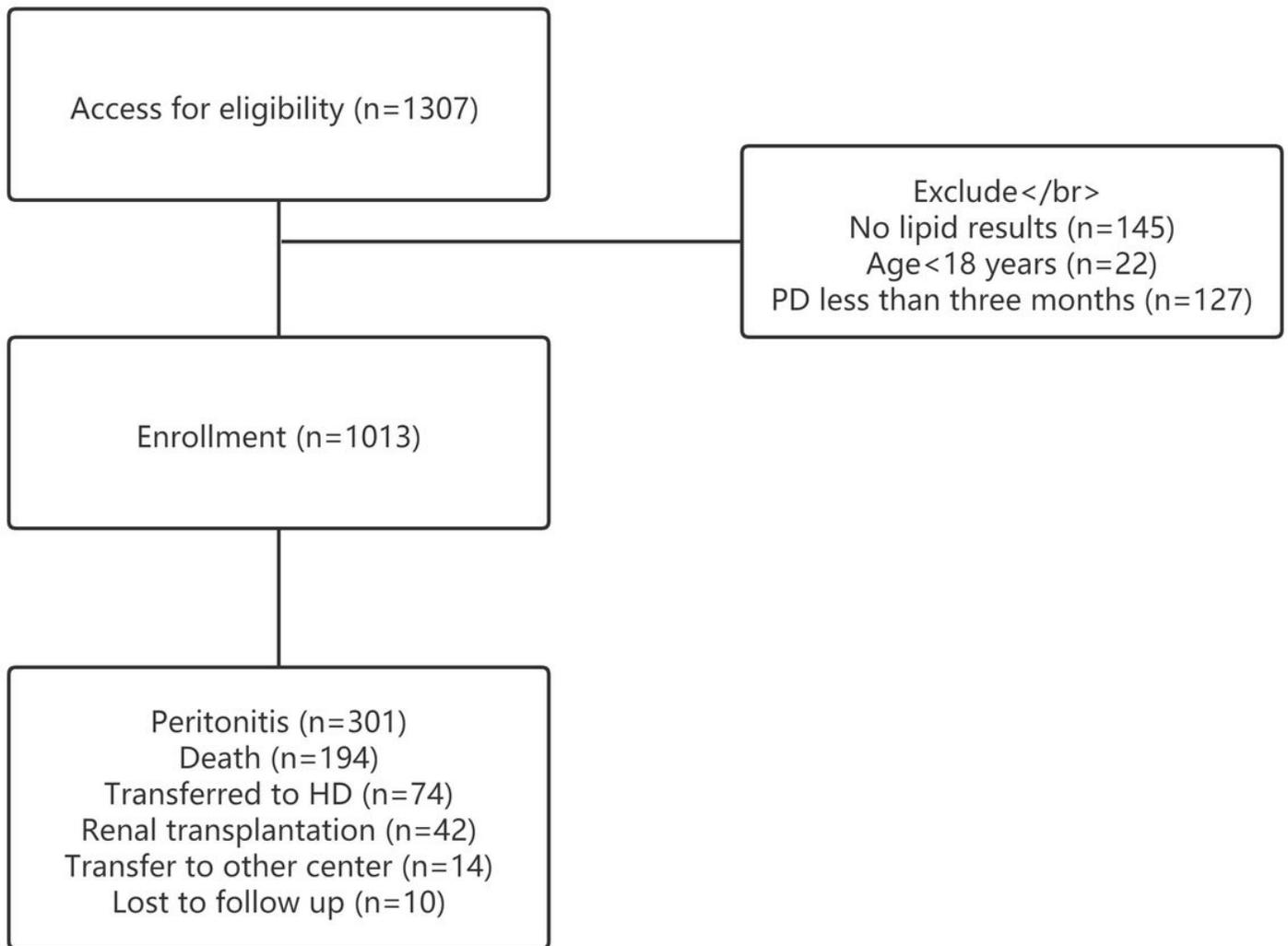
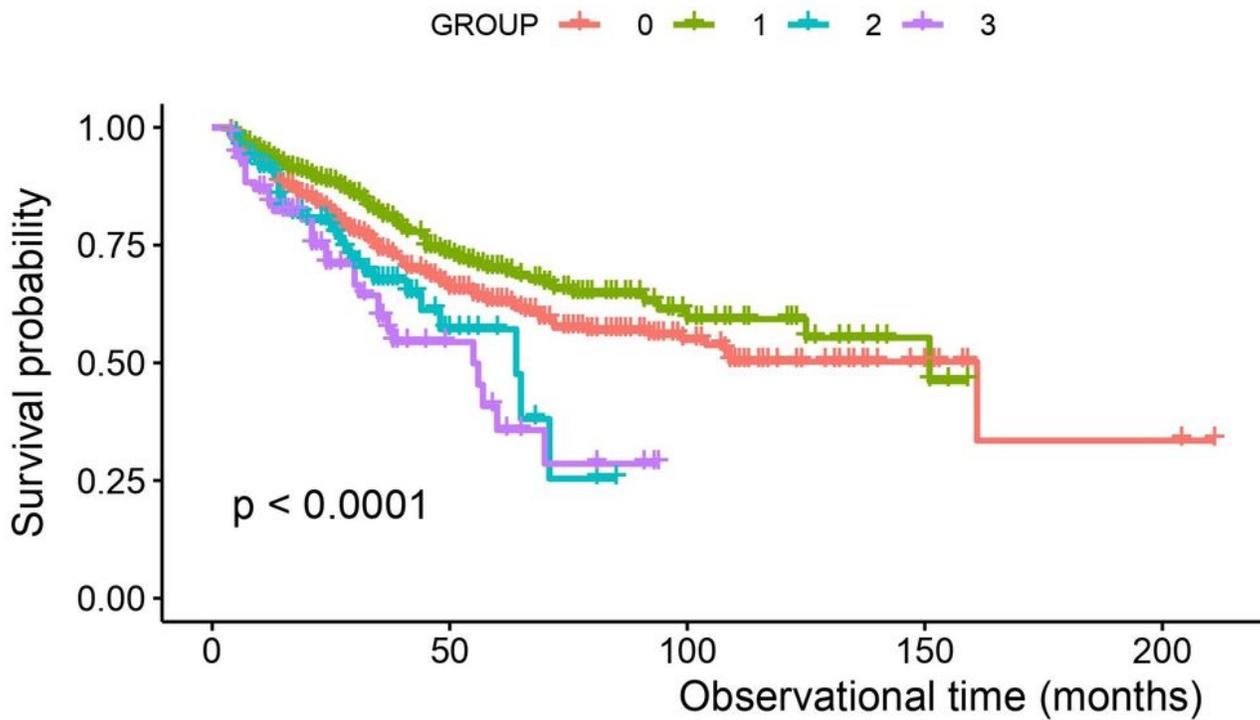


Figure 1

Legend not included with this version.



Number at risk

GROUP	0	50	100	150	200
0	472	173	52	9	2
1	374	121	31	6	0
2	95	13	0	0	0
3	72	12	0	0	0

Figure 2

Legend not included with this version.

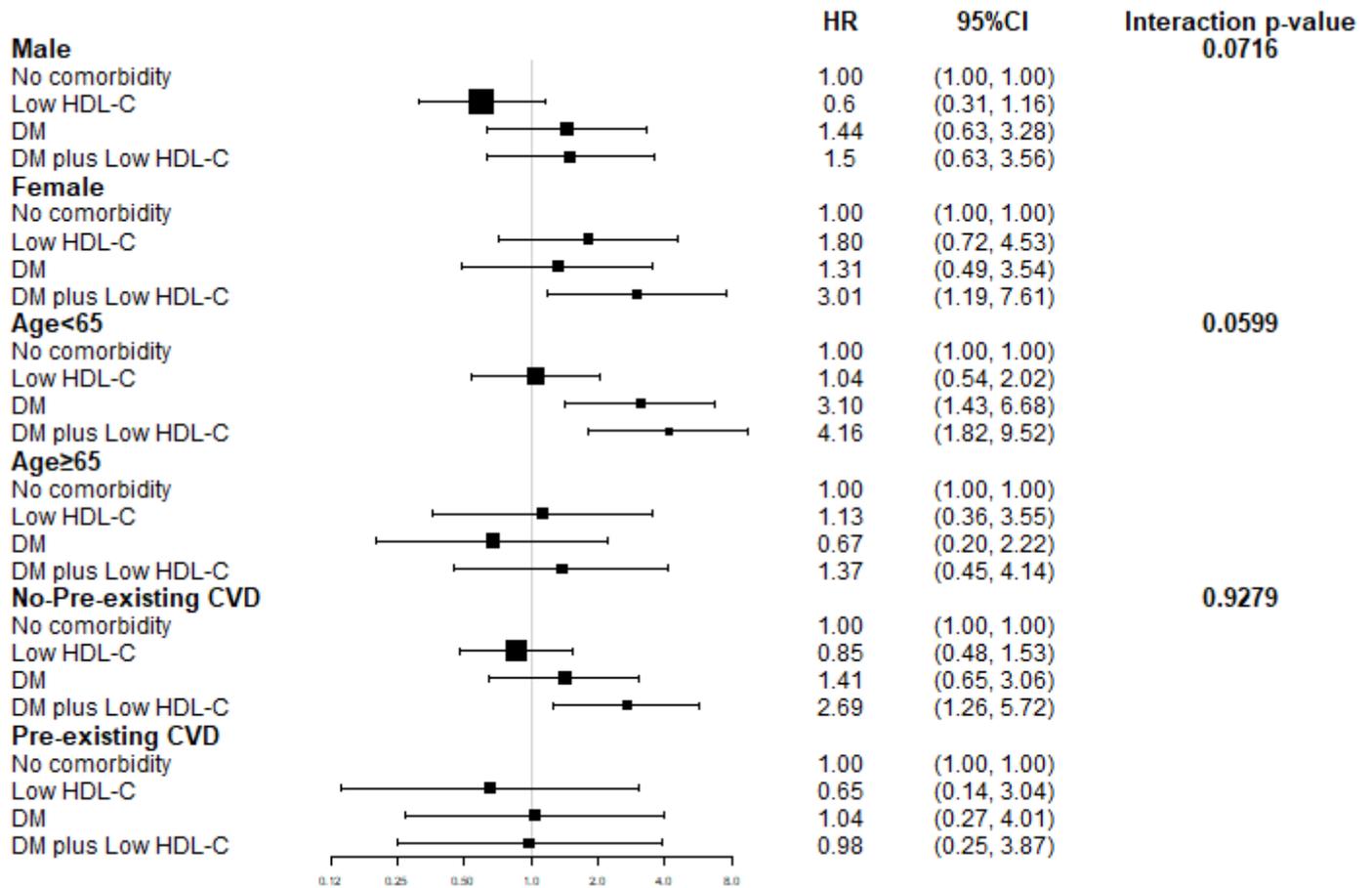


Figure 3

Legend not included with this version.