Original Article

# Elevated Serum Interleukin-18 Level is Correlated with Vascular Access Dysfunction in Patients on Maintenance Haemodialysis

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#### Abstract

Introduction: We evaluated the impact of serum interleukin-18 (IL-18) level on short-term vascular access (VA) function in chronic haemodialysis (HD) patients. Materials and Methods: Samples were collected from 80 clinically stable patients (58.8% were men) with a mean age of 60.9 years (standard deviation 11.7 years) who were undergoing maintenance HD and were followed up for 1 year. Multivariate logistic regression was used to analyse data on demographics, biochemical parameters and serum IL-18 level to predict VA dysfunction events. The cut-off for IL-18 was derived from the highest score obtained on Youden index. Survival data was analysed using Cox proportional hazards regression analysis and Kaplan-Meier method. Results: Patients were classified as having either low IL-18 (<199.3 pg/mL) or high IL-18 (≥199.3 pg/mL). Multivariate logistic regression showed that serum IL-18 level was independently correlated with VA dysfunction events; patients with high IL-18 had a higher risk of VA dysfunction events than those with low IL-18 (odds ratio 9.47, 95% confidence interval 1.75-51.31, P=0.009). In patients with high IL-18, Kaplan-Meier survival analysis found that incidence of VA dysfunction was significantly higher than patients with low IL-18 (P = 0.047). After adjustment for age, gender, inflammation (C-reactive protein) and calcium-phosphorus metabolism, decreased serum albumin and increased serum IL-18 levels were found to be independent prognostic predictors of VA dysfunction. Conclusion: HD patients with high IL-18 level tend to have worse rates of VA dysfunction. In HD outpatients, IL-18 is an independent risk factor for short-term VA dysfunction.

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Key words: Access survival, Cytokines, Short-term

#### Introduction

Renal replacement therapy (RRT) is a long-term, life-sustaining intervention in patients with endstage renal disease (ESRD) and most of them are on haemodialysis (HD).<sup>1</sup> Although various dialysis treatments have improved the prognosis in HD patients,<sup>2</sup> the establishment and maintenance of appropriate vascular access (VA) and reduction in incidence of VA dysfunction are important factors that can impact on their long-term prognoses.<sup>3</sup>

In the last few decades, extensive application of autologous arteriovenous fistula (AVF) and innovations

in VA—including arteriovenous graft (AVG) and tunnelled cuffed catheter (TCC)—have improved prognosis in HD patients. However, 9–16% of HD patients still experience insufficient dialysis that is attributed to VA dysfunction and complications of the access point.<sup>4</sup> Therefore, it is crucial to understand the pathogenesis of VA dysfunction, identify possible risk factors and provide early intervention.

Currently, it is believed that systemic abnormalities in ESRD patients—such as uraemic toxins, systemic inflammation, endothelial dysfunction, lipid abnormalities, hyperparathyroidism,

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hyperphosphataemia and hypercalcaemia—can easily remodel and narrow the vascular wall of mature AVF.<sup>5-7</sup> In ESRD patients, some studies have found that the levels of cytokines—such as interleukin-6 (IL-6), transforming growth factor beta (TGF-beta) and tumour necrosis factor alpha (TNF-alpha) are significantly higher than those in the general population. Elevated levels of cytokines may be linked to the development of neointimal hyperplasia (NIH) and progression of VA dysfunction; however, their pathogeneses remain unclear.<sup>8,9</sup>

Interleukin-18 (IL-18) is a member of the interleukin-1 superfamily and can induce an immune response and inflammatory reaction.<sup>10,11</sup> In patients with chronic kidney disease (CKD) and those who were on continuous ambulatory peritoneal dialysis (CAPD), studies have found evidence of chronic inflammation and increased levels of serum IL-18.<sup>12</sup> Formanowicz et al<sup>13</sup> have reported that IL-18 level can predict cardiovascular mortality in patients with CKD. Recently, Wang et al<sup>14</sup> found that serum IL-18 level is an independent risk factor for major adverse cardiovascular events in HD patients.

Other studies have reported a correlation between elevated IL-18 levels and increased hospitalisation in HD patients.<sup>15</sup> In their observational study, Liu et al<sup>16</sup> found that IL-18 level was an independent risk factor for all-cause mortality in patients on maintenance dialysis but no correlation was found with cardiovascular function. However, it is unclear whether IL-18 contributes to the development and progression of VA dysfunction, and if it can be used as an early predictor of VA dysfunction in patients on maintenance dialysis.

Consequently, we conducted a 1-year prospective, observational study to examine the correlation between serum IL-18 level and VA function in patients who were attending our outpatient HD centre. The primary outcome of interest was incidence of VA dysfunction, and a preliminary evaluation of risk factors for VA dysfunction in patients on maintenance HD was performed.

## **Materials and Methods**

The study commenced on 1 June 2017 and included 80 mainland Chinese patients who had been undergoing regular dialysis—4 hours per session—thrice a week for at least 1 month in our HD centre. All of them were followed up for 1 year until 31 May 2018. Information on their medical history, primary diagnosis and complications were collected. To ensure that all patients met the criteria for adequate dialysis, they were evaluated according to the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).<sup>17</sup> The study was approved by the Institutional Review Board (IRB No.: KY2016-394) of our centre and all patients provided written consent.

The definition of VA dysfunction is based on the consensus statement on VA to HD published by the Chinese Hospital Association<sup>18</sup> which stipulates the presence of any of the following signs and symptoms: 1) flow rate <600 mL/min and <500 mL/min for internal fistula graft and autologous internal fistula, respectively; 2) static pressure ratio of venous end of internal fistula graft or autologous internal fistula >0.5, or static pressure ratio of arterial end of internal fistula graft >0.75; 3) acute thrombosis; and 4) sufficient dialysis cannot be achieved when arterial pressure is <250 mmHg or venous pressure is >250 mmHg in the event that catheter blood flow is <200 mL/min or blood pump flow is <200 mL/min.

VA dysfunction event is defined as: 1) percutaneous angioplasty or surgery to treat AVF vascular stenosis; 2) Fogarty catheter thrombectomy, surgical thrombectomy or internal fistula reconstruction to treat AVF thrombosis; and 3) balloon dilatation and stent implantation to treat AVG stenosis.

Demographic and dialysis-related data were collected including age, gender, primary disease, dialysis age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) before dialysis and interval dialysis weight gain (IDWG). IDWG was derived by subtracting body weight before dialysis from body weight after previous dialysis and then dividing the result over body weight after previous dialysis.

In the middle of the week, fasting and resting venous blood was drawn from patients prior to dialysis. The blood samples were centrifuged at  $12,000 \times g$  at 4°C for 15 minutes to separate the serum from supernatant, and were stored at -80°C. Findings of biochemical parameters included haemoglobin (Hb), white blood cell (WBC), platelet (PLT), creatinine, albumin (Alb), total cholesterol (CHO), low-density lipoprotein cholesterol (LDL), B-type natriuretic peptide (BNP), C-reactive protein (CRP), intact parathyroid hormone (iPTH), blood calcium (Ca) and blood phosphorus (P). To evaluate adequacy of dialysis, urea Kt/V was used.<sup>17</sup>

Serum IL-18 was determined with enzyme-linked immunosorbent assay (Human IL-18 ELISA Kit, MyBioSource, San Diego, CA, USA). The cut-off for IL-18 was derived from the highest score obtained on Youden index.<sup>19</sup> Patients were classified as having either low (<199.3 pg/mL) or high ( $\geq$ 199.3 pg/mL) IL-18.

Statistical analyses were performed with Stata Statistical Software, Release 14 (StataCorp LP, College Station, TX, USA). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range; categorical variables were expressed as counts and percentages. Student's t-test or Mann-Whitney U test (non-normal distribution) was performed to compare differences among continuous variables; to compare categorical variables, chi-square test or Fisher's Exact test was used. Univariate or multifactorial logistic regression was used to analyse correlations between biochemical markers and dialysis-related data with VA dysfunction. Kaplan-Meier method and logarithmic rank test were used to compare adverse VA events between the 2 groups. Univariate and multivariate Cox regression analyses were used to examine risk factors for VA dysfunction. A value of P < 0.05 was considered statistically significant.

#### Results

There were 47 (58.8%) male and 33 (41.2%) female patients in the study. Their mean age was 60.93 years (SD 11.70 years, range 32–89 years). Median duration of dialysis was 3.14 years. Aetiologies of ESRD included chronic glomerulonephritis (n = 32, 40%), hypertensive nephropathy (n = 20, 25%), diabetic nephropathy (n = 9, 11.25%), polycystic kidney disease (n = 7, 8.75%) and other causes (n = 12, 15%). VA types included AVF (n = 64, 80%), AVG (n = 3, 3.75%) and TCC (n = 13, 16.25%).

There were 30 and 50 patients in the high and low IL-18 groups, respectively. In both groups, no differences were found in age, gender, dialysis age, diabetes-to-hypertension ratio, mean IDWG, SBP and DBP before dialysis (P > 0.05). Likewise, no differences were seen in results of biochemical parameters between the 2 groups (P > 0.05) including creatinine, BNP, CRP, iPTH, calcium-phosphorus product, Hb, WBC, PLT, CHO and LDL.

Serum albumin level was lower in the high IL-18 (41.6 g/L) group than low IL-18 (43.4 g/L) group (P = 0.003). During the study, 11 (13.75%) patients experienced VA dysfunction and required surgical intervention; 2 patients experienced VA events within half a year after access was established and the remainder had late-stage VA dysfunction. As shown in Table 1, although the incidence of VA dysfunction was higher in the high IL-18 group, the difference between the 2 groups (23.3% vs 8%) was not statistically significant (P = 0.973).

After adjustments for age, gender, dialysis age, iPTH, calcium-phosphorus product, CRP and albumin, multivariate logistic regression found that only IL-18 level was independently correlated with VA dysfunction events (Table 2). The high IL-18 group had a higher risk of VA dysfunction events than the low IL-18 group (odds ratio 9.47, 95% confidence interval 1.75–51.31, P = 0.009). Kaplan-Meier survival analysis (Fig. 1) showed that VA dysfunction in the high IL-18 group (P = 0.047).

Findings of multivariate Cox proportional hazards regression model revealed that decreased serum albumin level and increased serum IL-18 level were independent prognostic predictors of VA dysfunction events (Table 3). This predictive effect was still statistically significant even after adjustments were made for age, gender, inflammation (CRP) and calcium-phosphorus metabolism (calcium-phosphorus product). Additionally, a significant correlation between serum IL-18 level and reduced albumin level for VA dysfunction events was not found (P = 0.27). Findings from receiver operating characteristic curve analysis showed that when IL-18 and albumin levels were used with age and gender, short-term (within 1 year) risk of VA dysfunction can be predicted in HD patients (Fig. 2).

#### Discussion

This prospective cohort study demonstrated that elevated serum IL-18 level is correlated with VA dysfunction in patients on maintenance HD, and that it is also an independent risk factor for short-term VA dysfunction in them. Patients with high serum IL-18 concentration also had higher incidence of VA dysfunction. Additionally, the combination of albumin, IL-18, age and gender can be a better predictor of short-term risk of VA dysfunction in HD patients.

VA is the lifeline of HD patients,<sup>5</sup> and VA dysfunction is a major cause of insufficient dialysis that affects their long-term prognosis.<sup>4</sup> Due to its high patency rate, lower rate of complications and lower cost, AVF is recommended as the preferred access for HD by NKF-KDOQI.<sup>20</sup> This was clearly seen in our patients where 80% of them used AVF. In the 11 patients who experienced VA dysfunction, 4 (36.4%) of them had AVF, 5 (45.5%) had TCC and 2 (18.1%) had AVG. The issue of lowering the incidence of VA dysfunction, especially in HD patients with short- and long-term AVF dysfunction, continues to pose a huge challenge to dialysis physicians.

Variable	Aggregate (n = 80)	IL-18 <199.3 pg/mL (n = 50)	IL-18 ≥199.3 pg/mL (n = 30)	P Value
Mean age in years (SD)	60.9 (11.7)	60.3 (11.9)	62.0 (11.5)	0.731
Male gender (%)	47 (58.8)	32 (64.0)	15 (50.0)	0.109
Median dialysis age in years (IQR)	3.14 (2.25 - 6.75)	2.85 (2.15 - 6.23)	4.03 (2.42 - 7.42)	0.201
Diabetes mellitus (%)	9 (11.25)	6 (12)	3 (10)	0.392
Hypertension (%)	20 (25)	12 (24)	8 (26.7)	0.605
Mean IDWG, % (SD)	3.3 (1.2)	3.3 (1.2)	3.4 (1.2)	0.612
Median Kt/V (IQR)	1.36 (1.16 – 1.5)	1.37 (1.15 – 1.55)	1.30 (1.18 - 1.46)	0.538
Mean SBP, mmHg (SD)	142.1 (15.6)	143.8 (14.6)	139.4 (16.9)	0.122
Mean DBP, mmHg (SD)	79.8 (9.4)	80.7 (8.4)	78.3 (0.9)	0.154
Mean creatinine, µmol/L (SD)	1009.6 (250.2)	1014.8 (258.8)	1001 (239.1)	0.809
Median BNP, pg/mL (IQR)	2658 (1429 - 5084)	2978.5 (1362 - 5473)	1962 (1497 – 3712)	0.290
Median albumin, g/L (IQR)	42.2 (39.8 - 44.0)	43.4 (41.1 – 48.7)	41.6 (39.2 - 43.1)	0.003
Median C-reactive protein, mg/L (IQR)	2.9 (0.91 - 5.4)	2.6 (0.88 - 7.2)	3.0 (0.94 - 4.67)	0.992
Median iPTH, pg/mL (IQR)	385 (180.2 - 639.6)	353.2 (180.2 - 596.9)	390 (182.6 - 639.6)	0.936
Mean Ca $\times$ P, mg <sup>2</sup> /dL <sup>2</sup> (SD)	57.4 (16.8)	59.5 (15.8)	53.9 (18.2)	0.083
Median haemoglobin, g/L (IQR)	105.5 (95.5 – 113)	107 (97 – 115)	104 (94 – 113)	0.423
Median WBC count, $\times 10^{9}/L$ (IQR)	6.03 (5.24 - 7.36)	6.03 (5.41 - 7.48)	6.04 (5.18 - 7.24)	0.901
Median platelet count, $\times 10^{9}/L$ (IQR)	168 (138 – 211)	170 (139 – 212)	166 (136 – 211)	0.885
Median cholesterol, mmol/L (IQR)	4.2 (3.6 - 4.9)	4.1 (3.7 – 4.7)	4.6 (3.5 – 5.1)	0.604
Median LDL, mmol/L (IQR)	2.3 (1.9 – 2.8)	2.3 (1.9 – 2.7)	2.6 (1.8 - 3.3)	0.271
Vascular access dysfunction (%)	11 (13.75)	4 (8)	7 (23.3)	0.973

Table 1. Demographic and Clinical Characteristics of Haemodialysis Patients

BNP: B-type natriuretic peptide;  $Ca \times P$ : Calcium-phosphorus product; DBP: Diastolic blood pressure; IDWG: Interval dialysis weight gain; iPTH: Immunoreactive parathyroid hormone; IL-18: Interleukin-18; IQR: Interquartile range; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; SD: Standard deviation; WBC: White blood cell

The development and progression of AVF dysfunction is complex. In ESRD patients, some studies found that they often experienced systemic microinflammation of factors such as IL-6, interleukin-8 and TNF-alpha which contribute to the development of AVF dysplasia.<sup>21</sup> In uraemia, elevation of IL-6, TGF-beta and TNF-alpha also renders the vascular wall of mature AVF easy to remodel and narrow, and has been linked to the development of NIH and advanced AVF dysfunction.<sup>8,9</sup> However, the specific mechanisms that contribute to these adverse events have not been elucidated.

IL-18 is produced by an inactive 24-kDa precursor, preIL-18, that generates an 18-kDa protein with an endoprotease IL-1-beta-converting enzyme. IL-18 promotes maturation of T cells and natural killer

cells, as well as synthesis of cytokines and increased cytotoxicity.<sup>22</sup> IL-18 and its receptor are expressed in endothelial cells, vascular smooth muscle cells and macrophages.<sup>23</sup> Several studies have found that IL-18 is an important prognostic biomarker for atherosclerosis.<sup>24-6</sup> In a multifactorial analysis that controlled for age and gender, a significant correlation was found between IL-18 and carotid intima-media thickness that was independent of traditional risk factors for atherosclerosis.<sup>27</sup> It is postulated that IL-18 may contribute to the development of vascular diseases by inducing expression of IL-1-beta, TNF-alpha and NF-kappaB, inhibition of antiapoptosis factors (such as Bcl-2 and Bcl-XL), upregulation of expression of pro-apoptosis factors (such as Fas, Fas-L and Bcl-XS) and interference with mitogen-activated protein

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Parameter	Beta Coefficient	Standard Error	Odds Ratio (95% CI)	P Value
Univariate logistic regression				
Age	0.029	0.029	1.030 (0.974 – 1.089)	0.307
Male gender	1.300	3.004	3.671 (0.738 - 18.254)	0.112
Dialysis age	-0.007	0.085	0.918 (0.765 - 1.101)	0.356
Diabetes mellitus	-0.271	0.850	0.763 (0.086 - 6.771)	0.808
Hypertension	-0.463	0.522	0.630 (0.124 - 3.193)	0.577
IDWG	0.001	0.269	1.001 (0.591 – 1.696)	0.996
Systolic blood pressure	-0.007	0.021	0.994 (0.954 - 1.035)	0.753
Diastolic blood pressure	0.003	0.035	1.003 (0.937 – 1.073)	0.938
Albumin	-0.129	0.075	0.880 (0.744 - 1.039)	0.131
Haemoglobin	-0.013	0.021	0.987 (0.947 - 1.029)	0.543
iPTH	-0.001	0.001	0.999 (0.997 – 1.001)	0.269
Calcium-phosphorus product	-0.006	0.020	0.994 (0.957 – 1.034)	0.775
C-reactive protein	0.013	0.018	1.103 (0.977 – 1.049)	0.486
Interleukin-18	1.253	2.369	3.500 (0.929 - 13.188)	0.064
Multivariate logistic regression				
Age	0.029	0.038	1.030 (0.958 – 1.107)	0.429
Male gender	1.819	5.876	6.167 (0.953 - 39.910)	0.056
Dialysis age	-0.074	0.096	0.929 (0.759 – 1.137)	0.474
Albumin	-0.198	0.097	0.820 (0.650 - 1.035)	0.095
iPTH	-0.001	0.002	0.999 (0.996 - 1.002)	0.507
Calcium-phosphorus product	0.024	0.032	1.024 (0.964 – 1.088)	0.441
C-reactive protein	0.008	0.024	1.008 (0.962 - 1.056)	0.750
Interleukin-18	2.248	8.164	9.471 (1.748 - 51.307)	0.009

CI: Confidence interval; IDWG: Interval dialysis weight gain; iPTH: Immunoreactive parathyroid hormone

kinase-dependent signalling pathways. IL-18 may also promote proliferation and migration of vascular smooth muscle cells.<sup>28,29</sup>

While some studies had detected increased levels of serum IL-18 in CKD patients and those on CAPD,<sup>12</sup> others found a correlation between elevated IL-18 and poor prognosis in HD patients including increased hospitalisation.<sup>15</sup> Our study found that elevated IL-18 was significantly correlated with VA dysfunction and this finding persisted even after adjustment had been made for age, gender, blood pressure, diabetes, dialysis age, ultrafiltration volume, anaemia, infection, secondary hyperparathyroidism, nutrition status and blood lipid level. These findings were also similar to those found for the correlation between IL-18 and atherosclerosis.



Fig. 1. Kaplan-Meier survival analysis showed that haemodialysis patients with high IL-18 ( $\geq$ 199.3 pg/mL) level had more vascular access dysfunction events (P = 0.047).

Table 3. Multivariate (	Cox Regression Anal	ysis of Vascu	lar Access Dystuncti	ion 1n Haemo	dialysis Patients					
Covariate	Model	1	Model	2	Model .	3	Model 4		Model	10
	Hazards Ratio (95% CI)	<i>P</i> Value	Hazards Ratio (95% CI)	<i>P</i> Value	Hazards Ratio (95% CI)	<i>P</i> Value	Hazards Ratio (95% CI)	<i>P</i> Value	Hazards Ratio (95% CI)	<i>P</i> Value
Age	1.020 (0.97 - 1.07)	0.78					1.009 (0.97 - 1.05)	0.702	1.007 (0.96 - 1.05)	0.776
Male gender	4.004 (0.86 - 18.71)	0.078			3.883 (0.83 - 18.21)	0.085	3.700 (0.78 - 17.58)	0.1	3.766 (0.78 - 18.13)	0.098
IL-18	3.694 (1.07 – 12.79)	0.039	5.834 (1.63 - 20.83)	0.007	5.939 (1.71 – 20.66)	0.005	5.740 (1.63 - 20.22)	0.007	5.654 (1.51 – 21.1)	0.01
Albumin			0.827 (0.71 - 0.97)	0.017	0.811 (0.68 - 0.97)	0.022	0.817 ( $0.68 - 0.98$ )	0.03	0.817 (0.68 - 0.99)	0.036
CRP									1.004 (0.97 - 1.04)	0.795
$Ca\times P$									0.997 (0.96 - 1.04)	0.883
$Ca \times P$ : Calcium-phose	phorus product; CI: (	Confidence ir	terval; CRP: C-react	tive protein; l	IL-18: Interleukin-1	8				

Our finding that elevated IL-18 and decreased albumin levels are independent risk factors for VA dysfunction, and that the combination of IL-18, albumin, age and gender can better predict risk of short-term VA dysfunction in HD patients, suggests that the causes of VA dysfunction are attributed to multiple factors.

Late AVF dysfunction is closely correlated with NIH, and the contribution of IL-18 to AVF dysfunction requires further study. It is possible that IL-18 may have a role in the activation of the signal pathways described earlier, or it is involved in some causative mechanisms that are specific to ESRD patients.

Some of the limitations of our study included small sample size and short follow-up period. Consequently, our finding of a correlation between serum IL-18 level and VA dysfunction—and whether this correlation persists after a longer period of observation—may not be extrapolated to a larger HD population unless it is validated by further research. Also, the lack of regular ultrasound data on VA meant that our study recorded only adverse events that were related to access function in cases that required surgical intervention. Consequently, our results may be skewed. Finally, our study excluded IL-18 levels of healthy individuals from analysis.

### Conclusion

This study has shown that serum IL-18 level is closely correlated with VA function in HD patients, and that elevated IL-18 can be used as an independent risk factor for short-term, adverse VA-related events in outpatients on HD. IL-18 can be used with serum albumin, age and gender to predict likelihood of such events in HD patients. Future cohort studies could involve larger sample sizes to validate our finding on the correlation between IL-18 and VA function. Further research is needed to elucidate how IL-18 contributes to VA dysfunction and new interventions that can improve access function and prognosis in HD patients.



Fig. 2. Receiver operating characteristic (ROC) curve analysis of biochemical parameters in predicting vascular access dysfunction in haemodialysis patients. A: Serum albumin. B: Serum IL-18. C: Serum IL-18 with serum albumin. D: Serum IL-18 with serum albumin and gender. E: Serum IL-18 with serum albumin, gender and age. IL-18: Interleukin-18







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