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Serum IL-6, albumin and comorbidities are closely correlated with symptoms of depression in patients on maintenance haemodialysis

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Abstract

Background. Depression may be associated with activation of pro-inflammatory cytokines and increased long-term mortality in patients on maintenance haemodialysis (MHD). There are numerous reports regarding the association of depression with inflammatory status, co-morbidities and nutritional condition, but few of these studies have explored the possible correlations between depression, age and

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economic status. The study explores the possible correlations between depression and demographic, socio-economic, clinical and laboratory variables.

Methods. One hundred and forty-six MHD patients (65 males and 81 females, mean age: 63.8 ± 15.2 years) were enrolled in this cross-sectional study. Demographic and socio-economic status as well as clinical and laboratory variables including co-morbidities were obtained. The self-administered Beck Depression Inventory (BDI) was used to determine the presence or absence of depression symptoms. Biochemical parameters (serum albumin, triglyceride, cholesterol, etc.) and dialysis dosage delivery (Kt/V and urea reduction rate or URR) were examined. All the patients were on high-flux biocompatible dialysers for MHD. The presence of an inflammatory state was assessed by determinations of plasma interleukin-6 (IL-6) levels.

Results. The prevalence of depression (BDI ≥14) was 45.9%. In patients found to have symptoms of depression, no statistically significant difference was shown with respect to age, gender, smoking habits or clinical characteristics. However, these patients were more likely to have a number of co-morbidities. They also had higher levels of serum IL-6 and total cholesterol as well as lower serum albumin and Kt/V values. The BDI correlated significantly with Kt/V values ($r = -0.19$; $P < 0.05$), levels of serum albumin ($r = -0.28$; $P < 0.005$) and serum IL-6 ($r = 0.47$; $P < 0.001$). Multivariate stepwise forward logistic regression analysis showed a direct correlation between BDI and IL-6 levels (P = 0.001; OR = 1.537) and between BDI and co-morbidities (P = 0.037; OR = 3.584). There was an inverse correlation between BDI and serum albumin levels (P = 0.006; OR = 0.145) and between BDI and age (P = 0.007; OR = 0.96). The rate of depression was significantly lower for the elderly patients (age ≥75 years) compared with those below 64 years of age. The percentage of personal monthly disposable income at or above Taiwan dollar (TWD) >10 000 was similar in patients aged ≥75 and those below 64 years old.

Conclusions. Maintenance haemodialysis patients with symptoms of depression may have higher serum IL-6 and lower serum albumin levels. The prevalence of depression was lower in elderly patients at or above 75 years old, and no correlation was found with socio-economic status. Factors including co-morbid conditions, serum IL-6, albumin and age may help predict which patients may be predisposed to develop symptoms of depression.

Keywords: age; depression; haemodialysis; IL-6; Kt/V

Introduction

Depression is common in patients with end-stage renal disease on maintenance haemodialysis (MHD), with prevalence rates ranging between 30% and 60%. As is known in the general population as well as in people suffering from chronic diseases, there is evidence that depression is associated with mortality in MHD patients [1,2]. To date, possible theoretical explanations reported [3,4] include physical and emotional stress related to dietary constraints, time restrictions, functional limitations, co-morbidities and adverse effects of medications [5–7]. In addition, lack of adherence to dialysis treatment and its efficacy as well as hyperparathyroidism, malnutrition, chronic inflammation and elevated plasma cytokine levels may all have a significant role in bringing about symptoms of depression.

Previous studies have shown that activation of pro-inflammatory cytokines such as interleukin-6 (IL-6) or C-reactive protein (CRP) may be involved in the development of symptoms of depression in patients with end-stage renal disease (ESRD) [8–10]. However, apart from the correlations between depression and a number of socio-demographic characteristics, little is known about the clinical and laboratory variables (including inflammation markers such as IL-6) that may be associated with symptoms of depression in MHD patients [11].

Identification of the possible causative factors in the development of depression may allow medical providers to come up with adequate therapeutic strategies. However, few studies have evaluated the possible correlations of depression with problems inherent in ESRD patients, namely a state of chronic inflammation, the presence of co-morbidities and the nutritional status. In addition, none of these studies has examined the potential impact of age and personal disposable income as well, given the fact that the cost of MHD is fully covered by the Taiwan Bureau of National Health Insurance [12]. The present study investigates the correlations between depression and demographic, clinical, and laboratory variables in MHD patients, and attempts to identify the significant variables in the development of depressive symptoms in such patients in a single HD centre.

Materials and methods

One hundred and forty-six ESRD patients on MHD (65 males and 81 females) in a single nephrology unit (Cardinal Tien Hospital, CTH) were enrolled in this cross-sectional study, and informed consent was secured from all the subjects. Patients deemed eligible were between 18 and 90 years of age, known to have ESRD of at least 3 months duration, and receiving MHD three times every week. This study was approved by the hospital's Health Research and Ethics Committees.

Demographic data such as age, sex, marital status, education and religious affiliation were obtained by a questionnaire. Clinical data regarding the cause of renal failure, co-morbidities, current medications and the most recent laboratory exams (full blood count, pre- and post-dialysis urea and electrolytes, taken within the past 1 month) were obtained from the patients' respective medical records. Patients found to have major infections and patients who had been taking immunosuppressive agents for at least 1 month were excluded from the study.

Body weight (post-dialysis weight), body mass index (BMI), mean blood pressure, serum high-sensitivity CRP (hs-CRP), IL-6, albumin, creatinine (Cr), total cholesterol, haematocrit, clearance of urea per dialysis (Kt/V) and normalized protein catabolism rate (nPCR) were recorded at baseline. Mid-week pre-dialysis fasting blood samples were also collected from each patient. Pre- and post-dialysis levels of serum urea were recorded for evaluation of single-pool Kt/V (Daugirda method) [13]. The nPCR was calculated from monthly kinetic modelling sessions by applying the two-blood urea nitrogen (2-BUN) method [14] to pre-dialysis BUN level, and an estimate of equilibrated post-dialysis BUN level obtained using the Daugirdas–Schniditz equation. Body mass index (BMI in kg/m^2) was calculated from patient height obtained at study entry and post-dialysis weight measurements obtained at monthly kinetic modelling sessions.

Co-morbidity was defined as the sum total number of concurrent illnesses and problems, such as diabetes mellitus, hypertension, congestive heart failure, coronary artery disease, cerebrovascular disease, peripheral

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Table 1. Demographic and clinical characteristics of the patients classified according to BDI (n = 146)

		BDI <14 (n = 78)	BDI ≥14 (n = 68)	Chi-square test	P
Gender	Male	38	27	1.195	0.274
	Female	40	41		
Age	≤64 years	33	39	4.426	0.109
	65–74 years	19	16		
	≥75 years	26	13		
Spouse	Yes	54	37	3.398	0.065
	No	24	31		
Education	Below high school	44	42	3.260	0.196
	High school	19	20		
	Above high school	15	6		
Religion	Yes	68	60	0.037	0.847
	No	10	8		
Smoking	Yes	65	59	0.334	0.563
	No	13	9		
Co-morbidity[a]	Yes	60	61	4.183	0.041
	No	18	7		

[a]Co-morbidity includes diabetes mellitus, hypertension, congestive heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic lung disease, non-skin cancer or alcohol abuse.

vascular disease, chronic lung diseases, non-skin cancer or alcohol abuse [15]. The presence of an inflammatory state was assessed by IL-6 and hs-CRP levels. Because the use of cellulose-based dialysers has been related to depression, biocompatible polysulphone dialysers (FX60; Helixone) were used on all the subjects [16].

The following biochemical parameters were checked using an AU5000 automated chemistry analyser (Olympus, Tokyo, Japan): total calcium [normal value (NV) 8.5–10.5 mg/dL], serum phosphate (Pi, NV 2.3–4.6 mg/dL) and serum albumin (NV 3.5–4.5 g/dL). Serum iPTH levels were measured by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Serum hs-CRP (Immulite, DPC Cirrus Inc., Los Angeles, CA, USA) and IL-6 (R&D Systems, Minneapolis, MI, USA) were measured by the ELISA method.

The self-administered Beck Depression Inventory (BDI) was distributed by a healthcare assistant during a HD session. In the absence of standard BDI categories for patients with ESRD, the presence and/or severity of depression were categorized using BDI scores for the normal population: non-depression symptoms (scores of 0–13) and depression symptoms (14–63) [17].

Statistics

Continuous variables were expressed as means ± SD, and categorical values were expressed in percentages. Two group differences were analysed by t-test and Fisher's exact test, and $\chi 2$ analysis was used to analyse categorical data. Pearson correlations were derived to evaluate for possible correlations between biological markers and symptoms of depression. Linear regressions were used to analyse the role of biological parameters on depression. Multivariate stepwise forward logistic regression analysis was used to determine the independent risk factors for depression. Significance was defined as $P < 0.05$. Statistical analyses were performed using

Table 2. Laboratory characteristics of the patients stratified according to BDI (n = 146)

	BDI <14 (n = 78)	BDI ≥14 (n = 68)	P
Haematocrit (%)	30.8 ± 3.5	30.2 ± 4.9	0.412
Haemoglobin (g/dL)	11.0 ± 7.5	10.0 ± 1.6	0.267
Blood urea nitrogen (mmol/L)	24.6. ± 7.4	25.8 ± 7	0.337
Creatinine (umol/L)	892.8 ± 195	954.7 ± 221	0.106
Interleukin-6 (pg/mL)	6.89 ± 1.65	8.0 ± 1.55	<0.001
hs-CRP (mg/dL)	0.61 ± 0.73	0.74 ± 0.96	0.166
Potassium (mmol/L)	4.4 ± 0.8	4.2 ± 0.8	0.075
Calcium (mmol/L)	2.33 ± 0.2	2.28 ± 0.25	0.2
Phosphate (mmol/L)	1.58 ± 0.48	1.68 ± 0.48	0.3
Albumin (g/L)	39 ± 4	37 ± 3	0.004
Triglycerol (mmol/L)	1.44 ± 0.97	1.73 ± 1.06	0.089
Total cholesterol (mmol/L)	4.58 ± 1.11	4.22 ± 1.06	0.048
Fasting plasma glucose (mmol/L)	7.2 ± 3.4	7.7 ± 4.4	0.47
Kt/V	1.45 ± 0.4	1.36 ± 0.3	0.117
Urea reduction ratio	74.1 ± 11.5	72.7 ± 8.09	0.389
Ferritin (μg/L)	486.4 ± 466.7	500.7 ± 430	0.858
Iron saturation (fraction saturation, %)	0.32 ± 0.12	0.31 ± 0.14	0.676
Intact-parathyroid hormone (ng/L)	496.5 ± 520.5	431.3 ± 440	0.419
nPCR (g/kg/day)	1.2 ± 0.4	2.8 ± 13.3	0.342
Body mass index (kg/m^2)	22.4 ± 3.6	22.5 ± 3.8	0.931

Data are given as mean ± standard deviation.

Table 3. Correlates of BDI and multiple variance in MHD patients (Pearson's correlation)

Variables	r	P
Albumin	−0.281	<0.05
IL-6	0.466	<0.001
hs-CRP	0.358	0.166
K	−0.111	0.181
Ca	−0.067	0.425
P	0.079	0.343
Uric acid	0.049	0.561
Hb	−0.042	0.617
TG	0.122	0.143
T-Chol	−0.166	<0.05
Glucose	0.075	0.368
Kt/V	−0.188	<0.05
URR	−0.206	<0.05
Ferritin	0.074	0.372
TSAT	0.059	0.482
IPTH	−0.081	0.330
nPCR	0.098	0.241
Months on HD	−0.126	0.129
Disposable income	−0.059	0.481

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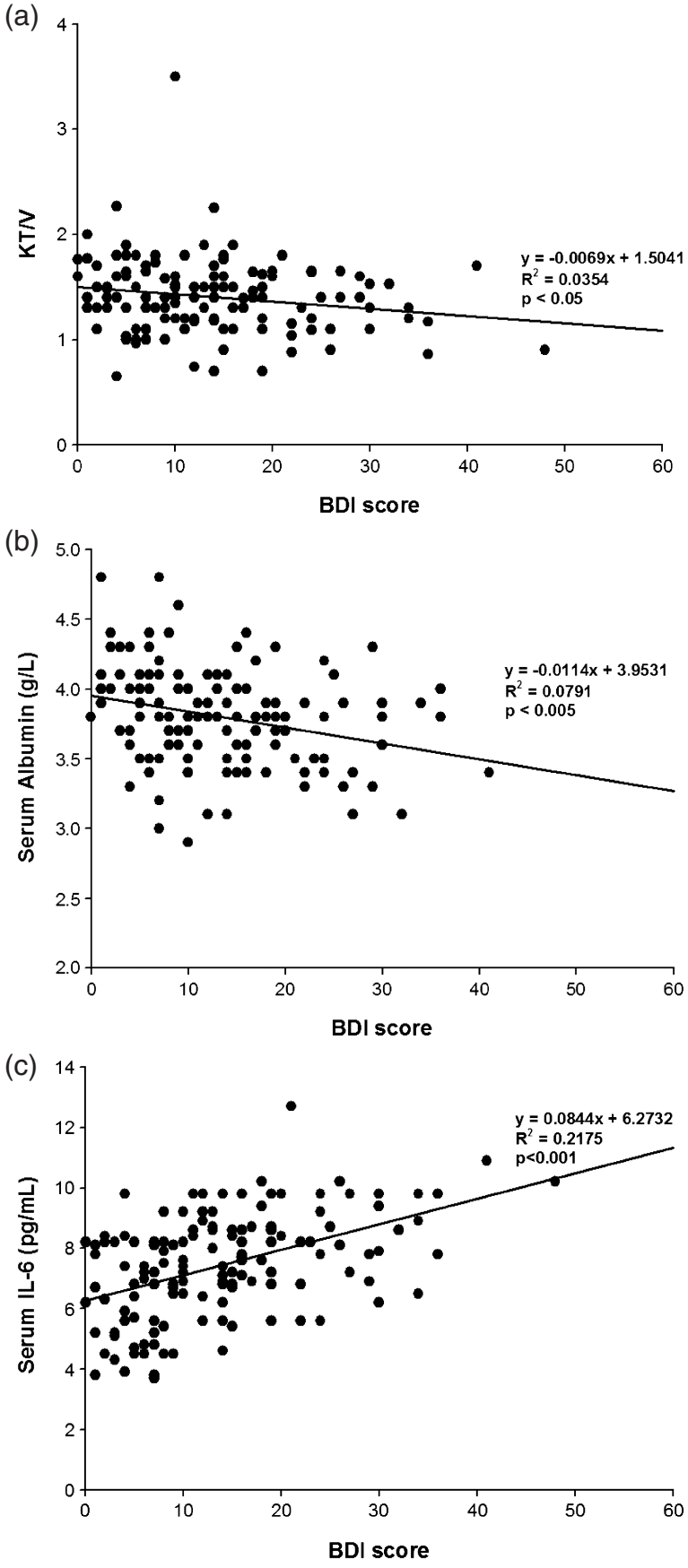

Fig. 1. Correlations between BDI scores and (**a**) Kt/V values, (**b**) serum albumin levels and (**c**) serum IL-6 levels.

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the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the 146 participants was 63.8 ± 15.2 years (range 18–94 years); 55.5% of whom were women. All the patients had been on MHD for 0.3–22.5 years (mean ± SD = 4.9 ± 4.4 years duration). A BDI cut-off score of ≥14 was used to determine whether any patient had symptoms of depression. The mean BDI score was 21.5 ± 7.6 in the group with symptoms of depression (n = 68, 46.6%) and 6.8 ± 3.6 in the group without symptoms of depression (n = 78).

Comparisons of the demographic and laboratory data for the patients with and without symptoms of depression are shown in Tables 1 and 2, respectively. No sex preponderance was observed in patients with BDI scores ≥14 (50.6% in females vs. 41.5% for males, P = 0.27). Likewise, there were no statistically significant differences in age, sex, smoking habits or clinical characteristics. However, patients who had symptoms of depression were more likely to have co-morbid states (60/78 vs. 61/68, P < 0.05, Table 1).

Table 2 shows that there were no significant differences in BMI, NPCR, Kt/V, serum ferritin, or iPTH in patients with and without depression. However, patients with symptoms of depression had higher levels of serum IL-6 (6.89 ± 1.65 vs. 8.0 ± 1.55 pg/mL, P < 0.001) and lower levels of serum albumin (39 ± 4 vs. 37 ± 3 g/L, P < 0.005) and total cholesterol (4.58 ± 1.11 vs. 4.22 ± 1.06 mmol/L, P < 0.005). With regard to the role of adequate dialysis, we found no significant difference in Kt/V and hs-CRP values between the two patient groups.

Upon analysis of correlations between BDI and other variables, BDI was found to be significantly correlated with levels of albumin (P = 0.001), IL-6 (P < 0.001), total cholesterol (P = 0.045), URR (P = 0.013) and Kt/V (P = 0.023) (Table 3). As shown in Figure 1, the BDI correlated significantly with Kt/V (r = −0.19; P < 0.05), serum albumin (r = −0.28; P < 0.005) and serum IL-6 (r = 0.47; P < 0.001), respectively. There was a trend towards a negative correlation between IL-6 and albumin levels, but this did not reach statistical significance.

Although numerous demographic, clinical and laboratory variables correlated with BDI in univariate analysis, multivariate stepwise forward logistic regression analysis showed only a direct correlation between BDI and IL-6 [P = 0.001, OR = 1.537 (95% CI = 1.18–1.99)] and between BDI and co-morbidities [P = 0.037, OR = 3.584 (95% CI = 1.08–1.99)]. There was an inverse correlation between BDI and albumin [P = 0.006, OR = 0.145 (95% CI = 0.037–0.574)] and between BDI and age [P = 0.007, OR = 0.96 (95% CI = 0.932–0.989)] (Table 4).

Table 4. Independent risk factors for depression in MHD patients based on logistic regression analysis

	B[a]	Standard error	Odds ratio	95% CI	P-value
Age	−0.41	0.015	0.96	0.932–0.989	0.007
Albumin	−1.930	0.702	0.145	0.037–0.574	0.006
IL-6	0.430	0.133	1.537	1.184–1.994	0.001
Co-morbidities	1.278	0.612	3.589	1.081–11.919	0.037

CI, confidence interval.
[a]Coefficient for the constant.

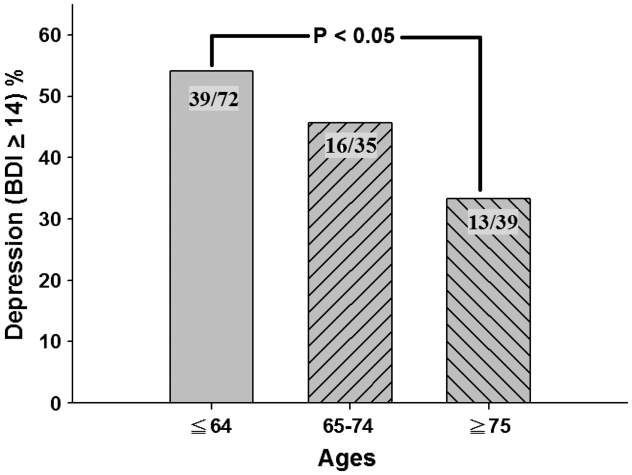

Fig. 2. The prevalence of depression was significantly lower in patients aged ≥75 compared with the patients ≤64 years old (13/39 = 33.3% vs. 39/72 = 54.2%, P < 0.05).

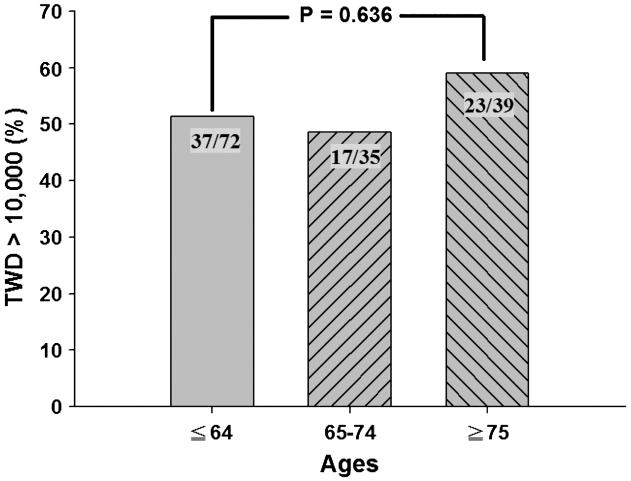

Fig. 3. The percentage of monthly disposable income more than TWD 10 000 was similar in patients aged ≥75 compared with the patients aged ≤64 (23/39 = 58.79% vs. 37/72 = 51.39%, P = 0.636).

Since logistic regression showed a negative correlation between BDI and age, we divided the patients into three age groups, namely ≤64 years, 65–74 years and ≥75 years, to determine the correlation between age and symptoms of depression. The prevalence of depression was significantly lower for patients aged ≥75 years compared with those ≤64 years (33.3% vs. 54.2%, P < 0.05) (Figure 2), but there was no significant difference with regard to the percentage of personal monthly disposable income at or above TWD >10 000 (USD 312.5) in these two patient groups (58.79% vs. 51.39%, P = 0.636) (Figure 3). However, those patients aged ≤64 years had higher levels of serum albumin (3.93 ± 0.32 vs. 3.67 ± 0.37 g/day, P ≤ 0.001) and lower number of co-morbid diseases (2.3 ± 1.5 vs. 3.0 ± 1.0 g/day, P ≤ 0.05)

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compared with patients aged ≥75 years. However, both groups had similar nPCR values (1.24 ± 0.32 vs. 1.19 ± 0.51, P = 0.58).

Discussion

Depression is common among patients on MHD, and we found that 46.6% of our patients had symptoms of depression. Worldwide, depression is ~1.5 to two times more common in women than men, and its initial onset peaks during the childbearing years [18–20]. This female preponderance is known to persist into older age, but in our patients, there was no significant role for a difference in gender that might have any influence on symptoms of depression in MHD patients.

It is well known that personal disposable income or financial security is an important factor influencing depression [21]. Patients who have been on MHD for quite a long time or who are relatively financially secure may be less likely to present with symptoms of depression [7,22]. Since 1995, the Taiwan Bureau of National Health Insurance (BNHI) has provided a full healthcare coverage for patients on MHD, including an exemption for payment of the monthly health insurance fee. This 'zero out-of-pocket' policy has significantly benefited MHD patients. Our data show no statistically significant difference with regard to personal disposable income for elderly patients (age ≥75 years) as well as for patients ≤64 years old, which suggests that economic status may not have a significant role in symptoms of depression.

A state of advanced chronic kidney disease and dialysis are known to be associated with a state of chronic inflammation, as evidenced by either elevated levels of various pro-inflammatory cytokines or increased levels of acute-phase proteins [12,23–25]. This state of chronic inflammation is also seen in patients with MHD and concurrent hyperhomocysteinaemia [26–29] or secondary hyperparathyroidism [10]. Depression is independently associated with markedly increased risks of morbidity and mortality [2,15,30–32]. There is numerous evidence to suggest that CRP and its precursor, IL-6, are positively associated with an increased incidence and severity of depression. We have also shown that patients with depression symptoms have higher levels of serum IL-6.

With regard to the role of the dialyser, it has been reported that the prevalence of depression is lower in MHD patients who are dialysed using more biocompatible polysulphone dialysers [16]. Since all of our patients were on this type of dialyser, the dialyser itself did not have any significant role in this study. Our results revealed the levels of IL-6 were not significantly correlated with Kt/V, which suggests that with adequate dialysis (average Kt/V in non-depression was 1.36 ± 0.3 vs. in depression was 1.45 ± 0.4, P = 0.017) and use of biocompatible dialysers, the dialysis dosage per se does not modulate serum IL-6 levels. However, the BDI scores were significantly correlated with IL-6. Multivariate stepwise forward logistic regression analysis showed a direct correlation between BDI scores and levels of serum IL-6, which suggests that IL-6 may play a significant role in the development of symptoms of depression in our MHD patients. A negative correlation between BDI and Kt/V implies that higher doses of dialysis may be associated with decreased symptoms of depression. Thus, levels of IL-6 and adequacy of dialysis were strongly associated with depression in our MHD patients.

Our study found that patients with BDI scores ≥14 have lower levels of serum albumin compared with patients with BDI scores <14. In states of inflammation, nuclear factor kappa B (NF-κB) causes decreased albumin gene expression, which leads to a decreased rate of albumin synthesis [33,34], and a reduced serum albumin concentration. Thus, we suspect that depression may be closely associated with inflammation and malnutrition [35].

Dialysis exacts both a physical and mental toll on patients, and chronic illness overshadows any other condition that might affect the severity of depression. As has been previously reported, we found that depressed patients often have more co-morbid states than patients without depression [15]. Despite the high prevalence of co-morbidities in older MHD patients, the prevalence of depression showed a tendency to decrease with age. Since our MHD patients had comparable economic status regardless of age, this finding may reflect a better adjustment to the psychological burden of dialysis on the part of elderly MHD patients [36]. Logistic regression analysis revealed that co-morbidity is the most important independent risk factor (OR 3.58, 95% CI 1.08–1.19, P < 0.05) for depression in our MHD patients. These underline the importance of treating co-morbidities in MHD patients.

In conclusion, patients on MHD with symptoms of depression may have higher serum IL-6 and lower serum albumin levels. Dialysis dosage is closely correlated to the severity of depression symptoms. Elderly patients (aged ≥75 years) had lower prevalence of depression which was not apparently related to economic status. Factors including co-morbid conditions, serum IL-6, albumin and age may play significant roles in predicting which patients may be predisposed to develop symptoms of depression. Whether attenuation of inflammation and amelioration of nutritional status, even in the presence of co-morbid illnesses, may alleviate symptoms of depression in MHD patients deserves further.

Conflict of interest statement. None declared.

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