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Summary at a Glance -

Peripheral arterial disease is shown to impact on the decline in residual renal function in PD patients in this paper. The authors used the ankle-brachial index to determine the presence of PVD and have assumed this reflects generalised vascular disease.

Relation of ankle-brachial index to the rate of decline of residual renal function in peritoneal dialysis patients

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Running title: ABI and residual renal function

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Abstract

Objective: The aim of this study was to determine whether ankle-brachial index (ABI) predicts the rate of decline of residual renal function (RRF) in peritoneal dialysis (PD) patients.

Background: Previous studies demonstrated the importance of loss of RRF in predicting all-cause risk and cardiovascular mortality in PD patients. It is also known that patients with a low ABI value have a greater risk for deteriorating renal function in the general population. The relationship between ABI and the declining rate of RRF in PD patients with an additional dialysis-specific risk factor is uncertain.

Methods: Seventy-four PD patients with RRF > 1 mL/min/1.73m^2 were analyzed. ABI was used as the surrogate measure of pre-existing cardiovascular disease and atherosclerosis

burden to further determine the outcome of RRF in this study. The slope of decline of RRF was used to determine the outcome.

Results: Based on the multivariate analysis, only ABI ($P < 0.001$), diabetes ($P = 0.02$) and baseline RRF ($P = 0.009$) independently predicted a faster decline in RRF. A stepwise multiple linear regression analysis demonstrated that ABI was an independent predictor for the slope of decline of RRF ($P < 0.001$).

Conclusion: A low ABI is an independent predictor of not only the known atherosclerotic events, but also of the rate of decline of RRF over time in PD patients.

KEY WORDS: ankle-brachial index, atherosclerosis, peritoneal dialysis, residual renal function.

INTRODUCTION

Preservation of residual renal function (RRF) may be the key factor to improve survival and cardiovascular outcomes in peritoneal dialysis (PD) patients[1-3]. Previous studies showed the importance of RRF not only in providing small-solute clearance, but also in maintaining cardiovascular health, nutritional status, and quality of life of PD patients[3-6]. Therefore, it is important to search for factors that influence the rate of decline of RRF in these patients. In a previous study, a strong independent association between inflammation and progressive peripheral atherosclerosis in the general population was reported[7]. On the other hand, it has also been revealed that there is an association between inflammation and changes in RRF in PD patients[8]. Whether peripheral atherosclerosis is still playing an important role in influencing the rate of decline of RRF over time in this population is unanswered.

The ankle-brachial index (ABI), which is the ratio of ankle to brachial systolic blood pressure, provides a simple, non-invasive, useful method for assessing subclinical peripheral vascular disease[9,10]. A low ABI indicates the presence of flow-limiting atherosclerosis in a peripheral artery and likely reflects the presence of generalized atherosclerosis. Therefore, it has been reported that a low ABI may be an important marker for systemic atherosclerosis[11,12]. A low ABI has also been reported as a marker for prediction of a decline in renal function over time in the general population[13]. In this study, the ABI is used as the surrogate measure of pre-existing cardiovascular disease for further determination of outcome of RRF. The

association between ABI value and the rate of decline of RRF in PD patients has not been studied before. The purpose of this study was to assess the association between a single time point ABI value and the rate of decline of RRF over time in PD patients.

METHODS

Study design and patients

This observational study was conducted in the dialysis center at the China Medical University Hospital in Taiwan from April 2005. All patients who fulfilled the following inclusion criteria were considered for enrollment into the study: patients who received regular PD at least for 3 months before entry. Moreover, patients had to be clinically stable for 3 months before entry without infections or other active diseases. Patients were asked to collect 24-hour urine and dialysate in the morning of their assessment to measure urea and creatinine concentration at the first study visit. Adequacy of dialysis was determined by measuring urea clearance (K/t/V urea) and creatinine clearance (CrCl). Urea and creatinine clearance were also normalized to 1.73 m^2 of body surface area. Residual glomerular filtration rate (GFR) was calculated as an average of the 24-hour urea and creatinine clearance[14]. Dialysate creatinine concentration was corrected for glucose interference according to the reference formula determined in our laboratory. Patients were included if they had a residual GFR > 1 mL/min/1.73m^2 before study entry. Included patients were selected from the PD centre. All patients signed an informed consent prior to inclusion into the study. Patients were requested to visit the outpatient department of the PD centre every month for dose adjustment of PD and medications according to clinical investigations and laboratory parameters. The PD therapeutic protocols were not influenced in this study and each patient's treatment was

independently adjusted by the patient's attending physician. Most of the patients had four exchanges per day, using the Dianeal solution (Baxter Healthcare, Singapore) with various glucose concentrations depending on the clinical situation. Icodextrin (Baxter Healthcare, Singapore), administered at night, was added to the prescription in patients with inadequate ultrafiltration. The study was approved by the institutional review board of the hospital.

Data collection

All data were based on information from hospital records and dialysis logs. Demographic information including age, gender, comorbid conditions, underlying disease, duration of PD and presence of diabetes mellitus were obtained at study baseline. Blood, urine, and dialysate samples were collected in order to calculate residual GFR, Kt/V urea and CrCl at study visits. Diabetes was defined as diagnosed by physician, use of diabetes medication, fasting glucose of > 126 mg/dL (7.0 mmol/L), or non-fasting glucose of > 200 mg/dL (11.1 mmol/L). Medication history was also reviewed in studied subjects. Individuals were classified as non-medication (no use, intermittent use, and/or withdrawal of medication) and medication (regular medication throughout the follow-up period). Blood samples were taken in the morning after an overnight fast of at least 12 hours. All of the biochemistries were determined with an automated clinical chemistry analyzer. Patients' clinical and laboratory data before dialysis and after initiation of the PD were collected retrospectively.

ABI measurement

ABI measurements were performed in a supine position and blood pressure was measured in both arms (brachial arteries) and both legs (posterior tibial arteries). Two readings were recorded 10 minutes apart. The mean of the 2 readings taken in the ankles and arms was used for ABI calculation. The ABI value was calculated by dividing systolic blood pressure either in the right or left ankle by systolic blood pressure in the arm. We calculated the ABI of each leg, and used the average of the two values as the clinical indices.

Estimated residual GFR over time and endpoint

Timed urine collections were performed initially and at 3-month intervals during the study to measure RRF in study patients. The mean slope of the decline of residual GFR was the main outcome measure in this study. The first endpoint was defined as the time when patients were treated with intravenous aminoglycosides, when radiocontrast media were used, when diuretics were used, peritonitis episode, and development of shock status during the study period. Patients who developed complete anuria were censored at the time of development for the outcomes analyses. The second endpoint was censored as 1-year follow-up in remaining patients.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, Illinois, USA). Continuous data were expressed as mean ± SD. The Student t test

was used when data were normally distributed; otherwise, the non-parametric Mann-Whitney U test was used. The decision of tests used for comparison of continuous data was based on the test for normality by the Shapiro-Wilk test. Categorical data were compared by a chi-square test if the observation numbers in all categories were larger than 5; otherwise, the Fisher exact test was used. A receiver-operating characteristic curve analysis and Youden index were used to determine the best cutoff point, which maximized the sum of sensitivity and specificity for predicting groups with faster decline of RRF. Factors independently associated with the rate of decline of RRF were explored by a multiple linear regression model, with forward stepwise selection. To analyse the correlation between ABI and the slope of RRF, a simple linear regression method was used.

RESULTS

A total of 84 suitable PD patients were identified at baseline. Ten patients were excluded due to peritonitis (n = 7), aminoglycoside and diuretic use (n = 2), and development of shock whilst hospitalized (n =1) during the study period. The remaining 74 patients (42 women and 32 men) with a mean age of 54.6 ± 14.2 years at study entry were enrolled. The mean residual GFR was 2.95 ± 1.45 mL/min/1.73m^2 in included patients at baseline. The ABI was not significantly different between both sides (right ABI vs left ABI = 1.08 ± 0.15 vs 1.07 ± 0.14; $P > 0.05$). Be comparative analysis, patients with a faster decline rate of RRF were more likely to be older, diabetic, have a higher baseline GFR and a lower ABI value (Table 1). Decline of RRF was not linked to gender, duration of PD, adequacy of dialysis, peritoneal membrane characteristics, total cholesterol, serum triglycerides, hematocrit, corrected serum calcium, serum phosphorus, uric acid level, serum albumin, and medication history [statin, angiotensin-coverting enzyme inhibitor or angiotensin receptor blocker (ACEI or ARB), and antiplatelet agent]. After incorporating the significant variables ($P < 0.05$) into a multivariate logistic regression model, only ABI ($P < 0.001$), diabetes ($P = 0.02$) and baseline residual GFR ($P = 0.009$) independently predicted a faster decline of RRF (Table 2).

On the basis of the receiver-operating characteristic curve, the most appropriate cutoff point for ABI to predict a faster rate of decline of RRF was 1.18 [sensitivity 56.8%; specificity 94.6%; area under the curve (AUC) = 0.792]. The most appropriate cutoff point for baseline GFR was 2.88 mL/min/1.73m^2 (sensitivity 64. 9%; specificity 70.3%; AUC =

0.666). Of the 74 patients, 50 patients with an ABI value < 1.18 showed significantly higher prevalence of faster decline of RRF compared to the other 24 patients who had an ABI ≥ 1.18 (68.0% vs 12.5%, P < 0.001). Forty patients with higher baseline GFR (≥ 2.88 mL/min/1.73m^2) demonstrated a higher prevalence of faster decline of RRFcompared to the other 34 patients who had lower baseline GFR (< 2.88 mL/min/1.73m^2)(65.0 % vs 32.4%, P = 0.005). When subgroup comparisons were made in patients with different diabetic status and ABI values, patients with higher ABI and non-diabetes had a significantly lower prevalence (2/21, 9.5%) of faster decline of RRF compared to diabetics, higher ABI (2/4, 50.0%, P = 0.106); non-diabetes, lower ABI (20/36, 55.6%, P = 0.001); and diabetes, lower ABI patients (13/13, 100.0%, P < 0.001) (Figure 1). When comparisons were made in subgroups with different status of baseline residual GFR and ABI values, patients with higher baseline GFR and lower ABI had a significantly higher prevalence (23/27, 82.4%) of faster decline of RRF compared to lower baseline GFR, higher ABI (0/11, 0%, P < 0.001); higher baseline GFR, higher ABI (2/12, 16.7%, P < 0.001); and lower baseline GFR, lower ABI patients (12/24, 50.0%, P = 0.014) (Figure 2).

Figure 3 shows the univariate correlation plots of ABI values against the slope of RRF. This correlation was statistically significant (r = 0.512, P < 0.001). Stepwise multiple linear regression analysis demonstrated that diabetes, ABI and baseline residual GFR were independent predictors of the slope of decline of RRF (Table 3).

DISCUSSION

The results from this study demonstrated the usefulness of ABI values in predicting the rate of decline of RRF, independent of age, diabetes and baseline residual GFR in PD patients. The lower the ABI value, the greater the increased risk of the rate of decline of RRF. To our knowledge, the analyses in this report are the first to demonstrate the association between low ABI values and an increased rate of decline of RRF in PD patients. This study demonstrated that, in additional to its previously demonstrated association with an increase in serum creatinine level over time in the general population[13], a low ABI is also associated with an increased rate of decline of RRF in PD patients. A low ABI is a specific measure of overall atherosclerotic burden and is also an indicator of generalized atherosclerosis, because lower levels have been associated with higher rates of concomitant coronary and cerebrovascular disease, and with the presence of cardiovascular risk factors[15-18]. The existence of a relationship between baseline ABI and subsequent rate of decline of RRF supports the concept that pre-existing atherosclerosis may be a risk factor for faster decline of RRF over time. Furthermore, the strong association between ABI and the rate of decline of RRF in both unadjusted and adjusted models highlights the possible importance of ABI measures as a means to identify patients at higher risk for rapid decline of RRF on PD.

It is well known that RRF may be preserved longer in patients on PD than those on

hemodialysis[19]. It has also been recognized that preservation of RRF was associated with a favorable outcome in PD patients[1,20,21]. Hence, it is important to identify factors which are associated with preservation of RRF and consider interventions to correct the modifiable factors that can improve preservation of RRF. Many investigators have reported that some factors such as nephrotoxic agents, the use of radiocontrast media, peritonitis, diabetes, hypotensive events, high baseline GFR, and pre-existing cardiovascular disease may influence the preservation of RRF[22-26]. In this study, these confounders were controlled through detailed review of dialysis charts and study design as far as possible. ABI was used as the surrogate measure of pre-existing cardiovascular disease and atherosclerosis burden to further determine the outcome of RRF in this study, which is different to other previous studies[22-26].

The kidney contains a highly consistent vascular network whose function is dependent on an intact circulation system. Thus, systemic atherosclerosis is likely to be a risk factor for decline in renal function[27]. Atherosclerosis has direct effects on the kidney, largely because of intrarenal microvascular and glomerular disease that precedes the onset of renal disease and represents the silent phase of ischemic renal disease[28,29]. In turn, progressive deterioration of renal function in chronic kidney disease may lead to production of free radicals. These free radicals can activate proinflammatory and fibrogenic factors, leading to vascular endothelial cell dysfunction and injury, favoring

development of atherosclerosis[30]. Many studies have reported both cross-sectional and longitudinal relationships between renal insufficiency and cardiovascular events[31-34]. Therefore, the kidney can be a villain or a victim during atherosclerosis as previously documented[30]. Most papers reported the association between loss of RRF and cardiovascular events or mortality in end-stage renal disease patients on PD[1-5]. The trend of atherosclerosis accelerated decline of RRF is rarely reported in PD patients. Whether the relationship of atherosclerosis is associated with exacerbation of the decline of RRF with mixed dialysis-specific factors in PD patients is still unanswered. While the association reported herein between low ABI and accelerated decline of RRF in PD patients. It may reflect a shared risk factor for the decline of renal function regardless of an additional dialysis-specific risk is added or not. Atherosclerosis may be contributed due to hypertension, hypervolemia, lipid abnormality, divalent ion changes, inflammatory processes and hyperhomocysteinemia in PD patients. Therefore, a possible explanation may be that atherosclerosis is also positively associated with declining RRF in PD patients, similar to general population.

It is important to note that the present study had a modest sample size. A large cohort of PD patients need to be studied and should be explored further. Secondly, our analysis did not include newly diagnosed PD patients. Whether the result is still consistent in those patients is still unanswered in the present report. Thirdly, whether overt peripheral arterial

disease is associated with a faster decline of RRF in PD patients is still unknown. We believe that the association between overt peripheral arterial disease and the rate of decline of RRF in PD patients is worthy of further investigation with a longitudinal, prospective, randomized trial. Fourthly, it has been reported that ACEI and/or ARB may reduce the rate of decline of RRF in PD patients[35]. Our data showed no effect of ACEI and/or ARB in rate of decline of RRF in PD patients. Because 10 patients had intermittent use or withdrew ACEI and/or ARB, they were classified as non-ACEI and/or ARB users during the study period according to the decision of their attending physicians. This decision may cause bias in determining the exact effect of ACEI and/or ARB in RRF in our patients studied. Finally, we did not measure blood pressure at the dorsalis pedis artery. It is usual practice to select the higher of the two ankle readings for each leg (posterior tibial artery or dorsalis pedis artey) to calculate ABI; thus, it may be a cause of bias in our study.

In conclusion, a low ABI is independently predictive not just of atherosclerotic events, but also of the rate of decline of RRF over time in PD patients. This finding supports the notion of atherosclerosis as a risk factor for decline of RRF in PD patients. Whether improved preservation of a high ABI value will slow down the rate of progression of decline of RRF in PD patients requires further determination.

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Figure Legend

Fig. 1. Comparison of the prevalence of the faster decline of residual renal function among patients with different status of diabetes and ankle brachial index.

*P = 0.106, **P = 0.001, ***P < 0.001 compared with patients with non-diabetes plus higher ankle brachial index

Figure legend

Fig. 2. Comparison of the prevalence of the faster decline of residual renal function among patients with different status of baseline residual glomerular filtration rate (GFR) and ankle brachial index. * $P < 0.001$, ** $P < 0.001$, *** $P = 0.014$ compared with patients with higher baseline residual GFR plus lower ankle brachial index

Figure legend

Fig. 3. Correlation of ankle brachial index to the rate of decline of residual renal function in our peritoneal dialysis patients.

Table 1 Clinical characteristics of the study subjects with faster and slower decline of residual glomerular filtration rate

	Faster (n = 37)	Slower (n = 37)	P value
Slope of residual GFR (mL/min/1.73m^2/month)	-0.167 ± 0.050	-0.062 ± 0.032	< 0.001*
Baseline residual GFR (mL/min/1.73m^2)	3.30 ± 1.40	2.60 ± 1.43	0.039*
Age (yrs)	58.9 ± 13.6	50.3 ± 13.6	0.008*
Gender (male/female)	12/25	20/17	0.10†
Duration of peritoneal dialysis (months)	22.6 ± 15.6	19.7 ± 14.4	0.402*
DM (yes/no)	14/23	2/35	0.001‡
Total Kt/V	2.05 ± 0.32	2.08 ± 0.36	0.700*
Total WCrCl (L/week/1.73m^2)	58.4 ± 12.7	65.5 ± 15.1	0.217*
D/P creatinine	0.67 ± 0.10	0.65 ± 0.12	0.498*
Ankle brachial index	0.99 ± 0.20	1.16 ± 0.09	< 0.001*
Cholesterol (mg/dL)	209.8 ± 43.1	195.9 ± 35.5	0.125$
Triglyceride (mg/dL)	215.6 ± 121.9	168.6 ± 86.5	0.166$
Hematocrit (%)	27.2 ± 3.3	27.4 ± 2.5	0.767*
Ca (mg/dL)	9.4 ± 1.1	9.3 ± 0.7	0.789*
P (mg/dL)	5.7 ± 1.3	5.2 ± 1.3	0.116*
Uric acid (mg/dL)	6.4 ± 0.9	6.2 ± 1.2	0.387*
Albumin (g/dL)	3.5 ± 0.4	3.7 ± 0.4	0.084*
Medication			
Statin (n)	3	6	0.479‡
ACEI or ARB (n)	14	13	0.809†
Antiplatelet (n)	5	8	0.543‡
Icodextrin use (n)	7	6	0.760†

ACEI = angiotensin-coverting enzyme inhibitor; ARB = angiotensin receptor blocker; Ca = serum total calcium; DM = diabetes mellitus; D/P = dialysate/plasma; GFR = glomerular filtration rate; Kt/V = urea clearance normalize to its volume of distribution; P = serum phosphorus; WCrCl = weekly creatinine clearance.

*Student t test; †Chi-square test; ‡Fisher exact test; $Mann-Whitney U test.

Table 2 Multivariate logistic regression analysis for group of faster decline of residual glomerular filtration rate

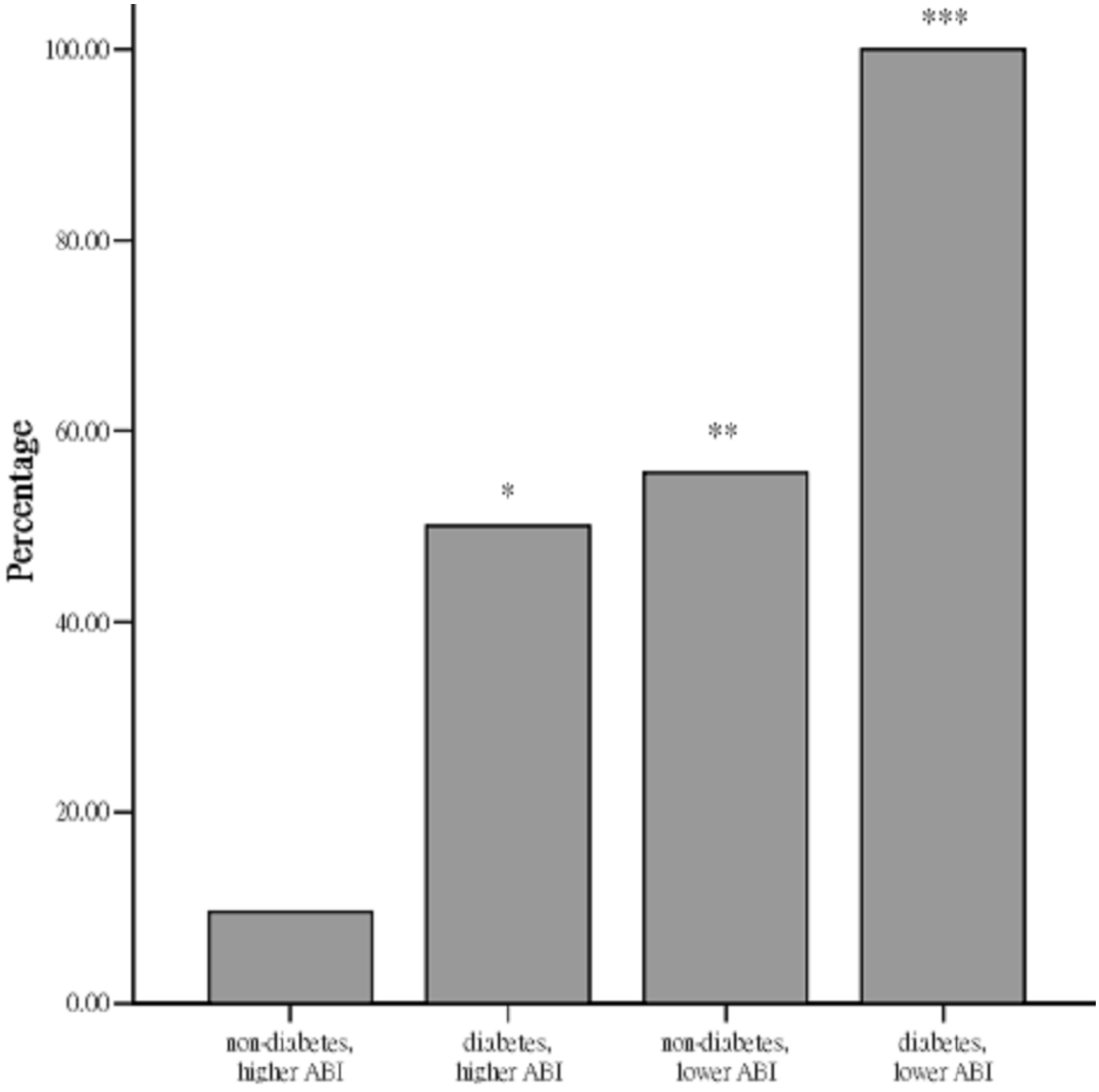
Variable	P value	Odds Ratio	95 % Confidence Interval	
			Lower	Upper
Ankle brachial index (per 0.01 unit increase)	< 0.001	0.896	0.840	0.955
Diabetes mellitus (yes vs no)	0.020	9.090	1.425	57.983
Baseline GFR (per mL/min/1.73m^2 increase)	0.009	1.968	1.184	3.270
Age (per year increase)	0.451	1.018	0.971	1.068

GFR = glomerular filtration rate.

Table 3 Multiple linear regression model of the slope of decline of residual glomerular filtration rate (minus value)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	P value
	B	Standard Error	Beta		
Constant	-0.247	0.036		-6.291	< 0.001
Diabetes mellitus	-6.70×10^{-2}	0.014	-0.410	-4.894	< 0.001
Ankle brachial index	0.180	1.968	0.473	5.494	< 0.001
Baseline GFR	-0.590×10^{-2}	1.018	-0.342	-4.142	< 0.001

GFR = glomerular filtration rate.



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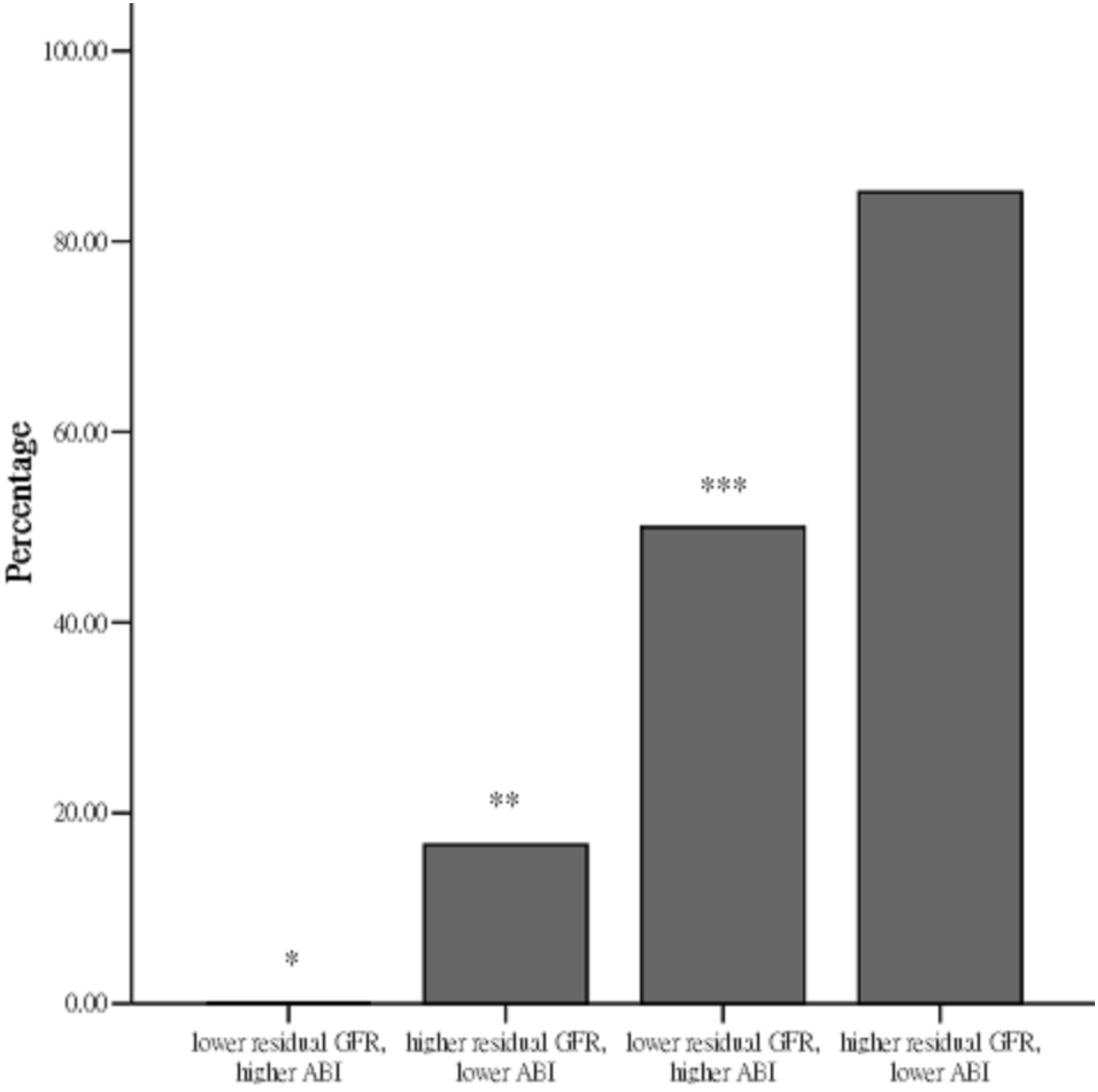

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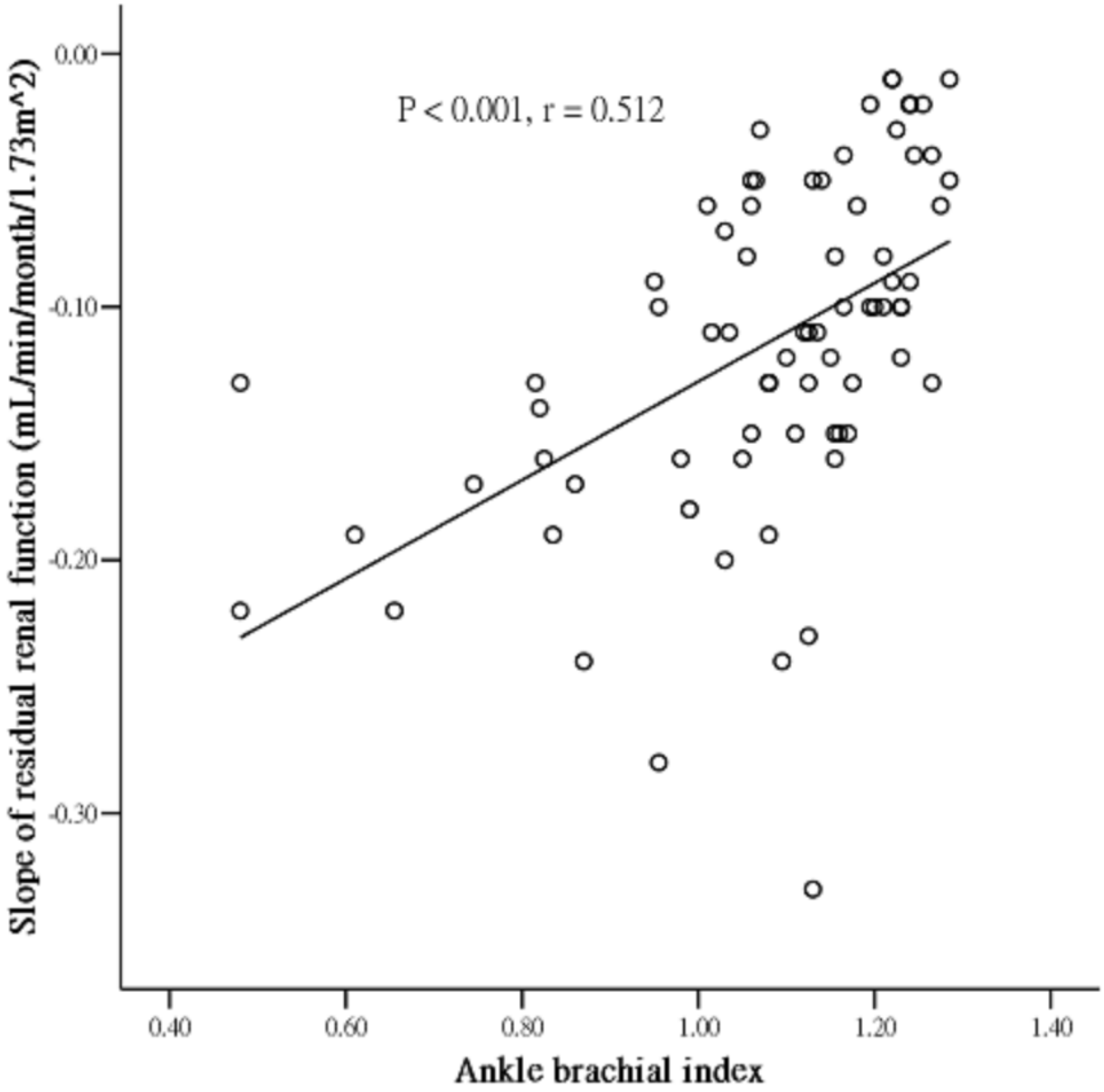

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