The ability of phase angle to predict death risk factors in maintenance hemodialysis patients

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Research Article

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Abstract

Objectives: To investigate the ability of phase angle and body composition to predict the death risk factors of maintenance hemodialysis (MHD) patients.

Methods: We studied the cause of death in 43 MHD patients treated at our hemodialysis center between January 2016 and December 2021 and compared them with the 71 patients who survived. Body composition was measured using direct segmental multifrequency bioelectrical impedance to obtain phase angle, fat-free mass(FFM), extracellular water/total body water(ECW/TBW), and waist circumference (WC). Laboratory test data were collected. Phase angle cut-off value associated variables were calculated using ROC analysis. The ability of body composition variables to predict death risk factors in MHD patients was evaluated.

Results: The most common cause of death was cardiovascular disease. ROC curve analysis showed that the optimal cut-off values for phase angle as death risk factors in MHD patients was 4.50°. Moreover, in MHD patients, lower phase angle, aging and hypoproteinemia are death risk factors.

Conclusion: Cardiovascular disease is the most common cause of death in MHD patients. Lower phase angle, aging, and hypoproteinemia can indicate risk of death in MHD patients. The potential mechanism of lower phase angle to predict the prognosis of MHD patients.

Introduction

The rate of chronic kidney disease (CKD) is rising worldwide[1]. With the delay and progression of the disease, some CKD patients develop end-stage renal disease (ESRD). ESRD patients need high medical resources for renal replacement therapy (RRT) and management of complications, resulting in heavy economic burden. Hemodialysis is a key RRT strategy. A key goal for nephrologists is to reduce the mortality rate, improve long-term survival, reduce medical costs, improve the quality of life, and minimize economic burden for hemodialysis patients as much as possible[2]. Recent studies have reported the application of bioelectrical impedance to a variety of chronic diseases and prognostic indicators in MHD patients[3–5]. Phase angle, a key indicator of bioelectrical impedance significantly correlates with prognosis in various diseases. Although some studies indicate that phase angle level has good correlation with the survival of chronic disease patients[6, 7], others have reported correlation between phase angle and risk of death in MHD patients. Here, we investigated the effect of phase angle level on the prediction of death risk factors in patients undergoing MHD.

Methods And Materials

Methods study design and participants

This study involved 196 patients who underwent regular hemodialysis at Shenzhen Traditional Chinese Medical Hospital, Guangdong Province, China, from January 2016 to June 2016. Follow-up data were collected from January 2016 to December 2021. Additional inclusion criteria were: 1) at least 2 dialysis days/week, and 2) a dialysis duration of ≥ 3 months. Exclusion criteria were: 1) missing baseline or follow-up data, and 2) having cancer (Fig. 1).

Data collection

Data collection and measures General information, medical histories, and laboratory data were collected by physicians. Direct segmental multi-frequency bioelectrical impedance technology was used to analyze body composition (InBody S10, Shanghai, China) and to obtain the phase angle, fat-free mass (FFM), extracellular water/total body water (ECW/TBW), body mass index (BMI), and waist circumference (WC). Phase angle was obtained at a frequency of 50 Hz. The study adhered to the guidelines of the Declaration of Helsinki. The study was approved by the human research ethics committees of the involved hospitals. Investigators or persons authorized by the investigators explained the benefits and risks of trial participation to all study participants or their legal representatives or notaries. Trial data were stored in a safe in the office of the first author, who performed all statistical analyses.

Biochemical analysis Serum samples were drawn at MHD commencement and analyzed locally. For all patients, serum creatinine (Cr), serum uric acid (UA), urea nitrogen (BUN), serum albumin (ALB), serum potassium (K), phosphorus (P), hemoglobin(HB), total cholesterol (TC), HDL-C, triglyceride (TG), and LDL-C, were measured.

Statistical analyses Statistical analyses were done on SPSS 22.0. Measurement data are presented as mean ± SD. T-test was used to compare differences between groups with normally distributed data. Rank sum test was used to compare differences between groups with non-normal data distribution. Differences between data groups expressed as proportions were compared using the $\chi 2$ test. Using a receiver operating characteristic curve (ROC) and area under the curve (AUC), cutoff values were calculated. Using the optimal ROC cut-off values, chi-square analysis was done and odds ratio and 95% confidence interval (95% CI) calculated. Kaplan-Meier and log-rank test were used for univariate survival analysis. Cox proportional risk regression model was used for multivariate analysis using the backward elimination method to analyze risk factors in the variables. Test level ▯=0.05. $P = < 0.05$ indicated statistically significant differences.

Results

Of the participants recruited into the study, 43 died. The most common cause of death in MHD patients was cardiovascular disease (67.44%, 29 cases) and stroke (18.6%, 8 cases). Other causes of death were infection (1 case), hyperkalemia (2 cases), systemic failure (2 cases), and gastrointestinal bleeding (1 case) (Fig. 2).

The age of the participants in the death group was significantly higher than in the control group (P = 0.001). There were more diabetic patients in the death group than in the control group (P = 0.022). Compared with the control group, ECW/TBW (P = 0.000), phase angle (P = 0.000), ALB, Ca, and TG, were significantly different in the death group. FFM, BMI, WC, protein, Cr, BUN, K, HB, P, UA, HDL-C, LDL-C, and TC did not differ significantly between the groups (P = > 0.05, Table 1).

Table 1
Comparisons of variables of two patient group

The control group(n = 71)	**The death group(n = 43)**	***P* Value**	
Gender			0.498
male, n (%)	40(%)	27(%)	
female, n (%)	31(%)	16(%)	
Age(years)	53.94 ± 14.33	63.56 ± 13.84	0.001
Diabetes			0.022
Yes	24(%)	23(%)	
No	47(%)	20(%)	
FFM(kg)	43.48 ± 8.19	45.34 ± 8.15	0.433
ECW/TBW	0.378 ± 0.019	0.397 ± 0.018	0.000
BMI(kg/m$^{2)}$	22.50 ± 2.46	22.39 ± 3.66	0.905
Phase angle	5.90 ± 1.35	4.72 ± 1.85	0.000
WC(cm)	82.07 ± 11.46	81.93 ± 12.21	0.951
ALB(g/L)	40.21 ± 2.94	37.15 ± 7.01	0.003
LDL-C(mmol/L)	2.07 ± 0.74	2.45 ± 1.34	0.123
HDL-C(mmol/L)	1.04 ± 0.28	0.99 ± 0.49	0.607
Ca(mmol/L)	2.24 ± 0.29	2.09 ± 0.30	0.000
TG (mmol/L)	1.68 ± 0.95	1.21 ± 0.40	0.032
Cr(umol/L)	909.98 ± 430.07	866.16 ± 263.61	0.436
BUN(mmol/L)	23.50 ± 6.90	25.46 ± 8.17	0.219
UA(mmol/L)	363.70 ± 157.56	418.89 ± 124.93	0.079
P(mmol/L)	1.89 ± 0.68	2.13 ± 0.82	0.448
HB (g/L)	110.17 ± 15.00	107.48 ± 18.62	0.417
TC(mmol/L)	0.403 ± 0.012	0.404 ± 0.02	0.853
K(mmol/L)	4.89 ± 0.72	5.18 ± 1.18	0.121

Correlations of body composition and biochemical variables with phase angle were analyzed (Table 2). The EW/TBW ($R = -.923$, $p = .000$) was negatively correlated with phase angle. FFM ($R = .258$, $p = .009$) was positively correlated with phase angle, while ALB ($R = .247$, $p = .012$) was correlated with phase angle.

Table 2
Correlation of body composition and biochemical variables with phase angle

R	P Value	
BMI	.112	.269
FFM	.258	.009
WC	-0.005	.959
ECW/TBW	− .923	.000
ALB	.247	.012

The variables of ROC curve were drawn (Fig. 3). AUC, the premium cutoff points, sensitivity, and specificity were calculated. The ability of lower phase angle to predict death risk factors in MHD is shown on Fig. 2. The AUC value and optimal cut-off for the phase angle were 0.754° and 4.50°, respectively. The AUC of the phase angle was > 0.7, indicating the greater capacity of lower phase angle to predict the death risk factors in MDH patients.

Kaplan-Meier univariate survival analysis showed that phase angle (< 4.5°), old age (≥ 65 years old), diabetes, hypoproteinemia (< 35g/L) and anemia (Hb = < 90g/L) were independent risk factors for death in MHD patients. Log rank test was performed on survival curve, and the difference was statistically significant (*P* = < 0.01, Fig. 4(a-e)).

Multivariate analysis using Cox proportional risk regression analysis found that lower phase angle (X1), old age (X2) and hypoalbuminemia (X3) affected the survival time of MHD patients and were risk factors for death in MHD patients. However, anemia and diabetes were not risk factors for death in MHD patients. MHD patients with low phase angle (< 4.5°) had 3.6 times higher the risk of death when compared with those with a high phase angle (≥ 4.5°). MHD patients aged ≥ 65 years had 3 times higher the risk of death compared with non-elderly patients (< 65 years). Patients with low albumin level (< 35g/L) had 7.4 times higher the risk of death (Table 3).

Table 3
Phase angle and other variables that predict death risk factors in MHD patients

HR	P Value	95%CL	
phase angle	3.624	.000	1.807–7.269
old age(≥ 65 years)	2.985	.003	1.440–6.189
hypoalbuminemia (< 35g/L)	7.447	.000	1.440–6.189
anemia(Hb < 90g/L)	1.368	.596	0.429–4.359
diabetes	1.398	.366	0.677–2.887

Discussion

Cardiovascular disease is the main factor in all-cause death in hemodialysis patients[8] .This is probably due to the unique risk factors in hemodialysis patients, including rapid electrolyte change, prolonged QT interval, calcium and phosphorus metabolism disorder, sympathetic excitation, uremic toxin invasion, and hemodialysis related hemodynamic changes[9]. In this study, the most common cause of death (29 cases) in MHD patients was cardiovascular diseases, including heart failure, arrhythmia, ischemic heart disease, and sudden cardiac death. Kaplan-Meier univariate analysis showed that old age was an independent risk factor for death in MHD patients, that serum albumin level could directly reflect the nutritional status of patients, and that protein-energy malnutrition is common in MHD patients (up to 23–73%). Univariate survival analysis suggested that an albumin level of < 35g/L was an independent risk factor for death in hemodialysis patients. Reduced albumin is mainly related to insufficient intake, uremic toxin invasion, delayed gastric emptying, loss of nutrients in dialysis, endocrine disorders, metabolic acidosis, and increased energy consumption due to complications, which aggravate malnutrition in MHD patients and increase their mortality[10]. Hypoproteinemia increases the mortality rate in MHD patients.

Phase angle is reported to be an independent risk factor associated with malnutrition in CKD patients[11]. Currently, phase angle is used in the study of cancer, liver cirrhosis, hemodialysis, and surgical outcomes, and found that phase angle with poor[12]. Phase angle is an affordable, objective, quantifiable, and convenient measurement without exposure to radiation. Phase angle, measure of cell resistivity, reflects cell membrane integrity and overall cellular health. As a sensitive indicator of malnutrition, phase angle can be used to detect clinical nutritional status changes that are related to changes in body composition due to muscle loss or fluid overload. A strong positive correlation between phase angle and traditional nutritional screening tools (e.g., MUST, SGN), as well as various nutritional risk markers has been demonstrated. Additionally, the European Society for Parenteral and Enteral Nutrition recognizes the prognostic value of phase angle in patients requiring nutritional therapy, whereby lower phase angles are associated with worse outcomes in ICU patients and higher phase angles are associated with improved survival. By monitoring the patient’s phase angle, intensive care specialists can noninvasively assess the patient’s nutritional status[13, 14]. Phase angle can reflect early cellular dysfunction, which can indicate the occurrence, development and prognosis of a disease, such as inflammation or cancer. Phase angle is calculated using the formula: arctangent (capacitive reactance/impedance×180°/π). The theoretical basis for phase angle representation of somatic health level is as follows[15, 16]: the “conductive part” of the human body includes ICW, ECW and other conductive components at the cellular level, which produce resistance to current. The voltage difference across the cell membrane is considered the capacitance, which produces capacitive reactance to the current. Due to the presence of capacitive reactance current passing through the body produces phase shifts in the cell membrane that are out of step with the voltage. Therefore, phase angle is closely associated with the number, integrity and continuity of cell membranes, as well as with the distribution of ECW and ICW. Hence, phase angle is a comprehensive reflection of the influence of inflammation, immunity, nutrition, and other factors on cell health and function. Gonzalez et al. [17]analyzed the phase angle of 1442 healthy subjects, and found that reduction in phase angle due to changes in ECW could be measured when sarcopenia had not occurred in the consumption state, such as inflammation. Here, phase angle was low, which may be associated with malnutrition and chronic inflammation in dialysis patients. Bioelectrical impedance analysis is a simple, noninvasive, and reliable technique for estimating body composition and has various applications, including in the prediction of Type 2 diabetes, muscle dysfunction, hydration, and nutritional status[18]. Phase angle is an indicator of bioelectrical impedance and significantly correlates with cancer prognosis. This study shows that MHD patients with low phase angles (< 4.5°) had 3.6 times higher the risk of death when compared with those with high phase angles (≥ 4.5°). The underlying mechanism by which low phase angle can predict prognosis in MHD patients. In addition to the amount of water in a patient’s body, phase angle also reflects the state of cell function and cell membrane integrity. Reduced phase angle often indicates reduced extracellular matrix and increased apoptosis[19].

Conclusion

Here, we found that phase angle might predict survival in MHD patients. Further investigation, involving a larger population, is needed to confirm our findings, alone or in comparison with other prognostic factors, and to assess their accuracy in MHD patients.

Abbreviations

MHD Maintenance hemodialysis

FFM Fat-free mass

ECW/TBW Extracellular water/total body water

ECW Extracellular water

ICW Intracellular water

WC Waist circumference

CKD	Chronic kidney disease
ESRD	End-stage renal disease
RRT	Renal replacement therapy
BMI	Body mass index
Cr	Creatinine
UA	Uric acid
BUN	Urea nitrogen
ALB	Albumin
K	Potassium
P	Phosphorus
HB	Hemoglobin
TC	Total cholesterol
TG	Triglyceride
ROC	Receiver operating characteristic curve
AUC	Area under the curve

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital (No.K2020–029-01). Because of the retrospective nature of the study, patient informed consent was waived by the hospital's Ethics Committee. All methods were performed in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

Authors had full access to all data. The datasets used and/or 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.

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Authors' contributions

Xu YZ: analysis and interpretation of data, drafting of the work. Ling SY: analysis of data, critical revision of the work. Liu ZY: collation and analysis of data. Luo DG: data acquisition and collation. Qi AR: concept and design, acquisition of data, analysis of data, critical revision of the work. Zeng YJ: concept and design, acquisition of data, critical revision of the work. Xu YZ and Ling SY contributed equally to this work. Qi AR and Zeng YJ are corresponding authors. All authors approve of the final work and take public responsibility for it.

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Figures

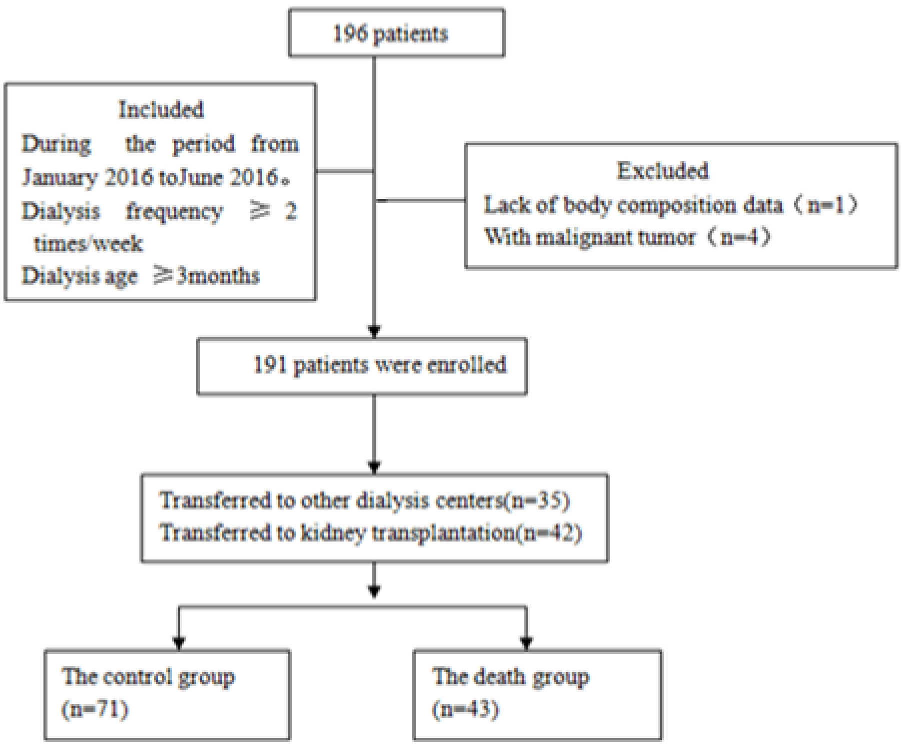

Figure 1

Flow chart of the study’s participants

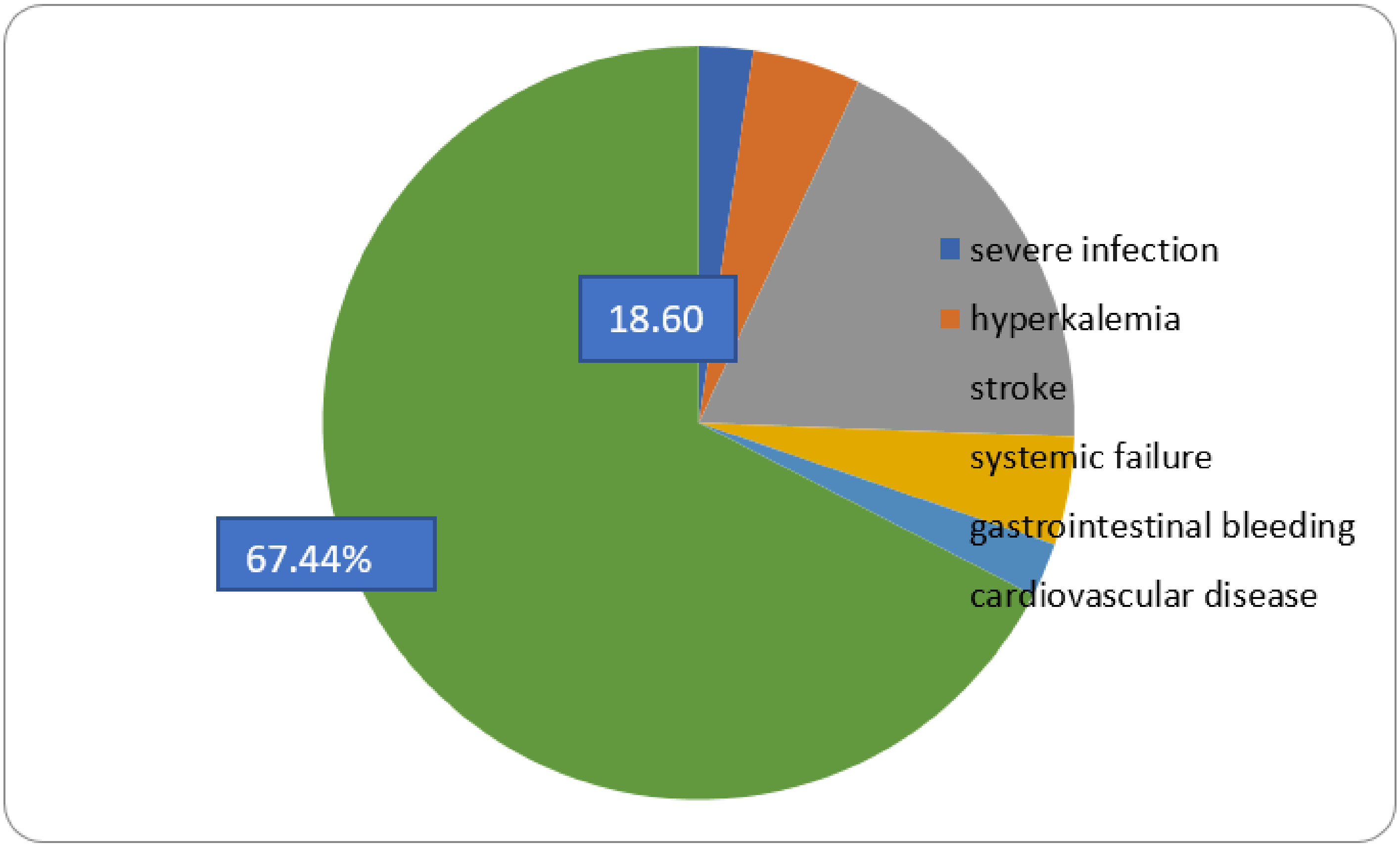

Figure 2

Causes of death in maintenance hemodialysis patients

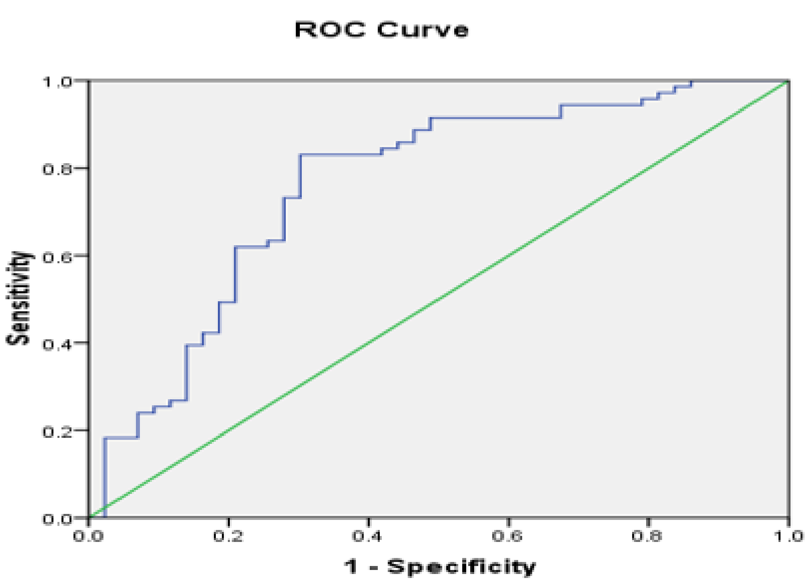

Figure 3

Phase angle as a predictor of death risk factors in MHD patients

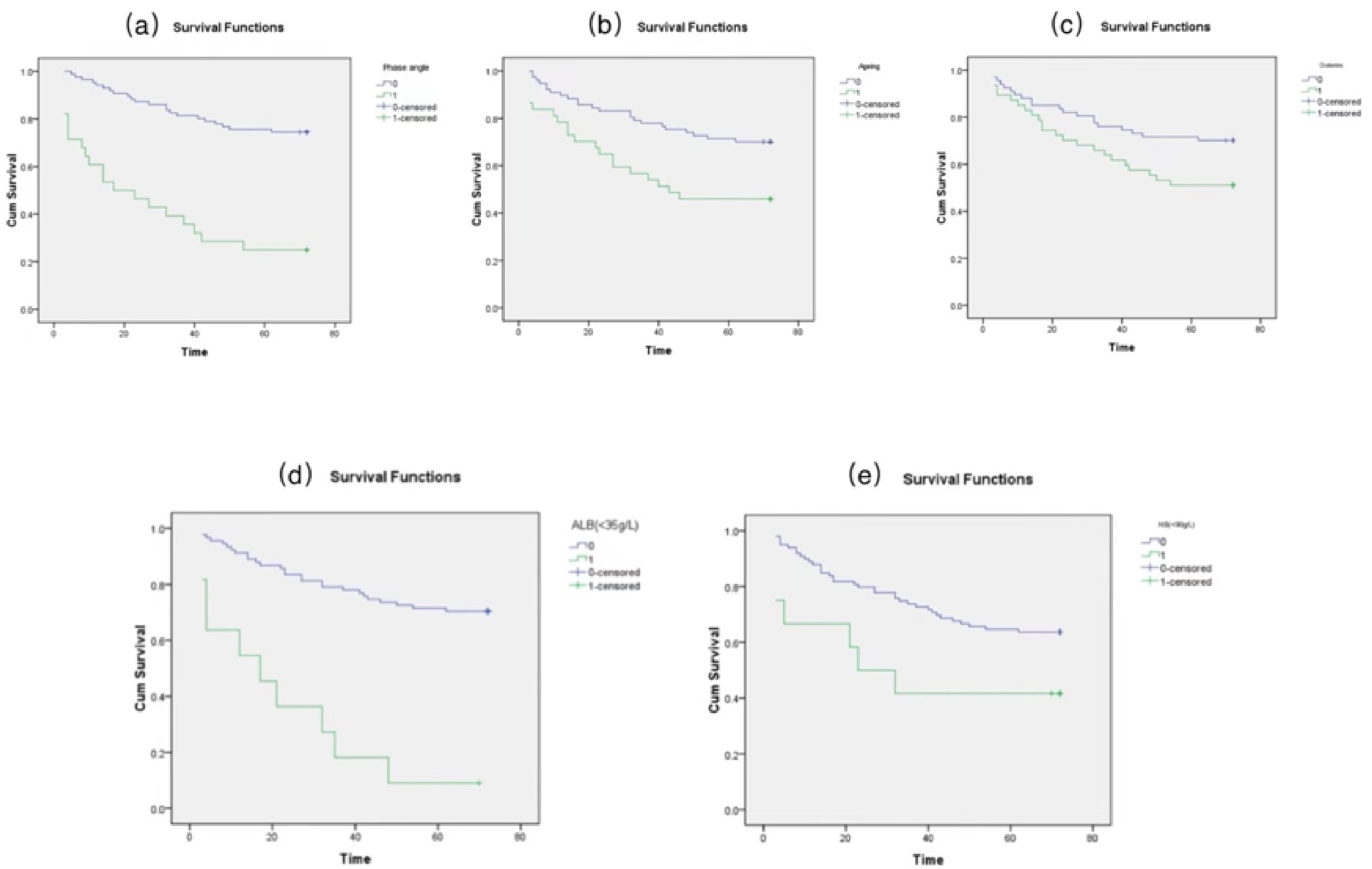

Figure 4

Univariate survival analysis