scientific reports

Check for updates

OPEN

The impact of depression on platelet activation, cardiocerebral vascular events and arteriovenous fistula dysfunction in patients undergoing haemodialysis

Ya Xu[1], Shunjuan Zhang[1], Wenyu Xia[2], Ying Xiong[1], Xianglei Wang[1], Yuhong Liu[1], Zhengrong Li[1] & Yunfeng Xia[1]✉

Depression is a common psychiatric disorder among patients undergoing maintenance haemodialysis (MHD). Depression may reportedly contribute to poor prognosis in several ways, including its effects on platelet function. We hypothesised that depression contributes to the occurrence of cardiocerebral vascular events (CCVE) and dysfunction of arteriovenous fistula (DAVF) in patients undergoing MHD through its effects on platelets. In this prospective cohort study, patients undergoing MHD were recruited and divided into depression and non-depression groups according to their Hamilton Depression Scale (HAMD) scores. The 286 enrolled patients had 103 occurrences of depressive symptoms (prevalence = 36.01%). Compared with the non-depression group, depression group had a significantly higher cumulative prevalence of CCVE and DAVF during follow-up. Cox regression analysis indicated that higher HAMD scores and lower plasma platelet distribution width (PDW) were common risk factors for CCVE and DAVF. Furthermore, HAMD scores were significantly negatively correlated with plasma PDW and was the main variable affecting changes in PDW, as indicated by multiple linear regression analysis. Depression may increase the risk of CCVE and DAVF in patients undergoing MHD by activating platelets. Plasma PDW may be a convenient indicator of platelet activation status and may predict the risk of CCVE and DAVF.

Keywords Depression, Haemodialysis, Cardiocerebral vascular events, Arteriovenous fistula dysfunction, Platelet

Cardiocerebral vascular events (CCVE) and dysfunction of arteriovenous fistula (DAVF) are two major categories of adverse events of concern for nephrologists. CCVE are the leading cause of death in patients undergoing maintenance haemodialysis (MHD). Its prevention and treatment are limited to the management of traditional risk factors such as hypertension, hyperlipidaemia, and diabetes mellitus etc. However, the efficacies of these approaches are considered insufficient. Other factors, such as depression, are also thought to be associated with cardiovascular mortality. Arteriovenous fistula (AVF) is the most popular vascular access currently used for haemodialysis. Compared with other vascular access, it can improve the prognosis for patients undergoing MHD[1]. Therefore, increasing the rate of AVF use and maintaining patency are particularly important. The Dialysis Outcomes and Practice Patterns Study has indicated that the primary patency rate (from establishing AVF to its dysfunction) in two years is only approximately 50% in many developed countries[2]. To better combat CCVE and DAVF beyond the management of traditional risk factors, identifying and actively preventing nonconventional risk factors for CCVE and DAVF may help achieve breakthroughs.

[1]Department of Nephrology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 40016, China. [2]Duke Kunshan University, 2020 Data Science, Kunshan 215300, China. ✉email: yunfengxia0920@126.com

Depression is a common complication in patients undergoing MHD, accounting for 20–40% of all patients[3]. It may serve as a non-conventional risk factor for CCVE[4]. Depression diminishes patients' adherence to treatment as well as beneficial diets and lifestyles[5]. Long-term depression may also lead to unfavourable pathological and physiological changes within the patient's body[6].

Platelets are involved in arteriovenous thrombosis and inflammatory responses, and their dysfunction is closely associated with the development of CCVE or DAVF[7,8]. Like neuronal cells, platelets contain signalling molecules that play important roles in the progression of depression, including 5-hydroxytryptamine (5-HT) transporter and brain-derived neurotrophic factor[9]. Increased 5-HT2A receptors[10,11] and decreased 5-HT transporters[12] have also been found in platelets of patients with depression, which may affect platelet transport, storage, and response to 5-HT. Mutations in the brain-derived neurotrophic factor gene are often accompanied by enhanced platelet aggregation capacity and an increased risk of thrombosis[13]. Based on the same material basis as platelets and central nervous system neurons, many clinical studies have shown an increase in platelet activation markers in patients with depression 11[14–16], In a study involving 300 patients with cardiovascular disease comorbid with depression, it was noted that patients had higher serotonin receptor levels and more platelet aggregation compared to those with uncomplicated depression[11]. Similarly, some studies also confirmed that patients with coronary artery disease combined with depression had elevated platelet specific volume and higher levels of platelet activation markers[17,18]. It is suggested that depression-induced platelet activation triggers the release of related factors that exacerbate the progression of atherosclerosis, thereby increasing the risk of adverse cardiovascular events. Based on these findings, it is plausible to hypothesize that depression is also associated with platelet activation in patients undergoing MHD, which may further worsen cardiovascular outcomes.

The platelet aggregation test is the gold standard for detecting platelet function, but its cost is high in clinical practice, and patient compliance is poor. Decreased platelet distribution width (PDW) is associated with platelet activation[19]. Clinical studies have shown that PDW may be a sensitive diagnostic indicator for certain cardiovascular events in patients with chronic kidney disease[20,21], which is also convenient and inexpensive. The impact of depression on platelet function, CCVE, and DAVF in patients undergoing MHD is currently unclear. This study aimed to conduct a preliminary exploration based on actual data from patients undergoing MHD at our blood purification centre.

Materials and methods

Study population

Patients undergoing MHD were recruited from the First Affiliated Hospital of Chongqing Medical University, China, between June 2022 and August 2023. These patients underwent dialysis for more than three months. At enrolment, their medical status was stable, and their expected survival period exceeded one year. The exclusion criteria were as follows: (1) patients with communication disorders or mental illnesses other than depression; (2) patients with cirrhosis, lymphoma, thrombocytopenic purpura, or other diseases that significantly affected platelet function; (3) patients with advanced malignant tumours, severe heart failure, or unstable medical conditions whose life expectancy did not exceed one year; and (4) patients unable or unwilling to cooperate with the researchers. All enrolled patients underwent routine haemodialysis through an AVF for 3–4 h, three times per week, and were routinely anticoagulated with unfractionated heparin or low-molecular-weight heparin in each dialysis session. Patients were administered other therapeutic medications, such as antihypertensive, anaemia-correcting, and phosphorus-reducing agents, according to their specific medical situations. This study was registered with the Clinical Trial Centre (NCT06070805) and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (permission number 2022–103). The study complied with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Grouping methods

The Hamilton Rating Scale for Depression (HAMD) was used to assess the depressive status of all enrolled patients. The HAMD Depression Scale, developed by Hamilton in 1960, has good reliability and validity and can be used to diagnose depression, assess severity, and measure treatment effectiveness[22]. The scale mainly includes cognitive disturbance, sleep disturbance, anxiety/somatisation, weight, diurnal variation, retardation, and other dimensions, and the 24 items cover almost all symptoms of depression[23]. Depression scoring was performed by a trained researcher during dialysis through observation and communication. Patients were assigned to the non-depression (NDP) group if their HAMD score was < 8 or to the depression (DP) group if their HAMD score was ≥ 8.

Data collection

General clinical data, including sex, age, primary disease, duration of dialysis, blood pressure, body mass index, history of alcohol consumption or smoking, comorbidities (including history of cardiocerebrovascular disease, diabetes, and stroke), and use of platelet inhibitor medications, were collected. Several laboratory tests were conducted during the enrolment and study period, including platelet count, mean platelet volume, PDW, platelet-large cell ratio, platelet crit, haemoglobin, calcium, phosphorus, intact parathyroid hormone, creatinine, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, C-reactive protein (CRP), and beta-2 microglobulin. Based on the results of the repeated examinations conducted over the entire study period, the mean value of each index was calculated for the final analysis.

Follow-up and definition of endpoints

The patients were monitored for health changes during each dialysis session, and information regarding the occurrence of CCVE and DAVF during the follow-up period was collected and compared between the groups.

CCVE were defined as the first occurrence of angina pectoris, myocardial infarction, episodes of heart failure requiring clinical intervention, arrhythmic episodes with clinically significant symptoms, transient ischaemic attack, cerebral infarction, or cerebral haemorrhage during the observational period. DAVF was diagnosed if a patient presented with one or more of the following conditions rendering the AVF unsatisfactory for effective haemodialysis: (1) loss of AVF murmur on clinical auscultation; (2) notable weakening or disappearance of pulsation in the AVF; (3) echocardiography showing interruption of blood flow, thrombosis within the fistula, or stenosis of the venous outflow tract at or near the anastomotic site; or (4) maximum blood flow < 200 mL/min in the AVF during dialysis.

Statistical methods

Normally distributed values were assessed using histograms. Normally distributed measures are expressed as mean ± standard deviation. An independent sample t-test was used to compare two groups, and analysis of variance (ANOVA) was used to compare multiple groups. Non-normally distributed measures are expressed as medians. Comparisons between two groups were performed using the Mann–Whitney *U* test, and comparisons among multiple groups were performed using the Kruskal – Wallis test. Categorical variables are expressed as numbers of cases and percentages (%), and comparisons between groups were performed using the chi-square test or Fisher's exact test, as appropriate. Based on the analytical results of the intergroup comparisons, statistical methods such as the Cox regression model, Kaplan–Meier analysis, and multiple linear regression models were used to analyse the risk factors for CCVE and DAVF, the effect of depression on patient survival status, and laboratory indices associated with changes in plasma PDW levels. Statistical analyses were performed using SPSS 26.0, and $p < 0.05$ was considered statistically significant.

Results

Comparison of baseline characteristics between the NDP and DP groups

There were approximately 500 patients undergoing long-term dialysis in our dialysis centre, and we included all patients who met the inclusion criteria and were willing to participate in the study. Finally, 297 patients undergoing dialysis were enrolled, 286 of whom were included in the statistical analysis. Of the 11 excluded patients, six had a significant loss of laboratory tests due to poor compliance, one underwent kidney transplantation in the middle of follow-up, and four were transferred to other dialysis centres. According to the HAMD scores, 103 of 286 (approximately 36%) patients were assigned to the DP group, and 183 were assigned to the NDP group (Fig. 1). The general clinical data and laboratory indicators of the groups are shown in Tables 1 and 2 separately, and the proportion of primary diseases is shown in Fig. 2. Compared with the NDP group, the DP group experienced more cardiovascular and cerebrovascular diseases. Lower diastolic blood pressure, blood creatinine, serum albumin, intact parathyroid hormone, and PDW were observed in the DP group compared with the NDP group. The differences between the groups were statistically significant ($p < 0.05$).

Comparison of CCVE and DAVF occurrence

The median follow-up duration was 274 days (237–376), during which 47 CCVE occurred, including 14 acute coronary syndromes, 16 acute heart failures, 10 cerebral infarctions, four cerebral haemorrhages, and three other CCVE (Fig. 3). CCVE were reported in 10% (18/183) and 28% (29/103) of patients in the NDP and DP groups, respectively ($\chi^2 = 15.93$, $p < 0.001$). DAVFs were reported in 9% (17/183) and 22% (23/103) of patients in the NDP and DP groups, respectively ($\chi^2 = 9.32$, $p = 0.002$). The incidence of CCVE and DAVF was significantly higher in the DP group than in the NDP group (Fig. 4).

Analysis of risk factors for CCVE and DAVF

A multivariate Cox regression analysis model was constructed, incorporating CCVE as a dependent variable and using the HAMD score, age, history of cardiovascular and cerebrovascular diseases, diabetes mellitus, diastolic

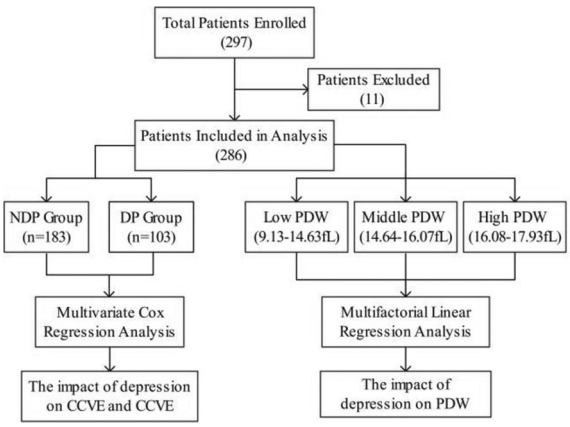

Fig. 1. Flow chart for the methodology. *NDP* non-depression (HAMD < 8); *DP* depression (HAMD ≥ 8); *PDW* platelet distribution width; *CCVE* cardio-cerebral vascular events; *DAVF* dysfunction of arteriovenous fistula.

Variable	All patients (n = 286)	NDP group (n = 183)	DP group (n = 103)	*t/z/χ2*	*p*-value
Age (y)	57.64 ± 14.44	56.83 ± 14.29	59.09 ± 14.65	−1.27	0.205[a]
Male (%)	122 (43)	76 (42)	46 (45)	0.26	0.607[b]
BMI (Kg/m^2)	22.47 ± 3.35	22.59 ± 3.47	22.25 ± 3.12	0.84	0.400[a]
Smoke (%)	127 (44)	79 (43)	48 (47)	0.32	0.575[b]
Drink (%)	102 (36)	63 (34)	39 (38)	0.34	0.560[b]
Time on dialysis (months)	64.55 ± 45.90	66.3 ± 46.32	61.9 ± 45.24	0.73	0.466[c]
With diabetes mellitus (%)	83 (29)	47 (26)	36 (35)	2.75	0.097[b]
With cardio-cerebrovascular disease (%)	129 (45)	68 (37)	61 (59)	12.96	0.000*
SBP (mmHg)	139.82 ± 15.25	139.45 ± 15.14	140.50 ± 15.52	−0.56	0.576[a]
DBP (mmHg)	75.30 ± 10.32	76.22 ± 10.62	73.65 ± 9.61	2.04	0.042[a]*
Antiplatelets user (%)	149 (52)	90 (49)	59 (57)	1.73	0.188[b]

Table 1. Basic information of the included patients undergoing MHD according to the HAMD scores. Data are shown as numbers (percentages) or $\bar{x}$±s. *NDP* non-depression (HAMD < 8); *DP* depression (HAMD ≥ 8); *SBP* systolic BP; *DBP* diastolic BP. *p-value < 0.05 shows a statistically significant difference. a, Independent samples t-test; b, Chi-square test; c, Mann–Whitney U test.

Variable	All patients (n = 286)	NDP group (n = 183)	DP group (n = 103)	*t /z*	*p*-value
β 2 M(mg/L)	33.50 (27.70, 39.40)	34.10 (27.80, 39.40)	33.36 (27.00, 40.30)	-0.36	0.723[c]
TG (mmol/L)	1.52 (0.99, 2.13)	1.51 (0.96, 2.15)	1.58 (1.17, 2.13)	-1.25	0.212[c]
TC (mmol/L)	3.71 (3.09, 4.48)	3.69 (3.17, 4.37)	3.88 (3.03, 4.59)	-0.09	0.930[c]
LDL-C (mmol/L)	1.97 (1.47, 2.51)	2.01 (1.54, 2.58)	1.92 (1.38, 2.44)	-1.52	0.129[c]
HDL-C (mmol/L)	1.11 (0.89, 1.35)	1.09 (0.89 ,1.32)	1.07 (0.84 ,1.35)	-0.08	0.936[c]
Cr (μmol/L)	966.15 ± 252.68	991.61 ± 256.78	920.58 ± 239.71	2.27	0.024[a]*
BUN (mmol/L)	21.93 ± 6.50	22.07 ± 6.21	21.67 ± 7.00	0.50	0.618[a]
Alb (g/L)	41.62 ± 3.98	42.24 ± 3.74	40.52 ± 4.17	3.59	0.000a*
CRP (mg/ml)	3.38 (2.04, 6.36)	3.20 (2.04, 3.20)	3.80 (2.17, 6.77)	-1.49	0.136[c]
iPTH (pg/ml)	293.30 (178.50, 457.40)	332.00 (178.53, 458.67)	266.13 (162.07, 457.40)	-2.32	0.020c*
Ca (mmol/L)	2.17 ± 0.16	2.16 ± 0.17	2.18 ± 0.15	-0.53	0.596[a]
P (mmol/L)	1.78 ± 0.41	1.79 ± 0.38	1.76 ± 0.46	0.68	0.499[a]
Hb (g/L)	114.99 ± 14.11	115.61 ± 13.58	113.89 ± 15.00	0.99	0.324[a]
PLT (×109/L)	175.28 ± 49.79	175.68 ± 48.96	174.58 ± 51.46	0.18	0.857[a]
MPV (fl)	10.14 ± 1.03	10.08 ± 1.01	10.24 ± 1.08	-1.27	0.206[a]
PDW (fl)	15.63 (14.20, 16.20)	15.80 (14.30, 16.23)	15.27 (14.06, 16.10)	-2.38	0.018c*
PCT (%)	0.18 ± 0.05	0.18 ± 0.05	0.18 ± 0.05	-0.04	0.966[a]

Table 2. Laboratory testing parameters of the included patients undergoing MHD according to HAMD scores. Data are shown as $\bar{x}$±s or median. *NDP* non-depression (HAMD < 8); *DP* depression (HAMD ≥ 8); *β2M* β2 Micro globulin; *TG* triglyceride; *TC* total cholesterol; *LDL-C* low-density lipoprotein; *HDL-C* high-density lipoprotein; *Cr* creatinine; *BUN* blood urea nitrogen; *Alb* albumin; *CRP* C-reactive protein; *iPTH* intact parathyroid hormone; *Ca* calcium; *P* phosphate; *Hb* haemoglobin; *PLT* platelet count; *MPV* mean platelet volume; *PDW* platelet distribution width; *P-LCR* platelet-large cell ratio; *PCT* platelet crit. *p-value < 0.05 shows a statistically significant difference. a, Independent samples t-test; c, Mann–Whitney U test.

blood pressure, PDW, blood calcium, creatinine, triglycerides, intact parathyroid hormone, CRP, and albumin as independent variables. Higher HAMD scores, advanced age, and lower PDW were independent prognostic indicators for CCVE. Using the same Cox regression model and replacing the dependent variable from CCVE with DAVF, we found that higher HAMD scores, hypertriglyceridaemia, and lower PDW were independent prognostic indicators of DAVF (Table 3). Kaplan–Meier survival curves also showed a statistically significantly greater cumulative incidence of CCVE and DAVF in the DP group than in the NDP group (Fig. 5).

Analysis of relevant factors affecting changes in plasma PDW levels

We categorised all patients into three groups according to plasma PDW levels and analysed the differences in laboratory parameters among the groups. Statistical analysis revealed significant differences across the subgroups in HAMD scores, time on dialysis, intact parathyroid hormone concentrations, and diastolic blood pressure (Table 4). Spearman's correlation analysis indicated a negative correlation between PDW and HAMD scores ($r = -0.15$, $p = 0.014$). However, no significant correlation was observed between other platelet factors and HAMD

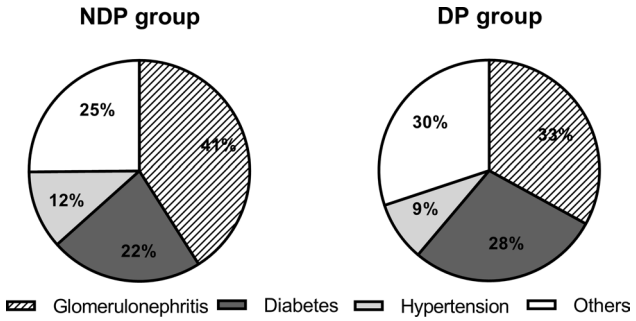

Fig. 2. The proportion of primary disease in the NDP and DP groups. *NDP* non-depression (HAMD < 8); *DP* depression (HAMD ≥ 8).

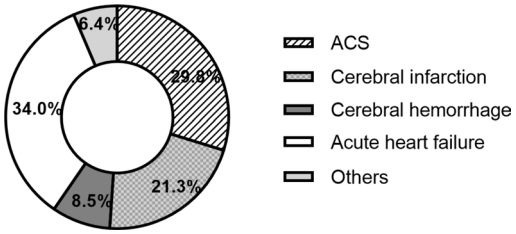

Fig. 3. The composition of cardiocerebral vascular events in all patients undergoing MHD during follow-up. *Note* Data are shown as percentages. *ACS* acute coronary syndrome.

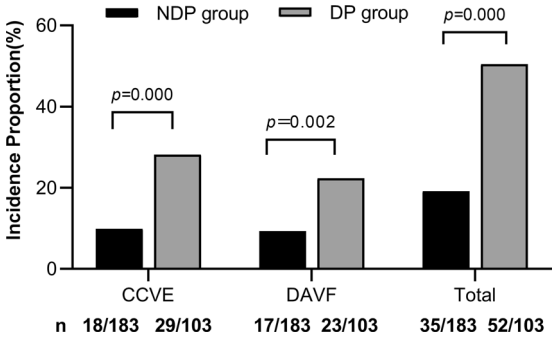

Fig. 4. Comparison of the occurrence of CCVE and DVAF in the NDP and NDP groups. *Note* Data are presented as percentages. The chi-square test was used for comparisons between groups. n denotes the achievement of the patients/overall patients. *NDP* non-depression (HAMD < 8); *DP* depression (HAMD ≥ 8); *CCVE* cardio-cerebral vascular events; *DAVF* dysfunction of arteriovenous fistula.

scores. A multifactorial linear regression analysis model was constructed with PDW as the dependent variable and HAMD score, time on dialysis, antiplatelet therapy use, diastolic blood pressure, intact parathyroid hormone, CRP, albumin, BMI, and HDL-C as the independent variables. Changes in PDW were significantly correlated with HAMD scores, dialysis duration, and diastolic blood pressure (Table 5).

Discussion

CCVE and DAVF are the most concerning clinical events in patients undergoing MHD, while the former is the leading cause of death in over 50% of patients undergoing MHD who ultimately die[24], and the latter directly shuts down the "lifeline" to regular dialysis. Given that patients have a limited number of vessels suitable for AVF, preventing DAVF and maximising longevity are important. CCVE and DAVF are closely associated with vasculopathy and varying degrees of coagulopathy, as well as related conditions, such as stenosis, embolism, or haemorrhage, in patients undergoing dialysis. Currently, clinical measures for the prevention and management of CCVE and DVAF include controlling blood pressure and glucose levels, lowering blood lipids, and using platelet inhibitors. However, these therapeutic measures predominantly focus on managing traditional risk factors and exhibit limited efficacy. The effects of nonconventional risk factors, such as depression, have not received sufficient attention from the public.

Variable	Cardio-cerebral vascular events				Dysfunction of arteriovenous fistula			
	Univariate cox regression		Multivariate cox regression		Univariate cox regression		Multivariate cox regression	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
HAMD	1.058 (1.029–1.088)	0.000	1.038 (1.002–1.075)	0.038*	1.046 (1.013–1.081)	0.01	1.037 (1.000–1.075)	0.048*
Age	1.084 (1.057–1.111)	0.000	1.053 (1.020–1.087)	0.001*	1.011 (0.989–1.033)	0.34	1.000 (0.969–1.031)	0.982
CCVD	0.165 (0.080–0.342)	0.000	0.434 (0.198–0.952)	0.037*	0.639 (0.343–1.189)	0.16	0.929 (0.457–1.889)	0.838
DM	0.242 (0.135–0.435)	0.000	0.579 (0.305–1.099)	0.095	0.939 (0.469–1.882)	0.86	1.233 (0.560–2.715)	0.604
DBP	0.930 (0.905–0.956)	0.000	0.971 (0.929–1.014)	0.179	0.979 (0.950–1.009)	0.17	0.975 (0.935–1.017)	0.239
PDW	0.930 (0.905–0.956)	0.000	0.832 (0.698–0.992)	0.040*	0.851 (0.732–0.990)	0.04	0.815 (0.690–0.962)	0.016*
Ca	0.762 (0.125–4.658)	0.77	0.720 (0.076–6.873)	0.776	0.224 (0.033–1.503)	0.12	0.311 (0.037–2.640)	0.285
Cr	0.998 (0.997–1.000)	0.01	1.000 (0.999–1.002)	0.753	0.999 (0.998–1.000)	0.09	0.999 (0.998–1.000)	0.169
TG	1.146 (0.984–1.333)	0.08	1.107 (0.922–1.328)	0.276	1.258 (1.103–1.434)	0.001	1.287 (1.104–1.501)	0.001*
iPTH	0.998 (0.997–1.000)	0.02	0.999 (0.998–1.001)	0.226	1.000 (0.999–1.001)	0.82	1.000 (0.999–1.001)	0.653
CRP	1.020 (1.010–1.030)	0.000	1.012 (0.998–1.026)	0.095	0.996 (0.962–1.032)	0.83	0.974 (0.916–1.035)	0.392
Alb	0.882 (0.831–0.937)	0.000	0.993 (0.916–1.075)	0.855	0.976 (0.903–1.054)	0.54	1.029 (0.938–1.129)	0.549

Table 3. Univariate and multivariate Cox regression predicting CCVE and DAVF in patients undergoing MHD. *CCVD* cardiovascular and cerebrovascular diseases; *DM* diabetes mellitus; *DBP* diastolic BP; *PDW* platelet distribution width; *Ca* calcium; *Cr* creatinine; *TG* triglyceride; *iPTH* intact parathyroid hormone; *CRP* C-reactive protein; *Alb* albumin. *p-value < 0.05 shows a statistically significant difference.

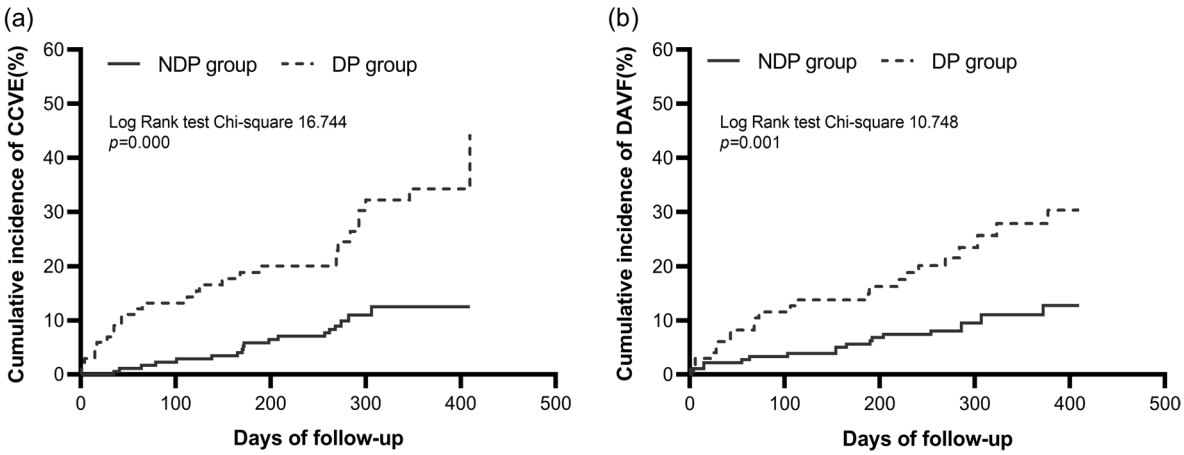

Fig. 5. Cumulative incidence curves for CCVE (**a**) and DAVF (**b**) for patients undergoing MHD with different patterns of depressive symptoms. *NDP* non, depression (HAMD < 8); *DP* depression (HAMD ≥ 8); *CCVE* cardiocerebral vascular events; *DAVF* dysfunction of arteriovenous fistula.

Depression is a common psychiatric disorder among patients undergoing MHD. Several studies have indicated that depression may promote CCVE through its effect on platelet function[25]. The present study also reported depressive symptoms in 36% of the patients undergoing MHD. Compared with non-depressed patients, depressed patients experienced a greater rate of comorbid cardiovascular disease; significantly lower levels of blood creatinine, albumin, parathyroid hormone, PDW, and diastolic blood pressure; and higher cumulative incidence rates of CCVE and DAVF during follow-up. Cox regression analysis indicated that higher HAMD scores and lower plasma PDW levels were common risk factors for CCVE and DAVF in patients undergoing MHD. Studies have shown that PDW is a marker of inflammatory thrombosis in several diseases[26–28]. In this study, changes in plasma PDW were significantly and negatively correlated with HAMD scores in patients undergoing MHD. Previous studies have also reported that plasma PDW levels are negatively correlated with platelet p-selectin, platelet/

	Low PDW group (9.13–14.63fL)	Middle PDW group (14.64–16.07fL)	High PDW group (16.08–17.93fL)	*p*-value
HAMD	4.00 (1.00, 11.25)	4.00 (2.00, 10.00)	3.00 (1.00, 9.75)	0.044c*
Age (y)	57.11 ± 16.34	58.32 ± 13.12	57.81 ± 13.62	0.849[a]
Time on dialysis (months)	42.00 (15.00, 64.00)	64.50 (24.75, 113.75)	67.50 (39.00, 100.25)	0.000c*
SBP (mmHg)	142.11 ± 14.42	137.70 ± 15.28	140.41 ± 15.80	0.093[a]
DBP (mmHg)	76.88 ± 9.84	72.81 ± 10.52	76.51 ± 10.29	0.007a*
β 2 M (mg/L)	34.10 (27.35, 38.75)	32.50 (27.76, 41.00)	34.82 (28.89, 40.22)	0.730[c]
TG (mmol/L)	1.53 (0.96, 2.33)	1.57 (1.17, 2.15)	1.42 (0.90, 2.10)	0.160[c]
TC (mmol/L)	3.68 (3.03, 4.50)	3.75 (3.28, 4.59)	3.83 (3.05, 4.31)	0.544[c]
LDL, C (mmol/L)	1.83 (1.46, 2.25)	2.08 (1.62, 2.68)	1.98 (1.45, 2.56)	0.309[c]
HDL, C (mmol/L)	1.11 (0.93, 1.31)	1.06 (0.84, 1.32)	1.15 (0.93, 1.41)	0.105[c]
Cr (μmol/L)	955.42 ± 239.17	962.00 ± 237.54	982.26 ± 283.18	0.760[a]
BUN (mmol/L)	21.35 ± 6.82	22.30 ± 6.30	22.14 ± 6.38	0.563[a]
Alb (g/L)	41.16 ± 4.28	41.33 ± 4.04	42.43 ± 3.54	0.070[a]
CRP (mg/ml)	4.04 (2.47, 7.65)	3.57 (1.79, 6.40)	2.89 (1.90, 5.95)	0.091[c]
iPTH (pg/ml)	250.75 (151.73, 382.70)	368.03 (221.43, 603.10)	292.28 (180.40, 506.05)	0.001c*
Ca (mmol/L)	2.15 ± 0.15	2.19 ± 0.16	2.17 ± 0.18	0.357[a]
P (mmol/L)	1.75 ± 0.39	1.80 ± 0.42	1.79 ± 0.42	0.619[a]
Hb (g/L)	115.29 ± 14.19	114.31 ± 15.13	115.52 ± 13.40	0.859[a]

Table 4. MHD patients cohort characteristics by PDW tertile. *PDW* platelet distribution width, *β2M* β2 microglobulin; *TG* triglyceride; *TC* total cholesterol; *LDL* C, low-density lipoprotein; *HDL* C, high-density lipoprotein; *Cr* creatinine; *BUN* blood urea nitrogen; *Alb* albumin; *CRP* C, reactive protein; *iPTH* intact parathyroid hormone; *Ca* calcium; *P* phosphate; *Hb* haemoglobin. Data are shown as $\overline{x}$±s or median. **p*-value < 0.05 shows a statistically significant difference. a, ANOVA; c, Kruskal – Wallis test.

Variable	*β*	SE	*p*	Lower	Upper
HAMD (per 1 increase)	−0.030	0.015	0.048*	−0.060	0.000
Time on dialysis (per 1 month increase)	0.010	0.002	0.000*	0.005	0.014
DBP (per 1 mmHg increase)	−0.027	0.010	0.008*	−0.047	0.007
iPTH (per 1 pg/ml increase)	0.000	0.000	0.457	0.000	0.001
CRP (per 1 mg/ml increase)	−0.002	0.009	0.816	−0.019	0.015
Antiplatelet drugs use (vs no)	0.060	0.206	0.772	−0.347	0.467
Alb (per 1 g/L increase)	0.052	0.028	0.064	−0.003	0.108
BMI (per 1 kg/m^2 increase)	−0.017	0.032	0.587	−0.080	0.045
HDL, C (per 1 mmol/L increase)	0.433	0.283	0.127	−0.125	0.991

Table 5. Multivariate linear regression analysis of factors influencing PDW. *DBP* diastolic blood pressure; *iPTH* intact parathyroid hormone; *CRP* C-reactive protein; *Alb* albumin; HDL, C, high-density lipoprotein. *β*, Regression coefficient; *SE,* standard error of *β*; *Lower* and *upper,* 95% confidence interval. **p*-value < 0.05 shows a statistically significant difference.

leukocyte aggregates, and vascular hemophilic factor levels and positively correlated with clotting time[19]. These findings suggest that diminished plasma PDW levels may be a marker of platelet activation.

Depression often leads to decreased appetite, malnutrition, and low medication adherence, all of which are important triggers for the development of CCVE[29,30]. A prospective cohort study has reported that depression is an independent risk factor for cardiovascular and all-cause mortality in patients undergoing MHD and that CCVE are a direct cause of cardiovascular and all-cause mortality[31], in agreement with the results of our study. Our study also revealed notably lower serum albumin and creatinine concentrations in depressed patients than in non-depressed patients, suggesting that depression may impair nutritional status. Malnutrition, chronic inflammation, and atherosclerosis mutually reinforce clinical syndromes, leading to poor prognosis in patients undergoing MHD[32]. Malnutrition can exacerbate metabolic disorders, promote the progression of chronic inflammatory states and atherosclerosis, and lead to severe cardiovascular and cerebrovascular pathologies[33].

The effects of depression in patients are not restricted to malnutrition or atherosclerosis. Long-term depression may be associated with platelet activation, thus disrupting the balance of the coagulation process and subsequently increasing susceptibility to CCVE in patients undergoing MHD[34]. The dysregulated metabolism of 5-HT in neuronal cells is a crucial mechanism in the pathogenesis of depression. The dense granules within platelets contain most of the 5-HT in the body. Moreover, the storage, transport, and metabolism of 5-HT within

platelets are similar to those observed in central nervous system neuronal cells and may underlie the effects of depression on platelet function[35,36]. Platelet activation plays a very important role in chronic inflammation, atherosclerosis, and thrombosis and may also potentially link depression, immune dysfunction, and coagulation complications[37]. A study has found that patients with cardiovascular disease and higher depression scores showed higher platelet 5-HT2A receptor density and were more likely to experience adverse cardiac events during follow-up[11]. A meta-analysis has also indicated that antidepressant use is an independent risk factor for haemorrhagic adverse events in patients with cardiovascular disease[16]. This study revealed a significant association between higher depression scores and lower plasma PDW. It was found in the Cox risk-proportionality model that both higher depression scores and lower plasma PDW were risk factors for the development of CCVE and DAVF, suggesting that depression may contribute to the occurrence of CCVE and DAVF, partly by platelet activation. Previous studies have reported that patients with emotional disorders, such as depression, have lower plasma PDW levels than healthy controls and have demonstrated a significant negative correlation between PDW and patient depression scores[38]. Another study has reported that plasma PDW is strongly associated with the occurrence of ST-elevation myocardial infarction in young patients with coronary artery disease[39]. In patients with chronic kidney disease not undergoing dialysis, a prospective cohort study has found that a lower PDW was an independent risk factor for cardiovascular events[21]. Based on prior findings combined with those of this study, we believe that PDW is an affordable and easily determined parameter with high potential to serve as a useful laboratory marker for assessing platelet function and thrombosis risk in patients undergoing MHD.

This study had some limitations. First, as this was a single-centre study with a small sample size, the findings require further confirmation. Second, owing to the relatively short follow-up period, only CCVE and DAVF were used as endpoints, and cardiovascular and all-cause deaths were not included in the analysis. Owing to patient noncompliance and budget constraints, the evaluation of platelet function was relatively limited, requiring further verification of the results through more accurate methods. This study revealed the mutual influence and possible mechanism between depression and malnutrition inflammatory syndrome, CCVE, DAVF, and platelet activation; however, the actual mechanism requires further confirmation.

Conclusion

This study is the first to simultaneously analyse the possible mechanisms of depression and its effects on CCVE and DAVF in patients undergoing MHD. Our results suggest that depression may increase the risk of CCVE and DAVF in patients undergoing MHD by activating platelets. Plasma PDW may be a convenient indicator of platelet activation status and may predict the risk of CCVE and DAVF. These findings provide insights in the prevention of CCVE and DAVF in MHD patients in the future.

Data availability

All data generated or analysed during this study are included in this published article and its Supplementary Information files.

Received: 31 October 2023; Accepted: 28 August 2024
Published online: 04 September 2024

References

1. Roca Tey, R. Vascular access for haemodialysis: An unresolved issue. *Nefrologia.* **30**, 280–287. https://doi.org/10.3265/Nefrologia.pre2010.Apr.10349 (2010).
2. Pisoni, R. L. *et al.* International comparisons of native arteriovenous fistula patency and time to becoming catheter-free: Findings from the dialysis outcomes and practice patterns study (DOPPS). *Am. J. Kidney Dis.* **77**, 245–254. https://doi.org/10.1053/j.ajkd.2020.06.020 (2021).
3. Palmer, S. *et al.* Prevalence of depression in chronic kidney disease: Systematic review and meta-analysis of observational studies. *Kidney Int.* **84**, 179–191. https://doi.org/10.1038/ki.2013.77 (2013).
4. Jiang, W. Depression and cardiovascular disorders in the elderly. *Clin. Geriatr. Med.* **36**, 211–219. https://doi.org/10.1016/j.cger.2019.11.003 (2020).
5. Theofilou, P. Medication adherence in Greek hemodialysis patients: The contribution of depression and health cognitions. *Int. J. Behav. Med.* **20**, 311–318. https://doi.org/10.1007/s12529-012-9231-8 (2013).
6. Tian, N., Chen, N. & Li, P.K.-T. Depression in dialysis. *Curr. Opin. Nephrol. Hypertens.* **30**, 600–612 (2021).
7. Kaplan, Z. S. & Jackson, S. P. The role of platelets in atherothrombosis. *Hematol. Am. Soc. Hematol. Educ. Program.* **2011**, 51–61. https://doi.org/10.1182/asheducation-2011.1.51 (2011).
8. Viecelli, A. K. *et al.* The pathogenesis of hemodialysis vascular access failure and systemic therapies for its prevention: Optimism unfulfilled. *Semin. Dial.* **31**, 244–257. https://doi.org/10.1111/sdi.12658 (2018).
9. Canobbio, I. Blood platelets: Circulating mirrors of neurons?. *Res. Pract. Thromb. Haemost.* **3**, 564–565. https://doi.org/10.1002/rth2.12254 (2019).
10. Mendelson, S. D. The current status of the platelet 5-HT(2A) receptor in depression. *J. Affect. Disord.* **57**(13), 24. https://doi.org/10.1016/s0165-0327(99)00177-9 (2000).
11. Williams, M. S. *et al.* Platelet serotonin signaling in patients with cardiovascular disease and comorbid depression. *Psychosom. Med.* **81**, 352–362 (2019).
12. Williams, M. S. Platelets and depression in cardiovascular disease: A brief review of the current literature. *World J. Psychiatry.* **2**, 114–123. https://doi.org/10.5498/wjp.v2.i6.114 (2012).
13. Amadio, P. *et al.* BDNFVal66met polymorphism: A potential bridge between depression and thrombosis. *Eur. Heart J.* **38**, 1426–1435. https://doi.org/10.1093/eurheartj/ehv655 (2017).
14. Musselman, D. L. *et al.* Platelet activation and secretion in patients with major depression, thoracic aortic atherosclerosis, or renal dialysis treatment. *Depress. Anxiety.* **15**, 91–101. https://doi.org/10.1002/da.10020 (2002).
15. Morel-Kopp, M.-C. *et al.* The association of depression with platelet activation: Evidence for a treatment effect. *J. Thromb. Haemost.* **7**, 573–581. https://doi.org/10.1111/j.1538-7836.2009.03278.x (2009).

16. Nochaiwong, S. *et al.* Use of serotonin reuptake inhibitor antidepressants and the risk of bleeding complications in patients on anticoagulant or antiplatelet agents: A systematic review and meta-analysis. *Ann. Med.* **54**, 80–97. https://doi.org/10.1080/07853890.2021.2017474 (2022).
17. Peng, M. *et al.* Association of BDNF gene polymorphisms with co-morbid depression in coronary heart disease and its mechanism of platelet activity. *Chin. J. Clin. Psychol.* **26**, 230–233. https://doi.org/10.16128/j.cnki.1005-3611.2018.02.005 (2018).
18. Delle Chiaie, R. *et al.* Persistence of subsyndromal residual symptoms after remission of major depression in patients without cardiovascular disease may condition maintenance of elevated platelet factor 4 and β-thromboglobulin plasma levels. *J. Affect. Disord.* **150**, 664–667. https://doi.org/10.1016/j.jad.2013.03.017 (2013).
19. Izzi, B. *et al.* Platelet distribution width is associated with p-selectin dependent platelet function: Results from the moli-family cohort study. *Cells.* **10**, 2737. https://doi.org/10.3390/cells10102737 (2021).
20. Su, N. *et al.* The relationship between platelet distribution width and new-onset cardiovascular disease events in patients with peritoneal dialysis. *Ren. Fail.* **44**, 1640–1648. https://doi.org/10.1080/0886022X.2022.2130802 (2022).
21. Yu, Z. *et al.* The association between platelet indices and cardiovascular events in chronic kidney disease patients without dialysis. *Int. Urol. Nephrol.* **53**, 961–971. https://doi.org/10.1007/s11255-020-02696-4 (2021).
22. Zheng, Y. P. *et al.* Validity and reliability of the Chinese Hamilton Depression Rating Scale. *Br. J. Psychiatry* **152**, 660–664. https://doi.org/10.1192/bjp.152.5.660 (1988).
23. Sun, X. Y., Li, Y. X., Yu, C. Q. & Li, L. M. Reliability and validity of depression scales of Chinese version: A systematic review. *Zhonghua Liu Xing Bing Xue Za Zhi.* **38**, 110–116 (2017).
24. Collins, A. J. *et al.* US Renal Data System 2013 Annual Data Report. https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/usrds/prior-data-reports/2013(2014).
25. Amadio, P., Zarà, M., Sandrini, L., Ieraci, A. & Barbieri, S. S. Depression and cardiovascular disease: The viewpoint of platelets. *Int. J. Mol. Sci.* **21**, e7560. https://doi.org/10.3390/ijms21207560 (2020).
26. Xia, W., Chen, W., Tu, J., Ni, C. & Meng, K. Prognostic value and clinicopathologic features of platelet distribution width in cancer: A meta-analysis. *Med. Sci. Monit.* **24**, 7130–7136. https://doi.org/10.12659/MSM.913040 (2018).
27. Zaccardi, F. *et al.* Platelet mean volume, distribution width, and count in type 2 diabetes, impaired fasting glucose, and metabolic syndrome: A meta-analysis. *Diabetes Metab. Res. Rev.* **31**, 402–410. https://doi.org/10.1002/dmrr.2625 (2015).
28. Weymann, A. *et al.* Platelets cellular and functional characteristics in patients with atrial fibrillation: A comprehensive meta-analysis and systematic review. *Med. Sci. Monit. Basic. Res.* **23**, 58–86. https://doi.org/10.12659/msmbr.902557 (2017).
29. Cukor, D., Rosenthal, D. S., Jindal, R. M., Brown, C. D. & Kimmel, P. L. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int.* **75**, 1223–1229. https://doi.org/10.1038/ki.2009.51 (2009).
30. Koo, J.-R. *et al.* Association of depression with malnutrition in chronic hemodialysis patients. *Am. J. Kidney Dis.* **41**, 1037–1042. https://doi.org/10.1016/s0272-6386(03)00201-4 (2003).
31. Van Dijk, S. *et al.* How baseline, new-onset, and persistent depressive symptoms are associated with cardiovascular and non-cardiovascular mortality in incident patients on chronic dialysis. *J. Psychosom Res.* **74**, 511–517. https://doi.org/10.1016/j.jpsychores.2013.03.001 (2013).
32. Stenvinkel, P. *et al.* Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int.* **55**, 1899–1911. https://doi.org/10.1046/j.1523-1755.1999.00422.x (1999).
33. Graterol Torres, F. *et al.* Evolving concepts on inflammatory biomarkers and malnutrition in chronic kidney disease. *Nutrients.* **14**, 4297. https://doi.org/10.3390/nu14204297 (2022).
34. Tagliarini, C., Carbone, M. G., Pagni, G., Marazziti, D. & Pomara, N. Is there a relationship between morphological and functional platelet changes and depressive disorder?. *CNS. Spectr.* **27**, 157–190. https://doi.org/10.1017/S1092852920001959 (2022).
35. Andres, A. H., Rao, M. L., Ostrowitzki, S. & Entzian, W. Human brain cortex and platelet serotonin2 receptor binding properties and their regulation by endogenous serotonin. *Life Sci.* **52**, 313–321. https://doi.org/10.1016/0024-3205(93)90223-p (1993).
36. Stahl, S. M., Woo, D. J., Mefford, I. N., Berger, P. A. & Ciaranello, R. D. Hyperserotonemia and platelet serotonin uptake and release in schizophrenia and affective disorders. *Am. J. Psychiatry.* **140**, 26–30. https://doi.org/10.1176/ajp.140.1.26 (1983).
37. Ponomarev, E. D. Fresh evidence for platelets as neuronal and innate immune cells: Their role in the activation, differentiation, and deactivation of Th1, Th17, and Tregs during tissue inflammation. *Front. Immunol.* **9**, 406. https://doi.org/10.3389/fimmu.2018.00406 (2018).
38. Wei, Y. *et al.* Characteristics of platelet-associated parameters and their predictive values in Chinese patients with affective disorders. *BMC Psychiatry.* **22**, 150. https://doi.org/10.1186/s12888-022-03775-9 (2022).
39. Cetin, M. S. *et al.* Platelet distribution width and plateletcrit: Novel biomarkers of ST elevation myocardial infarction in young patients. *Kardiol. Pol.* **75**, 1005–1012. https://doi.org/10.5603/KP.a2017.0135 (2017).

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing.

Author contributions

Y.X.: Conceptualization; data curation; formal analysis; investigation; methodology; visualization; writing—original draft. S.Z.: Conceptualization; investigation. W.X.: Conceptualization; investigation. Y.X.: Conceptualization; investigation. X.W.: Conceptualization; investigation. Y.L.: Conceptualization; investigation. Z.L.: Conceptualization; investigation. Y.X.: Conceptualization; methodology; writing—review and editing; project administration; supervision.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-71490-4.

Correspondence and requests for materials should be addressed to Y.X.