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DATABASE ANALYSIS

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Utility of Central Venous Oxygen Saturation Gradient in Predicting Mortality in Dialysis with Catheter Access

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Central venous oxygen saturation (ScvO2), a biomarker that is well-correlated with arterial oxygen saturation, can predict mortality. Few studies have focused on blood volume, ScvO2, and mortality in patients on maintenance dialysis. This retrospective study used hospital record data of 144 dialysis patients with central venous catheter access (CVC) and aimed to evaluate the ScvO2 gradient, blood volume, and patient mortality. We examined the associations among absolute blood volume (ABV), mean ScvO2, intradialytic slope of ScvO2, and mortality in patients on dialysis.

Material/Methods: Adult patients receiving dialysis via CVC from 2022 to 2024 were enrolled. ScvO2, ABV, and protocol-based ultrafiltration were monitored using Crit-Line IV (Fresenius Medical Care, Bad Homburg, Germany). Participants were assessed and followed until death or administrative censor. Multiple fractional polynomial (MFP) regression was used to determine best-fitting polynomial function between predictors and mortality. We also constructed proportional hazard model to compare trends of ScvO2 for mortality.

Results: In a total of 144 eligible patients, the incidence of mortality was 14.5 per 1000 patient-months. The correlation between mean ScvO2 and mortality was weak (r=-0.05), whereas the association between ABV change and mean ScvO2 were a reverse U curve. The intradialytic slope of ScvO2 was independently associated with mortality (adjusted odds ratio [95% CI]=0.421 [0.226-0.783], $P<0.05$). Those with descending slope of ScvO2 had higher risk of mortality than those with an ascending slope (HR [95% CI]=3.98 [1.22-13.03], $P<0.05$).

Conclusions: A negative trend of intradialytic ScvO2 was associated with mortality.

Keywords: Dialysis • Mortality • Oxygen Saturation • Ultrafiltration

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Introduction

Fluid and hemodynamic management is a modifiable cardiovascular risk factor in patients on maintenance dialysis. Fluid overload is associated with inflammation, left ventricular hypertrophy, and mortality [1-3]. To avoid fluid overload, a high ultrafiltration rate (UFR) is sometimes required. UFR exceeding the plasma refilling rate from interstitium into vascular space results in blood volume decline and intradialytic hypotension (IDH) [4], which is known to be associated with vascular thrombosis, inadequacy of dialysis, and ischemia of vital organ [5-7]. Overzealous ultrafiltration (UF) is associated with impaired myocardial blood flow and cardiac dysfunction [8]. It is imperative to maintain normohydration status for long-term survival.

Central venous oxygen saturation (ScvO2), a proxy measure of upper-body blood flow, is known to be a marker of mortality in cardiovascular surgery, cardiogenic shock, septic shock, and other critical settings [9]. It has been demonstrated low ScvO2 levels and high ScvO2 variability are associated with poor prognosis [10,11], and might be more specific to pathophysiologic events preceding IDH than blood volume change [12]. Intradialytic oxygen supplement and adequate UF volume can increase ScvO2 [13]. ScvO2 is well-correlated with arterial oxygen saturation (SaO2) and tissue oxygenation [14]. Given that hypoxemia is associated with cardiac arrhythmia, cardiovascular event, and mortality, ScvO2 might be a potential marker for prediction of adverse outcomes [14].

Fluid removal by adequate UF can achieve better SaO2, whereas overzealous UF results in high ScvO2 variability and IDH [10], and it also causes myocardial stunning and end-organ damage [15]. Several blood volume monitors, including biomarker, clinical, and instrumental assessments, have been introduced to avoid overzealous UF [7], but some of them are inaccurate or do not occur in real time [7]. Intradialytic monitoring of blood volume, including relative blood volume (RBV) and absolute blood volume (ABV), has been measured by hematocrit-based and UF jump-based methods to prevent IDH [15,16]. To counterbalance the hypotension, plasma refilling, sympathetic nerve system activation, and vasoactive hormone have been implemented [4]. The counter-regulatory mechanism is mainly activated according to ABV reduction [17]. ABV change was shown to be better correlated with UFR than is RBV change [18]. It is not reduced interstitial volume but intravascular underfilling that compromises adequate circulation [18]. Since the balance between UFR and capillary refilling is the determinant of IDH, ABV change might be better than RBV change as a real-time fluid monitor. As fluid depletion and overload both resulted in increased mortality, real-time intradialytic blood volume monitor is crucial. In the present study, we hypothesized that the intradialytic slope of ScvO2, affected by blood volume change, is a predictor of mortality. Therefore, this retrospective study used hospital record data of 144 dialysis patients with central venous catheter access and aimed to evaluate the ScvO2 gradient, blood volume, and patient mortality

Material and Methods

Ethics Statement

This study was conducted in adherence with the Declaration of Helsinki (2000) of the World Medical Association, and the study protocol was reviewed and approved by the institutional review board of Taoyuan General Hospital (TYGH.112057). Written informed consent was obtained from each patient.

Participants and Data Source

The cohort study enrolled 488 adult and incident hemodialysis subjects in Taoyuan General Hospital and Xinwu Branch since July, 2022. Dialysis was commenced in those with creatinine >0.53 mmol/L in combination with severe hyperkalemia, pulmonary edema, or severe metabolic acidosis. Inclusion criteria were: (1) age ≥20 years and (2) dialysis received for ≥3 months. We retrospectively reviewed medical records of eligible patients, including laboratory data, demographic data, underlying disease, dialysis information, and outcomes. All records about diseases were coded using the International Classification of Diseases, 10th Version, Clinical Modification (ICD-10-CM) in the electronic medical records of Taoyuan General Hospital. Care codes, exam codes, and procedure codes were also obtained. Long-term hemodialysis was confirmed by ICD-10-CM and RIGISTRY FOR CATASTROPHIC ILLNESS PATIENTS (code: 58001C, 58019C, 58020C, 58021C, 58022C, 58023C, 58024C, 58025C, 58027C, 58029C and N18.6). We also excluded those with dialysis time <180 min (n=15), on dialysis less than 3 times a week (n=24), cardiothoracic ratio (CTR) <0.5 (n=80), follow-up less than 3 months (n=16), and using arterio-venous fistula or graft as access (n=204). Those with initial ScvO2 >85% or <25% were regarded as laboratory error and were excluded (n=5). The baseline period was defined as 90 days after enrollment. The end of the baseline period was the initiation of cohort time and were followed up until the date of death, kidney transplantation, or administrative censor on July 31th, 2024. Consequently, a total 144 eligible patients were included for analysis (**Figure 1**).

Outcome Ascertainment

Demographic data, comorbidities, biochemical data, and date of death were recorded according to electronic medical records. Patients with last record on AMBULATORY CARE EXPENDITURES BY VISITS before the end of the study were diagnosed as death.

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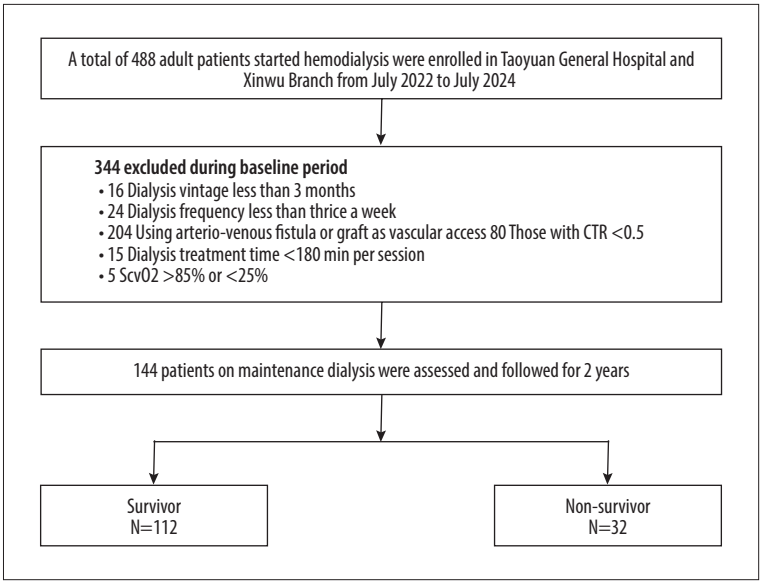

Figure 1. Data flow diagram. CTR – cardiothoracic ratio; ScvO2 – central venous oxygen saturation.

Participants who were lost to follow-up without death confirmation were censored at the last date of follow-up. Participants who were being followed for more than 2 years were censored and participants who survived over the administration censor date were censored on July 31th, 2024.

Blood Volume Monitor Protocol, ScvO2, and Blood Pressure Measurement

The real-time blood volume status was assessed by Crit-Line IV monitor (CLM IV) with blood chamber, which measures hematocrit non-invasively via photo-optical technology (Fresenius Medical Care AG & Co, Bad Homburg, Germany). Real-time hematocrit and ScvO2 were measured every 20 seconds during dialysis session and recorded every 20 minutes by well-trained nursing staff. Maximal ScvO2, minimal ScvO2, mean ScvO2, and ScvO2 at start and end after sessions were also recorded. Standard deviations (SD) of ScvO2 and intradialytic slope of ScvO2, calculated by linear regression during dialysis sessions, were also recorded using software after each session. Intradialytic ScvO2 trend was classified into either decreasing (mean slope <0) (negative trend) or increasing (mean slope >0) (positive trend) based on mean slope of ScvO2. To achieve better fluid management, we adjusted UFR according to the following protocol: (1) set UFR according to inter-dialysis weight gain divided by dialysis time, (2) keep RBV slope within 3-6% per hour, (3) up-titrate UFR 0.5 to 1 ml/Kg/hr while RBV slope is less than 3% per hour, (4) down-titrate UFR 0.5 to 1 ml/Kg/hr while RBV slope is more than 6% per hour, (5) cold dialysis, stop UFR, and oxygen supply once IDH occurred, (6) restart with half the UFR of the last time as IDH was corrected. Blood pressure is automatically measured every 30 minutes oscillometrically. To avoid hypoxemia, oxygen supply with nasal cannula was used routinely. IDH was defined as systolic blood pressure (SBP) less than 90 mmHg. Dialysis information, such as UFR, UF volume, dialysis treatment time, pre-dialysis SBP, frequency of IDH, and RBV and ABV slope, were also recorded. ABV was estimated from RBV around an abrupt change of UF rate [18]. We assumed that UF and capillary refilling are the only factors that change the blood volume during hemodialysis.

$$\frac{d}{dt}BV(\mathrm{t}) = Qr(\mathrm{t}) - Qu(\mathrm{t}), \quad 0 < t < T$$

Where *Qr*: capillary refilling rate, *Qu*: UFR; BV, blood volume

$$Hb(\mathrm{t}) = \frac{Hbmass(\mathrm{t})}{BV(\mathrm{t})} \quad \text{..... (A)}$$

$$Hbmass(\mathrm{t0})\frac{d}{dt}\left\{\frac{1}{Hb(\mathrm{t})}\right\} = Qr(\mathrm{t}) - Qu(\mathrm{t}),\ t0 - a < t < t0 + a$$

$$Qr(\mathrm{t}) = Hbmass(\mathrm{t0})\frac{d}{dt}\left\{\frac{1}{Hb(\mathrm{t})}\right\} + Qu(\mathrm{t}),\ t0 - a < t < t0 + a$$

Where *a* is a very short time.

We introduced a parameter, UF jump, as P

$$P0 = Qu(t0 + 0) - Qu(t0 - 0)$$

As *Qr* is continuous at t0; thus,

$$0 = Qr(\mathrm{t0} + 0) - Qr(\mathrm{t0} - 0)$$

$$0 = \mathrm{P0} + Hbmass(t0)\left(\frac{d}{dt}\left|\left(\frac{1}{Hb(t)}\right)\right|_{t=t0+0} - \frac{d}{dt}\left|\left(\frac{1}{Hb(t)}\right)\right|_{t=t0-0}\right)$$

If we have real-time, high frequency hemoglobin data, obtained from CLM IV and UF jump, we can obtain capillary refilling and ABV. As Hbmass (t0) was solved, we can calculate ABV, according to equation (A).

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RBV was easier to estimate as followed:

$$RBV = \frac{HCT(before)}{HCT(after)} - 1$$

Comorbidities Ascertainment and Laboratory Data Measurement

Laboratory measures were performed by the Department of Laboratory Medicine at Taoyuan General Hospital using standardized and automated methods. Hemoglobin was obtained by direct current detection method on microscopy (XN9000, Sysmex, Japan). Serum creatinine was measured by Kinetic Jaffe' method (reference range: 0.6-1.3 mg/dL for men and 0.5-1.1 mg/dL for women) (ADVIA 1800, Siemens Healthcare GmbH, Erlangen, Germany). Serum albumin was determined using the bromocresol green assay, whereas total protein was measured by biuret test (ADVIA 1800, Siemens Healthcare GmbH, Erlangen, Germany). Ferritin and intact parathyroid hormone (iPTH) were measured by chemiluminescence method (ADVIA 1800, Siemens Healthcare GmbH, Erlangen, Germany). Diabetes mellitus (DM) was diagnosed according to ICD-10-CM codes: E08-E14; whereas hypertension (HTN) was encoded as ICD-10-CM code: I10-I16. Congestive heart failure (CHF) was diagnosed according to ICD-10-CM code: I09.81, I40-I43, I50, I11, I13.

Statistical Analysis

Continuous variables with a normal distribution were summarized as mean±SD unless otherwise stated. Variables with a non-normal distribution are expressed as a median (interquartile range (IQR)). Normality was assessed by the Kolmogorov-Smirnov test. Pearson's chi-square, one-way analysis of variance (ANOVA), or Mann-Whitney U test was used to determine the differences in the demographic data, the laboratory variables, and clinical characteristics between survivors and non-survivors. Univariate and multivariate logistic regression were used to assess the association between parameters and mortality. To avoid missing possible predictors of death, parameters with $P<0.02$ were enrolled in the multivariate logistic model. To develop a flexible approach to modelling the nonlinear and asymmetric relationship between dialysis mortality and ScvO2 as well as blood volume, we implemented the multivariable fractional polynomials (MFP) method and maintained blood volume and ScvO2 as a continuous variable [19]. Instead of imposing a specific functional form, the MFP method allows the data to determine the best-fitting functional form for blood volume, ScvO2, and other adjustment variables. This method can capture the relationship between mortality and blood volume and ScvO2 in a compact, parsimonious model. The MFP performance and results were then compared against linear-quadratic models (Supplementary data).

Interactions (MFPI) between adjustment variables were tested to address the possibility of differences in the ScvO2-mortality curve. To integrate the effect of ABV change and mean ScvO2, we assessed the association between slope of mean ScvO2 and mortality. Intradialytic slope of ScvO2 was categorized into ascending (slope >0) or descending (slope <0) slope. Cumulative survival curves for mortality with different trend of ScvO2 were performed according to the log-rank test. Calculations and comparisons in hazard ratios for mortality were conducted using Cox proportional hazards model. The fit of the Cox proportional hazard model was tested by Schoenfeld residuals test. All statistical analyses and plots were performed using STATA 16.0 (StataCorp. College Station, Texas, USA). A two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

Demographic Characteristics and Clinical Outcomes

The cohort of the 144 subjects were followed up for a median of 14.8 months, ranging from 9.0 to 23.0 months. The mean age for the study population was 66.7 years, whereas the dialysis vintage was 4.8 years. The incidence of all-cause mortality was 16.7 per 1000 patient-months. The average dialysis treatments with CLM during baseline period were 6.9±0.3 times. The prevalences of DM, HTN, and CHF were 52.8%, 65.3%, and 20.8%, respectively. The median hourly RBV and ABV slope were -3.1% and -3.9%, whereas the ABV change at end of dialysis was -16.0% (-12.0% to -18.0%).

Comparisons Between Survivors and Non-Survivors

Table 1 shows comparisons between survivors and non-survivors. Non-survivors were older (71.2 y vs 65.5 y) and had a higher proportion of IDH (31% vs 12%), as well as lower creatinine (0.74 mmol/L vs 0.85 mmol/L), lower median treatment time per session (3.5 hr vs 3.9 h), lower mean ScvO2 (64.5% vs 68.0%), and descending slope of mean ScvO2 (-0.88% per h vs 0.69% per h). There were no differences among the 2 groups in BMI, length of follow-up, dialysis vintage, levels of albumin, total protein, hemoglobin, iPTH, and ferritin, as well as dialysis information, such as UF volume, pre-dialysis weight, dialysis adequacy(Kt/Vurea), ABV slope, RBV slope, other ScvO2 measurements, the proportions of sex and comorbidities (**Table 1**).

Model Fitting

The best-fitting model for ABV and mortality was identified by MFPI including ABV and squared ABV. The main adjustment model also included age, albumin, creatinine, total protein, mean ScvO2, and CV of ScvO2. The transformed model (Deviance difference=146.15) significantly improved

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Table 1. Baseline characteristics of study population.

Parameters	All participants N=144	Survivors N=112	Non-survivors N=32	*P* value
Age (year)	66.7±14.2	65.5±14.3	71.2±12.9	0.045*
Men (%)	64 (44.4)	48 (42.5)	16 (51.6)	0.417
BMI (Kg/m^2)	25.8±2.9	25.9±2.8	25.4±3.4	0.402
Vintage of dialysis (yr)	4.8±2.5	4.9±2.5	4.4±2.1	0.289
Length of follow-up (months)	14.8 (11.6, 19)	14.8 (11.6, 18.9)	12.4 (11.1, 18.0)	0.861
Comorbidities				
DM (n)	76	60	16	1.000
Hypertension (n)	94	82	12	0.120
CHF (n)	30	24	6	1.000
Laboratory data				
Albumin (g/L)	37.7±3.1	37.9±2.9	36.8±3.5	0.088
Total protein (g/L)	67.4±6.2	67.6±5.9	66.8±7.2	0.510
Creatinine (mmol/L)	0.83±0.21	0.85±0.23	0.74±0.24	0.020*
Hemoglobin (g/L)	100.9±11.2	100.6±11.7	101.8±9.3	0.595
iPTH (ng/L)	350 (177, 1626)	360 (189, 1625)	271 (110, 746)	0.525
Ferritin (nmol/L)	1.04±0.98	0.99±0.83	1.23±1.58	0.305
Mean ScvO2 (%)	67.3±6.9	68.0±7.2	64.5±4.9	0.015*
Max ScvO2 (%)	74.1±4.7	74.6±5.2	74.1±4.6	0.592
Min ScvO2 (%)	59.7±9.7	60.3±10.2	57.6±7.3	0.174
Start ScvO2 (%)	70.2±4.8	70.3±4.9	69.0±4.6	0.186
End ScvO2 (%)	61.7±11.5	62.2±12.0	59.8±8.9	0.291
SD of ScvO2	2.4±1.3	2.1±1.1	3.4±1.4	<0.001*
Average slope of ScvO2 (%/hr)	-0.02 (-0.89, 0.69)	0.69 (0.36, 1.14)	-0.88 (-1.49, -0.38)	0.001*
Dialysis information				
Mean pre-dialysis SBP (mmHg)	139±19	138±19	143±19	0.278
Mean UFV (liter)	2.4±0.8	2.4±0.8	2.4±0.8	0.956
Mean UFR (ml/Kg/hr)	10.4±2.6	10.4±2.7	10.4±2.2	0.924
Treatment time (hrs)	3.9 (3.5, 4.0)	3.9 (3.5, 4.0)	3.5 (3.3, 3.9)	0.001*
Proportion of IDH (%)	16±17	12±13	31±22	<0.001*
Equilibrated Kt/Vurea	1.67±0.29	1.67±0.29	1.63±0.29	0.490
Average preHD weight (Kg)	63.3±13.3	63.2±14.2	63.7±9.6	0.865
Average ABV change (%)	-16.0 (-12.0, -18.0)	-16.0 (-14.0, -18.0)	-14.0 (-7.3, -26.7)	0.515
Average ABV slope (%/h)	-3.9 (-3.2, -5.1)	-3.9 (-3.2, -5.1)	-3.9 (-3.3, -5.1)	0.861
Average RBV slope (%/h)	-3.1 (-2.0, -4.0)	-3.1 (-2.0, -4.0)	-3.0 (-2.1, -4.0)	0.417

Data were percentage, mean±standard deviation, median (interquartile range (IQR)). * P<0.05. BMI – body mass index; DM – diabetes mellitus; CHF – congestive heart failure; ScvO2 – central venous oxygen saturation; iPTH – intact parathyroid hormone; IDH – intradialytic hypotension; UFV – ultrafiltration volume; UFR – ultrafiltration rate; SD – standard deviation; ABV – absolute blood volume; RBV – relative blood volume.

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Table 2. Univariate logistic regression and final model including fractionally transformed absolute blood volume(ABV) and interaction identified significant.

Parameter	β coefficient	SE	OR (95% CI)	*p* value
Univariate analysis				
Age	0.032	0.016	1.032 (1.001-1.065)	0.048*
Female	-0.368	0.407	0.692 (0.312-1.536)	0.366
BMI	-0.059	0.070	0.943 (0.822-1.281)	0.400
Dialysis vintage	-0.093	0.037	0.912 (0.769-1.081)	0.287
DM	-0.001	0.418	0.990 (0.442-2.221)	0.981
preHD SBP	0.014	0.013	1.014 (0.989-1.040)	0.276
CHF	-0.117	0.509	0.890 (0.328-2.416)	0.819
Ultrafiltration rate	-0.081	0.079	0.993 (0.851-1.158)	0.924
Kt/Vurea	-0.532	0.764	0.587 (0.131-2.026)	0.486
Albumin	-1.085	0.644	0.338 (0.096-1.194)	0.092
Total protein	-0.071	0.034	0.932 (0.871-0.996)	0.039*
Creatinine	-0.192	0.084	0.825 (0.700-0.973)	0.022*
Hemoglobin	0.096	0.179	1.100 (0.775-1.562)	0.593
Ferritin	0.192	0.193	1.212 (0.831-1.768)	0.231
iPTH	0.001	0.001	1.001 (1.000-1.001)	0.186
ABV slope	0.139	0.134	1.149 (0.885-1.493)	0.297
RBV slope	-0.079	0.126	0.924 (0.722-1.182)	0.530
(ABV-mean ABV)	-0.012	0.031	0.989 (0.930-1.051)	0.711
$(ABV-meanABV)^2$	0.013	0.004	1.013 (1.006-1.020)	0.001*
(UFR-meanUFR)	0.081	0.079	1.085 (0.928-1.268)	0.305
$(UFR-meanUFR)^2$	-0.014	0.024	0.986 (0.941-1.034)	0.566
Mean ScvO2	-0.032	0.040	0.876 (0.810-0.948)	0.001*
Final model				
(ABV-mean ABV)	1.389	0.700	4.010 (1.071-15.520)	0.049*
$(ABV-mean ABV)^2$	-0.150	0.060	0.860 (0.75-0.999)	0.047*
$(ABV-mean ABV)^2$×Mean ScvO2	0.002	0.001	1.001 (1.000-1.004)	0.047*

* P<0.05. SE – standard error; OR – odds ratio; BMI – body mass index; UFR – ultrafiltration rate; DM – diabetes mellitus; CHF – congestive heart failure; Kt/Vurea – dialysis adequacy; iPTH – intact parathyroid hormone; ABV – absolute blood volume; RBV – relative blood volume, ScvO2 – central vein oxygen saturation; (ABV-mean ABV) – centered ABV; $(ABV-mean ABV)^2$ – squared term of centered ABV; $(ABV-mean ABV)^2$×Mean ScvO2 – interaction term between squared term of centered ABV and mean ScvO2.

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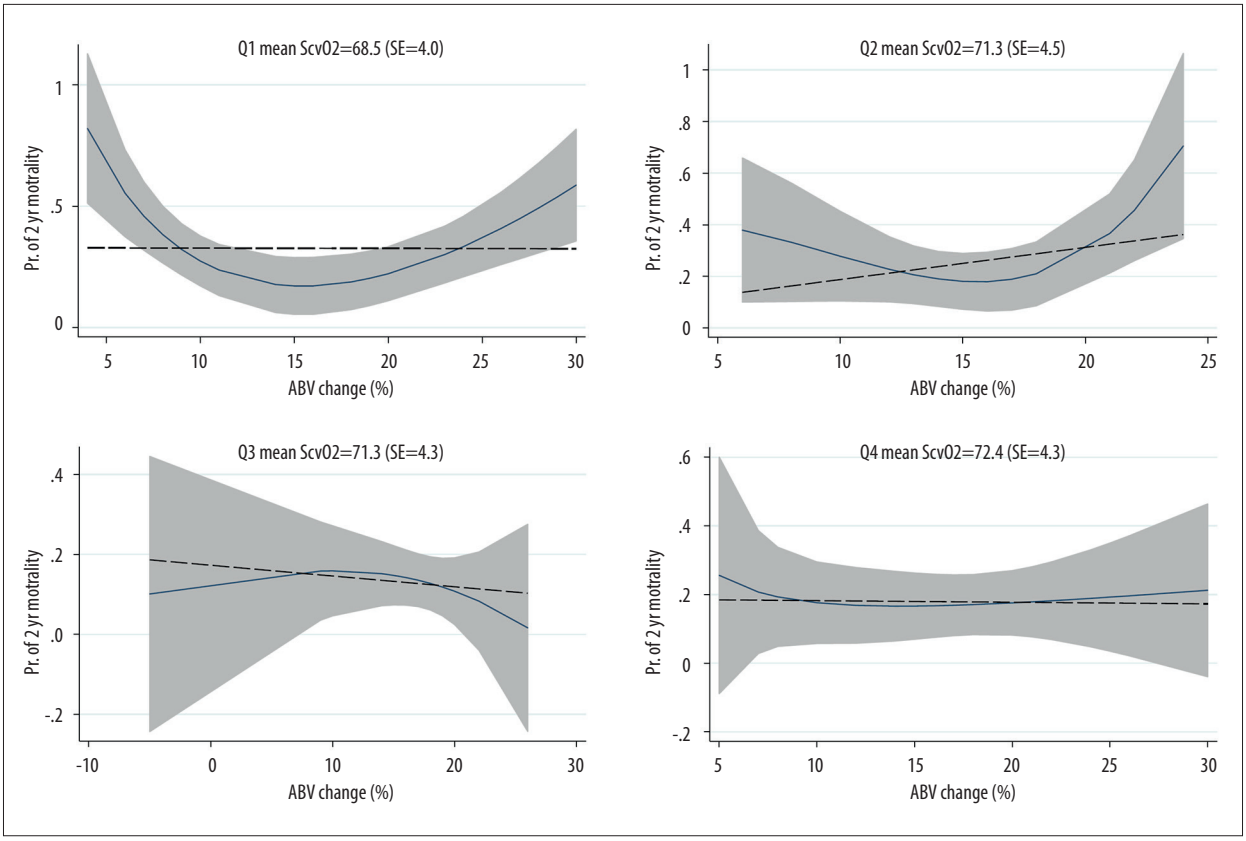

Figure 2. The association between absolute blood volume(ABV) change and probability of 2-year mortality(Pr. of 2-year mortality) among different quartile(Q1-Q4) of central venous oxygen saturation (ScvO2).

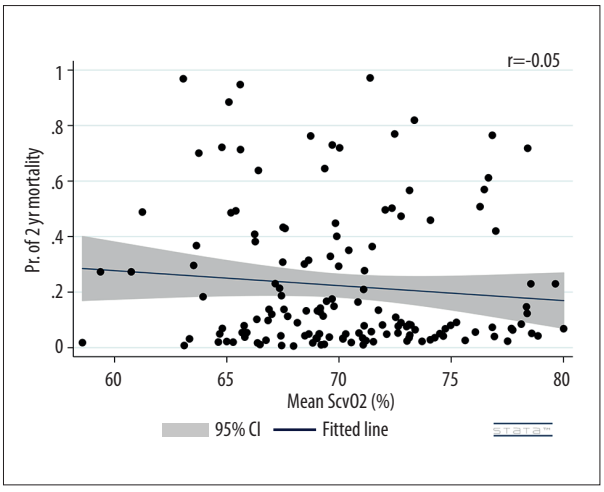

Figure 3. The association between mean central venous oxygen saturation (ScvO2) and probability of 2-year mortality (Pr. of 2-year mortality).

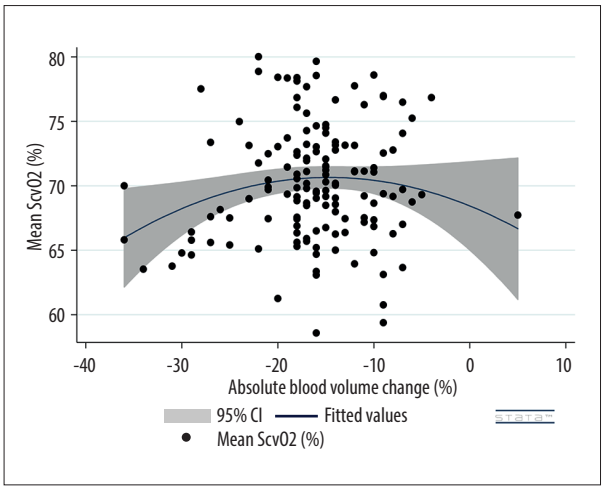

Figure 4. The association between absolute blood volume change and mean central venous oxygen saturation (ScvO2).

model fit relative to the untransformed model (Deviance difference=100.70) and linear-quadratic model (Deviance difference=123.66, $P<0.05$). After finding the best fit for the main model, the ScvO2-ABV interaction were also identified (Deviance difference=9.77, $P=0.007$). After including the above interaction terms, the final model remained fit the untransformed model (Deviance difference=123.34, $P<0.05$). **Table 2** shows the logistic regression for the final model including fractionally transformed ABV and interaction term.

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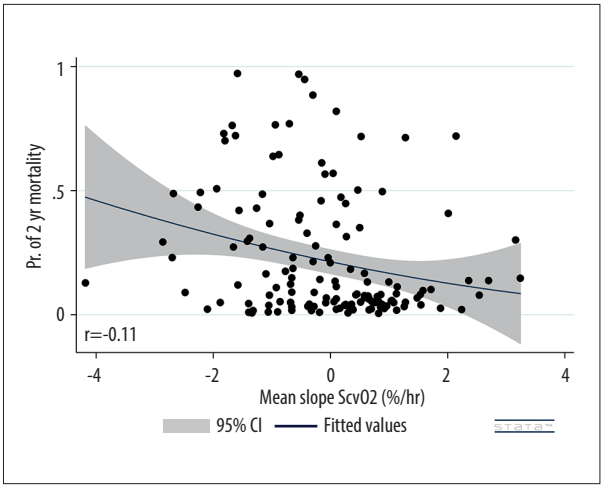

Figure 5. The association between slope of central venous oxygen saturation (ScvO2) and probability of 2-year mortality(Pr. of 2-year mortality).

ScvO2-Mortality Curve and ABV Change-Mortality Curve

The fitted curve showed the association between ABV change and probability of 2-year mortality (**Figure 2**). In those below mean ScvO2, increases in ABV reduction were associated with increased mortality, whereas in those above mean ScvO2, the increases in ABV reduction were associated with decreased mortality. The wide confidence interval at the left tail of the high ScvO2 group was due to the low proportion of negative ultrafiltration. The association between mean ScvO2 and 2-year mortality is shown in **Figure 3**. The correlation between mean ScvO2 and mortality was weak (r=-0.05), whereas the association between ABV change and mean ScvO2 were a reverse U curve (**Figure 4**). We used the intradialytic slope of mean ScvO2 to integrate the effect of ABV change and mean ScvO2. The intradialytic slope of ScvO2 remained significant predictors of mortality after multivariate adjustment (adjusted odds ratio and 95% CI=0.421(0.226-0.783), $P<0.05$), and the intradialytic slope of ScvO2 was also negatively associated with mortality (r=-0.11) (**Figure 5**). We also categorized our subjects into decreasing slope or increasing slope according to the intradialytic trend of ScvO2. In the crude Cox model, those with a descending slope of ScvO2 had significantly higher risks of mortality than those with an ascending slope (HR [95% CI]=3.43 [1.40-8.44]). After adjusting demographic data, comorbidities, and laboratory data other than ABV change, decreasing ScvO2 remained a predictor of mortality (HR [95% CI]=3.98 [1.22-13.03], $P<0.05$). The cumulative survival curve also demonstrated that patients with increasing ScvO2 also had better prognosis than those with decreasing ScvO2 (log-rank chi-sq=8.43, $P=0.004$) (**Figure 6**).

Discussion

This cohort study demonstrated that mean ScvO2 and ABV change were both associated with mortality. The association between ABV change and mortality was a reverse U shape. Decreasing intradialytic slope of ScvO2, an integrated effect of overzealous UF in those with low ScvO2 or inadequate UF in those with high ScvO2, is associated with poor prognosis.

ScvO2 is a well-known predictor of mortality and is determined by upper-body blood flow (UBBF), hemoglobin, SaO2, and oxygen extraction by adjacent tissue or organ [9-11]. UBBF is associated with cardiac output [20], whereas tissue hypoxemia is associated with cardiac arrhythmia [14]. Anemia is known to result in increased cardiac output and vascular remodeling, and is also a marker for an underlying inflammatory process [21]. Not surprisingly, ScvO2 can predict mortality in those on dialysis. ScvO2 rise is positively correlated with UF volume at

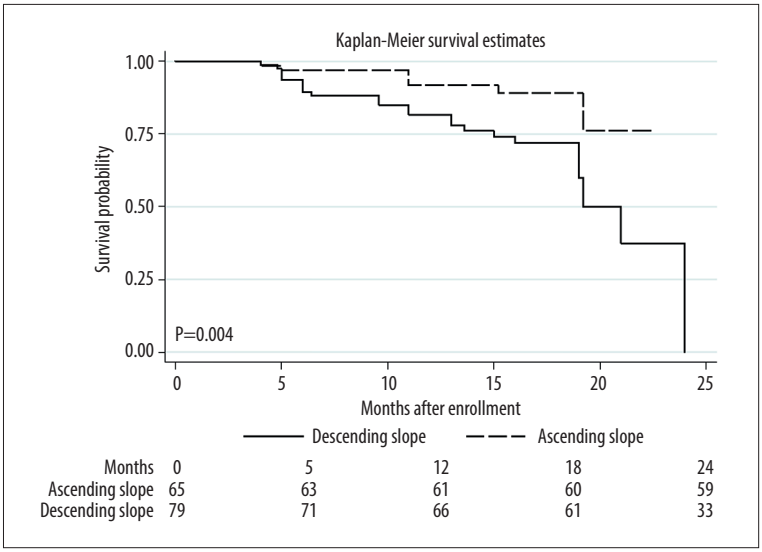

Figure 6. Cumulative survival curve between ascending and descending slope of central venous oxygen saturation (ScvO2).

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the early phase of dialysis, whereas ScvO2 decline is inversely associated with UF volume in the late phase [13]. Overzealous UF can lead to impaired myocardial blood flow and myocardial stunning, followed by cardiovascular events [8]. Excess fluid removal can impact intradialytic hemodynamic stability. Thus, the association between dynamic change of ScvO2, blood volume, and mortality is conceivable. There are several explanations for the associations among dynamic change of ScvO2, ABV, and mortality. Initial SaO2 decline might be attributed to leukocyte activation and migration because of membrane-blood bioincompatibility [22]. Bicarbonate diffusion from dialysate into patient's blood results in a reduced respiratory drive [23]. Excess fluid removal can impact intradialytic hemodynamic stability and cardiac output. Alternation of cardiac output leads to UBBF and ScvO2 variation. Finally, intermittent atrial fibrillation is common during dialysis [24]. Cardiac arrhythmia is associated cardiac output instability and ScvO2 variability. In our study, intradialytic slope of ScvO2, an integrated effect of fluid removal, and cardiac output, was negatively correlated with mortality.

Some studies found that high variability of ScvO2 and high UF volume were associated with mortality [10,13]. Variability of ScvO2 is reflected by standard deviation divided by mean ScvO2 [10], whereas high UF volume results in steeper ScvO2 drop [13]. As the trend of ScvO2 was attributed to mean ScvO2 and dynamic change of ABV, the slope of ScvO2 might predict mortality. Some studies also indicated high ScvO2 and low blood volume change were associated with better prognosis [25]. Although blood volume monitoring was advised in previous studies, some intradialytic fluid monitoring showed a negative result [26], possibly explained by a low adherence to study protocol and setting of critical RBV reduction. The acceptable hourly RBV reduction was 3-6%, rather than the >8% reported in previous studies [25,27]. Excessively rapid UF (>13 ml/Kg/h) had an increased risk of mortality, especially in those with high CTR or CHF [28,29]. It was also reported that predialytic fluid depletion was associated with an increased risk of mortality, whereas post-dialytic fluid depletion reduced the risk of death [30,31]. As our study population was monitored with appropriate RBV reduction and most of our subjects had a high CTR, the results are reliable.

Several methods have been proposed to access fluid status, including inferior vena cava diameter (IVCD), bioimpedance analysis (BIA), lung ultrasound, and sodium magnetic resonance imaging (MRI) [7]. IVCD had poor predictive value on blood pressure in probing dry weight, whereas BIA was limited by non-real-time monitoring of fluid status. It is also inaccurate at extremes of BMI and requires repeat measurements [32]. Sodium MRI is limited by its complex setting and number of scanning devices required [7]. Blood volume monitoring is a simple and non-invasive method to monitor hydration status and capillary refilling. RBV and ABV have roles in fluid management in HD subjects [18]. However, ABV changes seem to be more relevant to clinical outcomes. As IDH is a predictor of death, blood pressure and tissue perfusion are concerned. The counter-regulatory mechanism is activated while ABV, but not RBV, at 20% below normal [17,18]. RBV changes usually underestimate ABV change. Blood shifts from microvascular to macrovascular system, leading to central hemodilution. Thus, RBV is relatively high and underestimates ABV change. ABV can be easily converted to RBV but not vice versa. Adjust dry weight based on ABV, but not RBV, reduced intradialytic morbid events [33]. RBV is affected by posture change, exercise, diet, and intravenous fluid infusion [16]. ABV measurement was used to demonstrate that vascular refilling is dependent on UF volume, but not fluid overload. UFR affects RBV change in the late phase of dialysis, whereas total protein was associated with UFR in the early phase [34]. As ABV was estimated based on UF jump and hematocrit in our study, the correlation between hourly ABV changes with UFR is better than those between RBV changes and UFR.

Limitations of the Study

First, it was a retrospective observational study within a single medical center; thus, causal inference is impossible. Secondly, the sample size was limited. Thirdly, despite multivariate adjustment, residual confounding factors cannot be excluded. Those with UF intolerance, such as the elderly, CHF, and high comorbidity, might have distorted the association between ScvO2 and death [35]. We lacked data on residual renal function, which is associated with UF volume and blood volume change [36]. Furthermore, objective indicators of fluid status, especially post-dialytic bioimpedance analysis, were not available, but they can help clarify the relationship between fluid status and ABV change. Finally, ABV measurement might be affected by technical- and treatment-related intervention, such as wrong placement of the measurement chamber and intravenous bolus of fluid.

Conclusions

In summary, a negative trend of intradialytic ScvO2 was associated with mortality. Mean ScvO2 and ABV change were independently associated with mortality. The association between mean ScvO2 and ABV change was a reverse U curve. The integrated effect of mean ScvO2 and ABV change, reflected by intradialytic slope of ScvO2, was a predictor of mortality. This study was limited by study design and sample size. Objective fluid indicators are needed to confirm the association and effect modification between ScvO2 and mortality.

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Ethics Approval Statement

The study was approved by the institutional review board of Taoyuan General Hospital (TYGH.112057).

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Wang Y, Gu Z. Effect of bioimpedance-defined overhydration parameters on mortality and cardiovascular events in patients undergoing dialysis: A systematic review and meta-analysis. J Int Med Res. 2021;49(9):3000605211031063
2. Xu Y, Chen Y, Li D, et al. Hypertension, fluid overload and micro inflammation are associated with left ventricular hypertrophy in maintenance hemodialysis patients. Ren Fail. 2013;35(9):1204-9
3. Dekker MJE, van der Sande FM, van den Berghe F, et al. Fluid overload and inflammation axis. Blood Purif. 2018;45(1-3):159-65
4. Chou JA, Kalantar-Zadeh K, Mathew AT. A brief review of intradialytic hypotension with a focus on survival. Semin Dial. 2017;30:473-80
5. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. J Am Soc Nephrol. 2011;22:1526-33
6. Sars B, van der Sande FM, Kooman JP. Intradialytic hypotension: Mechanisms and outcome. Blood Purif. 2020;49(1-2):158-67
7. Canaud B, Chazot C, Koomans J, et al. Fluid and hemodynamic management in hemodialysis patients: challenges and opportunities. J Bras Nefrol. 2019;41(4):550-59
8. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol. 2008;3(1):19-26
9. Reid M. Central venous oxygen saturation: Analysis, clinical use and effects on mortality. Nurs Crit Care. 2013;18(5):245-50
10. Zhang H, Campos I, Chan L, et al. Association of central venous oxygen saturation variability and mortality in hemodialysis patients. Blood Purif. 2019;47(1-3):246-53
11. Chan L, Zhang H, Meyring-Wösten A, et al. Intradialytic central venous oxygen saturation is associated with clinical outcomes in hemodialysis patients. Sci Rep. 2017;7(1):8581
12. Cordtz J, Olde B, Solem K, et al. Central venous oxygen saturation and thoracic admittance during dialysis: New approaches to hemodynamic monitoring. Hemodial Int. 2008;12(3):369-77
13. Zhang H, Chan L, Meyring-Wösten A, et al. Association between intradialytic central venous oxygen saturation and ultrafiltration volume in chronic hemodialysis patients. Nephrol Dial Transplant. 2018;33(9):1636-42
14. Campos I, Chan L, Zhang H, et al. Intradialytic hypoxemia in chronic hemodialysis patients. Blood Purif. 2016;41(1-3):177-87
15. Kron J, Schneditz D, Leimbach T, et al. A simple and feasible method to determine absolute blood volume in hemodialysis patients in clinical practice. Blood Purif. 2014;38(3-4):180-87
16. Dasselaar JJ, Huisman RM, de Jong PE, et al. Measurement of relative blood volume changes during haemodialysis: Merits and limitations. Nephrol Dial Transplant. 2005;20(10):2043-49
17. Van Buren PN. Relative blood volume monitoring in hemodialysis patients: Identifying its appropriate role. Nephrol Dial Transplant. 2019;34(8):1251-53
18. Thijssen S, Kappel F, Kotanko P. Absolute blood volume in hemodialysis patients: Why is it relevant, and how to measure it? Blood Purif. 2013;35(1-3):63-71
19. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. Stat Med. 2004;23(16):2509-25
20. Perner A, Haase N, Wiis J, et al. Central venous oxygen saturation for the diagnosis of low cardiac output in septic shock patients. Acta Anaesthesiol Scand. 2010;54(1):98-102
21. Lee G, Choi S, Kim K, et al. Association of hemoglobin concentration and its change with cardiovascular and all-cause mortality. J Am Heart Assoc. 2018;7(3):e007723
22. Yilmaz H, Bozkurt A, Cakmak M, et al. Relationship between late arteriovenous fistula (AVF) stenosis and neutrophil-lymphocyte ratio (NLR) in chronic hemodialysis patients. Ren Fail. 2014;36(9):1390-94
23. Alfakir M, Moammar MQ, Ali MI, et al. Pulmonary gas exchange during hemodialysis: A comparison of subjects with and without COPD on bicarbonate hemodialysis. Ann Clin Lab Sci. 2011;41(4):315-20
24. Zimmerman D, Sood MM, Rigatto C, et al. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrol Dial Transplant. 2012;27(10):3816-22
25. Preciado P, Zhang H, Thijssen S, et al. All-cause mortality in relation to changes in relative blood volume during hemodialysis. Nephrol Dial Transplant. 2019;34(8):1401-8
26. Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. Hypertension. 2010;56(3):512-17
27. Reddan DN, Szczech LA, Hasselblad V, et al. Intradialytic blood volume monitoring in ambulatory hemodialysis patients: A randomized trial. J Am Soc Nephrol. 2005;16(7):2162-69
28. Yang LJ, Chao YL, Kuo IC, et al. High ultrafiltration rate is associated with increased all-cause mortality in incident hemodialysis patients with a high cardiothoracic ratio. J Pers Med. 2022;12(12):2059
29. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int. 2011;79(2):250-57
30. Chazot C, Wabel P, Chamney P, et al. Importance of normohydration for the long-term survival of haemodialysis patients. Nephrol Dial Transplant. 2012;27(6):2404-10
31. Flythe JE, Kshirsagar AV, Falk RJ, et al. Associations of post hemodialysis weights above and below target weight with all-cause and cardiovascular mortality. Clin J Am Soc Nephrol. 2015;10(5):808-16
32. El-Kateb S, Davenport A. Changes in hydration following haemodialysis estimated with bioimpedance spectroscopy. Nephrology (Carlton). 2016;21(5):410-15
33. Kron S, Schneditz D, Czerny J, et al. Adjustment of target weight based on absolute blood volume reduces the frequency of intradialytic morbid events. Hemodial Int. 2018;22(2):254-60
34. Tanaka T, Kawakubo Y, Shigematsu T, et al. The changes in relative blood volume during dialysis are characterized by ultrafiltration rate and predialysis blood test values. Blood Purif. 2024;53(6):505-10
35. Ramírez-Guerrero G, Ronco C. Ultrafiltration tolerance: A phenotype that we need to recognize. Blood Purif. 2024;53(7):541-47
36. Steinwandel U, Kheirkhah H, Davies H. Residual renal function – how fast does the residual urine output function decline in the first year of haemodialysis? – a scoping review. Front Nephrol. 2022;1:808909

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