

Article

The Dominant Role of Depression over Cognitive Impairment in Determining Quality of Life Among Hemodialysis Patients: Evidence from Mediation Analysis

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Abstract

Background and Aims: Cognitive impairment (CI) and depression are frequent comorbidities in chronic hemodialysis (HD) patients with substantial impact on health-related quality of life (HRQoL). This study examined their prevalence, predictors, and independent associations with HRQoL. **Methods:** A cross-sectional study enrolled 70 adult maintenance HD patients. Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA); depressive symptoms with the Beck Depression Inventory (BDI); and HRQoL with the Kidney Disease Quality of Life instrument (KDQOL-SF). Logistic regression, multiple linear regression, and mediation analysis were applied. **Results:** CI (MoCA ≤ 24) was present in 54.3% of patients; clinically significant depressive symptoms (BDI ≥ 14) were present in 44.4%. BDI was not correlated with MoCA ($p = 0.656$) or MMSE ($p = 0.880$), confirming independence of the two dimensions in cross-section. Older age (OR = 1.106, $p = 0.001$) and male sex (OR = 4.523, $p = 0.022$) were independent predictors of CI. BDI significantly correlated with 15 of 19 KDQOL domains and was the dominant predictor across 10 domains in multiple linear regression (Adj. R^2 up to 0.358). MoCA correlated with only two KDQOL domains. Mediation analysis confirmed that MoCA does not mediate the BDI–HRQoL relationship (indirect effect: -0.004 , 95% bootstrap CI: -0.106 to $+0.097$). **Conclusions:** CI and depression are highly prevalent and clinically distinct dimensions in HD patients, though subtle longitudinal interactions cannot be excluded. Depression is the dominant determinant of impaired HRQoL, acting through a direct, cognitively independent pathway, and represents the primary modifiable target for improving quality of life in this population.



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1. Introduction

1.1. Cognitive Impairment in Hemodialysis Patients

End-stage kidney disease (ESKD) requiring maintenance hemodialysis (HD) represents a growing global health burden, with millions of patients dependent on regular renal replacement therapy for survival [1]. Despite continuous advances in dialysis technology and clinical management, patients on long-term HD experience a disproportionately high

burden of both somatic and neuropsychiatric complications, which profoundly compromise their functional independence and overall well-being [2]. Cognitive impairment has emerged as one of the most prevalent yet systematically underrecognized complications in patients undergoing maintenance hemodialysis. A recent systematic review pooling data from more than 25,000 patients with chronic kidney disease found an overall prevalence of cognitive impairment of 40% (95% CI 33–46%), with the highest rates observed in hemodialysis patients, where it reached 53% [3,4]. Earlier cohort studies report that up to 70% of hemodialysis patients aged 55 years and older exhibit moderate to severe chronic cognitive impairment, with only approximately 13% demonstrating entirely normal cognitive function on comprehensive neuropsychological assessment [1,5].

The pathophysiology underlying HD-associated cognitive decline is multifactorial. Uremic toxin accumulation—including indoxyl sulfate, p-cresyl sulfate, and other protein-bound solutes—directly impairs neuronal function, disrupts synaptic plasticity, and promotes cerebrovascular injury [1]. Furthermore, recurrent intradialytic hypotension causes episodes of reduced cerebral perfusion, contributing to ischemic neuronal loss, white matter disease, and microvascular injury—all of which are strongly associated with vascular cognitive impairment [6]. The risk of clinically manifest or silent stroke is up to nine times higher in dialysis patients than in the general population, doubling the risk of dementia [3]. The cognitive domains most consistently affected in HD patients include complex attention, executive function, learning and memory, language, and perceptual–motor performance [3].

Early identification of cognitive impairment in the hemodialysis setting is critical, as it influences treatment adherence, the capacity to provide informed consent, and the overall quality of clinical care. Validated screening instruments—ranging from brief global tools to more comprehensive multi-domain assessments—are increasingly recommended for routine use in patients with chronic kidney disease, given the high prevalence of subtle deficits that may otherwise go undetected in clinical practice [7–9].

1.2. Depression and Its Clinical Consequences

Depression is the most common psychiatric comorbidity in hemodialysis patients, with prevalence estimates ranging widely across studies depending on the assessment method used [1]. Clinically significant depressive symptoms are present in a substantial proportion of dialysis patients and are consistently associated with poor treatment adherence, higher rates of hospitalization, and reduced health-related quality of life (HRQoL) [10]. Importantly, depression is also an independent predictor of all-cause mortality in hemodialysis patients, with adjusted hazard ratios between 1.44 and 1.51 in prospective cohort studies [11]. Beyond its direct effects, depression frequently co-occurs with cognitive impairment in HD patients and may both exacerbate and be exacerbated by cognitive dysfunction, creating a clinically significant bidirectional interaction [12]. Unlike cognitive impairment, which largely reflects irreversible organic brain injury, depression is a therapeutically modifiable condition: evidence-based interventions including cognitive–behavioral therapy, antidepressant pharmacotherapy, and structured psychosocial support programs have demonstrated efficacy in reducing depressive burden and improving functional outcomes in patients with chronic kidney disease. Systematic identification and active management of depression in the dialysis setting therefore represents a high-priority clinical strategy with potential to meaningfully improve patient well-being.

1.3. Health-Related Quality of Life: The KDQOL Framework

Despite a growing international evidence base, data on the prevalence and determinants of cognitive impairment in hemodialysis patients from Southeastern Europe remain sparse, and systematic concurrent assessment of cognitive function, depression, and multi-

dimensional quality of life is rarely performed in clinical practice in this region. A more complete characterization of these interrelated domains in a real-world dialysis cohort may help identify high-risk patients and inform the development of targeted psychosocial and rehabilitative interventions.

The present cross-sectional study therefore aimed to: (1) determine the prevalence and severity of cognitive impairment in a cohort of maintenance hemodialysis patients using complementary screening tools; (2) assess the burden of depressive symptoms; (3) evaluate health-related quality of life across multiple disease-specific and generic domains; and (4) explore the associations between cognitive status, depressive symptoms, selected sociodemographic characteristics (age, sex, educational level, marital status, employment status), and individual quality-of-life subscale scores.

2. Materials and Methods

2.1. Study Design and Setting

This was an observational, cross-sectional, single-center study conducted at the Dialysis Unit, Clinic for Nephrology and Clinical Immunology, Clinical Centre of Vojvodina, Novi Sad, Serbia. Data were collected from patients receiving maintenance hemodialysis at this centre. No a priori formal sample size calculation was performed; all eligible patients treated at the unit during the data collection period were consecutively approached (convenience sampling). Of the patients screened for eligibility, those who met the inclusion criteria and provided written informed consent were enrolled. The overall response rate was 100% among eligible consenting patients, as no participant withdrew after enrolment; however, seven participants did not complete the Beck Depression Inventory (BDI), resulting in a dataset of 63 patients with complete data for all three instruments (MMSE, MoCA, and BDI). The handling of missing BDI data is addressed in the Statistical Analysis section. The study was conducted in accordance with the ethical principles for research involving human subjects set forth in the Declaration of Helsinki and was approved by the local Ethics Committee. Written informed consent was obtained from all participants prior to enrolment.

2.2. Inclusion Criteria

Patients were eligible for inclusion if they met all of the following criteria:

- Age $\geq$ 18 years;
- Receiving maintenance hemodialysis three times per week for a minimum of three months;
- Clinically stable condition at the time of assessment (absence of acute illness, active infection, or recent hospitalization within the preceding four weeks);
- Ability to provide written informed consent.

Patients were excluded if they had: a pre-existing diagnosis of dementia or a severe neurological or psychiatric disorder documented prior to initiation of hemodialysis; active psychosis or severe hearing/visual impairment that would preclude reliable cognitive testing; a severe language barrier preventing comprehension of questionnaire items; or refusal to participate or withdrawal of consent.

2.3. Data Collection and Assessed Variables

Data were collected using a structured self-report questionnaire administered during or immediately after a dialysis session. The following sociodemographic and clinical variables were recorded: age (years); sex; highest level of educational attainment (categorized as: primary school, secondary school, post-secondary/higher vocational school, university degree); employment status; marital status; number of children; number of

grandchildren; frequency of contact with children; participation in childcare for grandchildren; self-reported financial status; leisure time activities; frequency of social engagement; perceived life expectancy; and subjective satisfaction with hemodialysis treatment and level of adherence to the dialysis regimen. Adherence to the dialysis regimen was assessed by self-report: patients were asked to indicate how often they missed or shortened dialysis sessions and whether they consistently followed dietary and fluid restrictions as prescribed, using a structured questionnaire item with Likert-type response categories.

2.4. Assessment Instruments

2.4.1. Mini-Mental State Examination (MMSE)

Global cognitive function was assessed using the Mini-Mental State Examination (MMSE), a widely used 30-point screening instrument covering orientation, registration, attention and calculation, recall, language, and visuoconstructive ability. A total score of ≤ 26 was used to indicate potential cognitive impairment, consistent with conventional cut-off criteria applied in clinical research. Scores were further interpreted as: 27–30 (normal), 21–26 (mild impairment), 11–20 (moderate impairment), and ≤ 10 (severe impairment). The MMSE was administered alongside the MoCA to enable direct comparison of the two instruments' prevalence estimates and to confirm convergent validity; results from both tools are reported to allow assessment of instrument-dependent differences in cognitive impairment detection rates. However, the MoCA was designated as the primary cognitive screening instrument for all group stratification, regression, and mediation analyses, given its established superior sensitivity for mild cognitive impairment in hemodialysis populations.

2.4.2. Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) was used as the primary cognitive screening instrument, given its established superior sensitivity for mild cognitive impairment in hemodialysis populations compared with the MMSE. The MoCA is a 30-point test assessing eight cognitive domains: visuospatial/executive abilities, naming, memory, attention, language, abstraction, delayed recall, and orientation. A cut-off score of ≤ 24 points was applied to define cognitive impairment, as validated specifically in chronic hemodialysis patients in whom a cut-off of ≤ 24 demonstrated a sensitivity of 76.7% and specificity of 78.6% (AUC = 0.755). An additional point was added for patients with fewer than 12 years of formal education, as per the original MoCA administration protocol.

2.4.3. Depressive Symptoms: Beck Depression Inventory (BDI)

Depressive symptoms were evaluated using the Beck Depression Inventory (BDI), a validated 21-item self-report questionnaire yielding a total score of 0–63, with higher scores indicating greater severity of depressive symptoms. BDI scores were categorized as follows: 0–13 (minimal/no depression), 14–19 (mild depression), 20–28 (moderate depression), and 29–63 (severe depression). The BDI has been validated for use in patients with end-stage renal disease on hemodialysis and represents one of the most widely used screening instruments for depression in this population.

2.4.4. Health-Related Quality of Life: KDQOL

Health-related quality of life (HRQoL) was assessed using the Kidney Disease Quality of Life (KDQOL) questionnaire, a disease-specific instrument designed for patients with chronic kidney disease and those on renal replacement therapy [11,12]. The KDQOL-SF is a single integrated instrument that combines kidney disease-targeted subscales with generic health domains adapted from the SF-36; it is not two separate questionnaires. All domain scores are transformed to a 0–100 scale, with higher scores indicating better quality of life or functioning. The kidney disease-targeted subscales assessed were: Symp-

tom/Problem List; Effects of Kidney Disease on Daily Life; Burden of Kidney Disease; Work Status; Cognitive Functioning; Quality of Social Interaction; Sexual Function; Sleep; Social Support; Encouragement by Dialysis Staff; and Patient Satisfaction with Dialysis. The generic SF-36-derived subscales assessed were: Physical Functioning; Role-Physical; Pain; General Health Perceptions; Emotional Well-Being; Role-Emotional; Social Functioning; and Energy/Fatigue [13–15].

2.4.5. Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 26.0. A two-tailed p -value of <0.05 was considered statistically significant for all analyses. Continuous variables are reported as mean $\pm$ standard deviation (SD) if normally distributed, or as median (interquartile range, IQR) if non-normally distributed. Normality was assessed using the Shapiro–Wilk test. Categorical variables are reported as absolute frequencies and percentages. Patients were classified into two groups based on MoCA score: those with cognitive impairment ($\text{MoCA} \leq 24$) and those without cognitive impairment ($\text{MoCA} > 24$). A parallel classification was performed using the MMSE cutoff of ≤ 26 . BDI scores were categorized into four severity groups as described above. Differences between the cognitively impaired and non-impaired groups with respect to continuous variables (age, individual KDQOL domain scores, BDI scores) were assessed using the independent samples t -test or the Mann–Whitney U test, as appropriate. Differences in the distribution of categorical variables (sex, educational level, marital status, employment status) between groups were assessed using the Pearson chi-square test or Fisher’s exact test, as appropriate. Spearman’s rank correlation coefficient was used to examine pairwise associations between: (i) MoCA and MMSE scores; (ii) MoCA/MMSE scores and BDI total score; and (iii) MoCA/MMSE scores and individual KDQOL domain scores. Correlation strength was interpreted as: weak ($r = 0.10$ – 0.29), moderate ($r = 0.30$ – 0.49), and strong ($r \geq 0.50$). Binary logistic regression analysis was performed to identify independent predictors of cognitive impairment (dependent variable: $\text{MoCA} \leq 24$, yes/no). Candidate predictor variables entered into the model were: age, sex, educational level (ordinal), BDI total score, and self-reported financial status. Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Seven participants did not complete the BDI, leaving 63 patients with complete data across all three instruments (MMSE, MoCA, and BDI). These participants did not differ significantly from the full sample on age, sex, or cognitive scores. All analyses involving the BDI—including correlations with KDQOL domains, logistic regression, and mediation analysis—were therefore conducted in this subset of 63 patients. Analyses not involving the BDI (cognitive group comparisons, KDQOL descriptive statistics) used all 70 participants; the varying sample sizes reported in tables reflect instrument-specific missingness in individual KDQOL domains.

3. Results

3.1. Demographic and Clinical Characteristics of the Study Population

The study enrolled 70 patients undergoing chronic hemodialysis (HD), of whom 42 (60.0%) were male and 28 (40.0%) female. The median age was 64.5 years (IQR 56.5–71.8; range 34–86 years). The majority of participants held secondary school education ($n = 37$, 52.9%), followed by primary school ($n = 17$, 24.3%), university ($n = 9$, 12.9%), and higher vocational education ($n = 7$, 10.0%). Most patients were retired ($n = 55$, 78.6%) and married or in a partnership ($n = 49$, 70.0%). In terms of self-reported financial status, 53 patients (75.7%) described their financial situation as average, while 11 (15.7%) reported good and 6 (8.6%) poor financial status. Full demographic data are presented in Table 1.

Table 1. Sociodemographic Characteristics of Hemodialysis Patients.

Variable	n (%)	Median/Mean $\pm$ SD
Sex		
Male	42 (60.0%)	
Female	28 (40.0%)	
Age (years)		
Mean $\pm$ SD		64.1 $\pm$ 11.9
Median (IQR)		64 (56–72)
Range		34–86
Educational level		
Primary school	17 (24.3%)	
Secondary school	37 (52.9%)	
Higher vocational school	7 (10.0%)	
University degree	9 (12.9%)	
Employment status		
Retired (pensioner)	56 (80.0%)	
Unemployed	7 (10.0%)	
Homemaker	3 (4.3%)	
Other	4 (5.7%)	
Marital status		
Married/partnered	49 (70.0%)	
Single	16 (22.9%)	
Divorced	5 (7.1%)	
Self-reported financial status		
Average	39 (55.7%)	
Good	27 (38.6%)	
Poor	4 (5.7%)	

Note for Table 1: SD = Standard Deviation; IQR = Interquartile Range; n = number of patients; % = percentage of total sample (N = 70).

3.2. Cognitive Functioning

3.2.1. MMSE Scores

The Mini-Mental State Examination (MMSE) was completed by all 70 participants. The mean MMSE score was 26.20 ± 3.31 (median 27, IQR 25–29; range 16–30). Applying the standard classification, 39 patients (55.7%) scored within the normal range (MMSE ≥ 27), 25 (35.7%) demonstrated mild cognitive impairment (MMSE 21–26), and 6 (8.6%) fell within the range indicative of moderate cognitive impairment (MMSE 11–20). Accordingly, cognitive impairment defined by MMSE ≤ 26 was present in 31 patients (44.3%).

3.2.2. MoCA Scores

The Montreal Cognitive Assessment (MoCA) was similarly administered to all 70 participants. The mean MoCA score was 23.77 ± 4.44 (median 24, IQR 22–27; range 10–30). Based on established cut-offs, 26 patients (37.1%) achieved scores in the normal range (MoCA ≥ 26), 39 (55.7%) demonstrated mild cognitive impairment (MoCA 18–25), and

5 (7.1%) exhibited scores consistent with moderate cognitive impairment (MoCA 10–17). Using the cut-off of $\text{MoCA} \leq 24$, cognitive impairment was identified in 38 patients (54.3%).

MoCA and MMSE scores demonstrated a significant positive correlation (Spearman $r_s = 0.689$, $p < 0.001$), confirming convergent validity between the two instruments. Despite this strong association, the prevalence of cognitive impairment differed by instrument (54.3% by MoCA vs. 44.3% by MMSE), suggesting that MoCA may be more sensitive for the detection of subtle cognitive changes in this population.

3.2.3. Depressive Symptoms

The mean BDI score was 13.30 ± 8.04 (median 13, IQR 7–17; range 0–35). Categorized by severity, 35 patients (55.6%) had minimal or no depressive symptoms (BDI 0–13), 18 (28.6%) reported mild depression (BDI 14–19), 5 (7.9%) moderate depression (BDI 20–28), and 5 (7.9%) severe depression (BDI ≥ 29). Consequently, clinically significant depressive symptoms (BDI ≥ 14) were present in 28 patients (44.4%). No statistically significant correlation was found between BDI and MoCA ($r_s = -0.057$, $p = 0.656$) or between BDI and MMSE ($r_s = -0.019$, $p = 0.880$), indicating that cognitive impairment and depressive symptom burden represent independent clinical dimensions in this cohort (Table 2).

Table 2. Cognitive Assessment (MMSE, MoCA) and Depression (BDI)—Descriptive Statistics.

Instrument/Variable	N	Value
MMSE		
Mean $\pm$ SD	70	26.20 ± 3.31
Median (IQR)	70	27 (25–29)
Range	70	16–30
Normal (≥ 27), n (%)	70	39 (55.7%)
Mild impairment (21–26), n (%)	70	25 (35.7%)
Moderate impairment (11–20), n (%)	70	6 (8.6%)
MoCA		
Mean $\pm$ SD	70	23.77 ± 4.44
Median (IQR)	70	24 (22–27)
Range	70	10–30
Normal (≥ 26), n (%)	70	26 (37.1%)
Mild impairment (18–25), n (%)	70	39 (55.7%)
Moderate impairment (10–17), n (%)	70	5 (7.1%)
Cognitive impairment ($\text{MoCA} \leq 24$), n (%)	70	38 (54.3%)
Cognitive impairment ($\text{MMSE} \leq 26$), n (%)	70	31 (44.3%)
BDI (Beck Depression Inventory)		
Mean $\pm$ SD	63	13.30 ± 8.04
Median (IQR)	63	13 (7–17)
Range	63	0–35
Minimal depression (0–13), n (%)	63	35 (55.6%)
Mild depression (14–19), n (%)	63	18 (28.6%)
Moderate depression (20–28), n (%)	63	5 (7.9%)
Severe depression (≥ 29), n (%)	63	5 (7.9%)

Table 2. *Cont.*

Instrument/Variable	N	Value
Spearman Correlations		
MoCA vs. MMSE	70	$r = 0.689, p < 0.001$
MoCA vs. BDI	63	$r = -0.057, p = 0.656$
MMSE vs. BDI	63	$r = -0.019, p = 0.880$
Age vs. MoCA	70	$r = -0.434, p < 0.001$
Age vs. MMSE	70	$r = -0.368, p = 0.002$

Note for Table 2: SD = Standard Deviation; IQR = Interquartile Range; N = number of patients with available data for each instrument; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; BDI = Beck Depression Inventory. BDI data available for 63 of 70 patients (seven patients did not complete the BDI). r = Spearman rank correlation coefficient.

3.2.4. Comparison of Cognitively Impaired and Non-Impaired Groups

Patients were stratified into two groups according to MoCA performance: the cognitively impaired (CI) group (MoCA ≤ 24 ; $n = 38$) and the non-impaired (NI) group (MoCA > 24 ; $n = 32$). Comparison of demographic and clinical variables between groups is presented in Table 3.

Table 3. Comparison of Cognitively Impaired (CI) vs. Non-Impaired (NI) Groups.

Variable	CI Group (n = 38)	NI Group (n = 32)	Test Statistic	p-Value
Demographics				
Age, years—median (IQR)	68 (60–76)	59 (52–68)	U = 842	0.006
Male sex, n (%)	26 (68.4%)	16 (50.0%)	$\chi^2 = 1.75$	0.186
Education (ordinal)—median	2 (secondary)	2 (secondary)	U = 511	0.213
Financial status (ordinal)—median	2 (average)	2 (average)	U = 582	0.597
Cognitive scores				
MoCA—median (IQR)	22 (19–24)	27 (26–28)	—	—
MMSE—median (IQR)	26 (24–27)	28 (27–29)	U = 250	<0.001
Depression (bdi)				
BDI total—median (IQR)	13 (8–17)	11 (7–17)	U = 518	0.698
BDI: Minimal (0–13), n (%)	19 (54.3%)	16 (57.1%)	—	—
BDI: Mild (14–19), n (%)	10 (28.6%)	8 (28.6%)	—	—
BDI: Moderate–Severe (≥ 20), n (%)	6 (17.1%)	4 (14.3%)	—	—

Note for Table 3: CI = Cognitively Impaired group (MoCA ≤ 24 , $n = 38$); NI = Non-Impaired group (MoCA > 24 , $n = 32$); IQR = Interquartile Range; U = Mann–Whitney U statistic; χ^2 = Pearson chi-square statistic. BDI data available for 35 CI and 28 NI patients.

The CI group was significantly older than the NI group (median age 68 years, IQR 60–76 vs. 59 years, IQR 52–68; Mann–Whitney U = 842, $p = 0.006$). Although male sex was more prevalent in the CI group (68.4% vs. 50.0% in the NI group), this difference did not reach statistical significance ($\chi^2 = 1.75$, $p = 0.186$). As expected, CI patients demonstrated significantly lower MMSE scores (median 26, IQR 24–27 vs. 28, IQR 27–29; U = 250, $p < 0.001$). Depressive symptom severity as measured by BDI did not differ significantly between groups (median BDI 13 vs. 11; U = 518, $p = 0.698$), reinforcing the independence of depression and cognitive impairment identified in the correlation analyses. Similarly, no

statistically significant differences were observed between groups with respect to level of education or self-reported financial status.

3.2.5. Predictors of Cognitive Impairment: Binary Logistic Regression

To identify independent predictors of cognitive impairment (defined as MoCA $\leq$ 24), binary logistic regression was performed in 63 patients with complete data. The model included age, sex, education level, BDI total score, and financial status as covariates. The overall model was statistically significant ($\chi^2 = 13.7$, $p = 0.003$) and explained 21.1% of the variance in cognitive impairment status (Nagelkerke pseudo- $R^2 = 0.211$).

Older age was an independent and significant predictor of cognitive impairment (OR = 1.106 per year, 95% CI 1.042–1.174, $p = 0.001$). Male sex was also independently associated with cognitive impairment (OR = 4.523, 95% CI 1.242–16.464, $p = 0.022$). Neither education level (OR = 0.602, 95% CI 0.304–1.194, $p = 0.147$), BDI score (OR = 0.986, 95% CI 0.912–1.065, $p = 0.712$), nor financial status (OR = 0.745, 95% CI 0.251–2.216, $p = 0.597$) reached statistical significance in the multivariable model. Full regression results are provided in Table 4.

Table 4. Binary Logistic Regression: Predictors of Cognitive Impairment (MoCA $\leq$ 24).

Predictor	β (Coef.)	OR	95% CI	p -Value
Age (years)	0.101	1.106	1.042–1.174	0.001
Male sex	1.509	4.523	1.242–16.464	0.022
Education (ordinal)	−0.507	0.602	0.304–1.194	0.147
BDI total score	−0.015	0.986	0.912–1.065	0.712
Financial status (ordinal)	−0.294	0.745	0.251–2.216	0.597

Note for Table 4: β = regression coefficient (log-odds); OR = Odds Ratio; CI = 95% Confidence Interval; $n = 63$ patients with complete data. Bold OR values indicate independent predictors reaching statistical significance ($p < 0.05$). Model fit: $\chi^2 = 13.7$, $p = 0.003$; Nagelkerke $R^2 = 0.211$.

3.2.6. ROC Curve Analysis: Diagnostic Performance

Receiver operating characteristic (ROC) analysis was performed to evaluate the discriminatory ability of continuous predictor variables for cognitive impairment (MoCA $\leq$ 24). MMSE demonstrated good discriminatory ability (AUC = 0.795), confirming its validity as a screening instrument in this population. Age yielded acceptable discriminatory ability (AUC = 0.692), consistent with its role as a significant predictor in the logistic regression model. In contrast, BDI total score showed no meaningful discriminatory ability (AUC = 0.529), consistent with the absence of a correlation between BDI and MoCA scores. For the optimal MoCA cut-off of ≤ 25 , determined by the Youden index, sensitivity was 90.3% and specificity was 59.0% (AUC = 0.836), suggesting that a cut-off of ≤ 25 may offer superior sensitivity for the detection of cognitive impairment in HD patients compared to the conventional ≤ 24 threshold.

3.2.7. Health-Related Quality of Life: KDQOL Descriptive Results

Health-related quality of life (HRQoL) was assessed using the Kidney Disease Quality of Life instrument (KDQOL-SF). Among the kidney disease-targeted subscales, the highest median scores were observed for Social Support (median 83.3), Staff Encouragement (median 75.0), and Treatment Satisfaction (median 66.7), indicating relatively preserved perceptions of social and institutional support. The lowest scores were recorded for Work Status (median 0.0), reflecting near-universal functional disability with respect to employment in this retired population, followed by Physical Functioning (median 40.0) and Energy/Fatigue (median 50.0). Among the generic SF-36-derived subscales, Emotional

Well-Being (median 60.0) and Social Functioning (median 62.5) achieved the highest scores, whereas Role-Physical (median 25.0) and Role-Emotional (median 33.3) were most severely impaired. Detailed KDQOL domain descriptive statistics are presented in Table 5.

Table 5. KDQOL Domain Scores—Descriptive Statistics and Comparison by Cognitive Status.

KDQOL Domain	N	Mean $\pm$ SD	Mdn	CI Median (IQR)	NI Median (IQR)	U	<i>p</i>
Kidney disease-targeted subscales							
Symptom/Problem List	70	76.3 $\pm$ 15.6	79.0	74.0 (60.6–89.4)	82.7 (76.4–87.0)	478	0.125
Effects of Kidney Disease	68	63.5 $\pm$ 21.6	63.4	64.1 (49.0–82.0)	63.4 (53.1–75.8)	566	0.9069
Burden of Kidney Disease	70	39.6 $\pm$ 26.0	37.5	35.4 (14.1–54.7)	43.8 (25.0–62.5)	469	0.101
Work Status	69	14.5 $\pm$ 28.6	0.0	0.0 (0.0–0.0)	0.0 (0.0–50.0)	415	0.0045 *
Cognitive Functioning	66	80.4 $\pm$ 16.0	80.0	80.0 (66.7–93.3)	83.3 (78.3–93.3)	427	0.1305
Quality of Social Interaction	69	75.2 $\pm$ 18.8	80.0	73.3 (66.7–86.7)	80.0 (65.0–88.3)	518	0.37
Sexual Function	53	70.8 $\pm$ 35.7	87.5	87.5 (50.0–100.0)	87.5 (50.0–100.0)	335	0.768
Sleep	69	61.1 $\pm$ 19.0	60.0	57.5 (47.5–72.5)	62.5 (46.9–78.1)	558	0.6821
Social Support	68	82.8 $\pm$ 23.7	83.3	83.3 (70.8–100.0)	91.7 (66.7–100.0)	583	0.8681
Staff Encouragement	67	73.5 $\pm$ 22.8	75.0	75.0 (75.0–100.0)	75.0 (50.0–78.1)	738	0.0214 *
Treatment Satisfaction	69	65.5 $\pm$ 23.1	66.7	66.7 (50.0–100.0)	66.7 (50.0–83.3)	684	0.2577
Generic health subscales (SF-36 derived)							
Physical Functioning	70	42.6 $\pm$ 25.0	40.0	40.0 (25.0–50.0)	45.0 (25.0–70.0)	500	0.2039
Role-Physical	64	47.1 $\pm$ 27.8	50.0	50.0 (25.0–68.8)	50.0 (25.0–62.5)	516	0.9457
Pain	68	57.2 $\pm$ 30.9	56.2	52.5 (30.0–77.5)	65.0 (45.0–77.5)	508	0.4236
General Health Perceptions	70	41.9 $\pm$ 18.3	40.0	42.5 (30.0–50.0)	40.0 (30.0–55.0)	566	0.6227
Emotional Well-Being	64	63.4 $\pm$ 18.1	60.0	60.0 (48.0–72.0)	60.0 (56.0–78.0)	491	0.7874
Role-Emotional	64	59.5 $\pm$ 30.4	66.7	58.3 (33.3–75.0)	66.7 (50.0–79.2)	452	0.4196
Social Functioning	69	58.5 $\pm$ 28.9	65.0	57.5 (35.0–67.5)	66.2 (44.4–87.5)	498	0.2588
Energy/Fatigue	69	51.3 $\pm$ 20.7	50.0	50.0 (40.0–60.0)	52.5 (40.0–67.1)	543	0.5563

Note for Table 5: Mdn = Median; IQR = Interquartile Range; CI = Cognitively Impaired group (MoCA $\leq$ 24); NI = Non-Impaired group (MoCA $>$ 24); U = Mann–Whitney U statistic; *p* = *p*-value. Scores range from 0 to 100, with higher scores indicating better quality of life or functioning. Bold *p*-values indicate statistically significant differences between CI and NI groups (*p* $<$ 0.05). * *p* $<$ 0.05. Statistically significant between-group differences were observed for Work Status (*p* = 0.0045) and Staff Encouragement (*p* = 0.0214); all other domains did not reach statistical significance.

3.2.8. KDQOL Domain Scores by Cognitive Status

Whereas Section 3.2.7 and Table 5 present descriptive statistics for KDQOL domain scores across the full cohort (N = 70), this subsection addresses the between-group comparison of those scores according to cognitive status (CI group: MoCA $\leq$ 24, *n* = 38; NI group: MoCA $>$ 24, *n* = 32), as reported in columns 5 (CI Median, IQR) and 6 (NI Median, IQR) of Table 5. Comparisons of KDQOL domain scores between the CI and NI groups revealed no statistically significant differences for any kidney disease-targeted subscale after applying Mann–Whitney U testing (all *p* $>$ 0.05), with the exception of Work Status (*p* = 0.0045) and Staff Encouragement (*p* = 0.0214). Similarly, among the SF-36-derived generic subscales, no domain reached statistical significance at the *p* $<$ 0.05 threshold, although Physical Functioning tended to be lower in the CI group (median 40.0 vs. 45.0; *p* = 0.089) and Work Status tended to be lower overall (median 0.0 vs. 12.5; *p* = 0.057). These findings indicate that cognitive impairment, as classified by MoCA, is not broadly associated with worse self-reported HRQoL across most KDQOL domains in this cohort, a pattern further explored in the correlation and regression analyses below.

3.3. Correlations Between Cognitive Scores, Depression, and KDQOL Domains

3.3.1. Spearman Correlations

Spearman correlation analyses were performed between MoCA, MMSE, BDI, and all 19 KDQOL domains. Results are presented in full in Table 6. BDI consistently demonstrated the strongest and most pervasive associations across KDQOL domains. The five strongest BDI–KDQOL correlations were observed for Energy/Fatigue ($r_s = -0.591$, $p < 0.001$), Burden of Kidney Disease ($r_s = -0.561$, $p < 0.001$), General Health ($r_s = -0.560$, $p < 0.001$), Emotional Well-Being ($r_s = -0.538$, $p < 0.001$), and Social Functioning ($r_s = -0.522$, $p < 0.001$). In total, BDI was significantly correlated with 15 of 19 KDQOL domains (all $p < 0.05$).

Table 6. Spearman Correlations: MoCA, MMSE, and BDI with KDQOL Domains.

KDQOL Domain	MoCA r	p (MoCA)	MMSE r	p (MMSE)	BDI r	p (BDI)
Kidney disease-targeted subscales						
Symptom/Problem List	0.272 *	0.031	0.210	0.099	−0.407 ***	0.001
Effects of Kidney Disease	0.074	0.568	0.015	0.905	−0.233	0.071
Burden of Kidney Disease	0.218	0.086	0.041	0.751	−0.561 ***	<0.001
Work Status	0.343 **	0.006	0.363 **	0.004	−0.058	0.655
Cognitive Functioning	0.174	0.182	0.141	0.281	−0.399 **	0.002
Quality of Social Interaction	0.036	0.783	−0.038	0.770	−0.428 ***	0.006
Sexual Function	0.028	0.851	0.059	0.694	−0.385 **	0.007
Sleep	0.220	0.086	0.049	0.707	−0.421 ***	0.001
Social Support	−0.012	0.924	0.006	0.964	−0.353 **	0.004
Staff Encouragement	−0.244	0.058	−0.277 *	0.031	−0.011	0.933
Treatment Satisfaction	−0.088	0.498	−0.184	0.152	0.068	0.599
GENERIC HEALTH SUBSCALES (SF-36 DERIVED)						
Physical Functioning	0.378 **	0.002	0.347 **	0.005	−0.258 *	0.041
Role-Physical	0.087	0.515	0.044	0.744	−0.324 *	0.0131
Pain	0.183	0.157	0.113	0.385	−0.329 **	0.0097
General Health	0.040	0.756	−0.167	0.190	−0.560 ***	<0.001
Emotional Well-Being	0.124	0.348	0.003	0.983	−0.537 ***	<0.001
Role-Emotional	0.207	0.122	0.155	0.250	−0.324 *	0.0139
Social Functioning	0.229	0.074	0.058	0.652	−0.502 ***	<0.001
Energy/Fatigue	0.184	0.152	0.166	0.197	−0.591 ***	<0.001

Note for Table 6: r = Spearman rank correlation coefficient; p = p -value; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; BDI = Beck Depression Inventory. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

In contrast, MoCA demonstrated significant positive correlations with only two domains: Work Status ($r_s = 0.343$, $p = 0.006$) and Physical Functioning ($r_s = 0.378$, $p = 0.002$). MMSE showed significant associations with Work Status ($r_s = 0.363$, $p = 0.004$) and Staff Encouragement ($r_s = -0.277$, $p = 0.031$), as reported in Table 6. The divergent correlation patterns between BDI and MoCA/MMSE across KDQOL domains confirm that depressive symptoms, rather than cognitive impairment per se, are the primary correlate of impaired HRQoL in this population.

3.3.2. Partial Correlations Adjusted for Age

Given the association between age and cognitive performance, partial correlations controlling for age were computed for all BDI-KDQOL and MoCA-KDQOL pairs. The BDI-KDQOL correlations were fully maintained or modestly strengthened after adjustment for age: the strongest partial correlations were observed for Energy/Fatigue ($r_p = -0.626$, $p < 0.001$), General Health ($r_p = -0.570$, $p < 0.001$), Burden of Kidney Disease ($r_p = -0.567$, $p < 0.001$), Emotional Well-Being ($r_p = -0.537$, $p < 0.001$), and Social Functioning ($r_p = -0.514$, $p < 0.001$). Significant partial correlations between BDI and KDQOL were retained for 15 of 19 domains. This confirms that the association between depression and impaired HRQoL is independent of age and cannot be attributed to confounding by age-related cognitive or functional decline. In contrast, after controlling for age, no significant partial correlations were observed between MoCA and any KDQOL domain, with the exception of a weak negative correlation with Staff Encouragement ($r_p = -0.281$, $p = 0.021$), whose direction is not readily interpretable in clinical terms (Table 7).

Table 7. Partial Correlations Controlling for Age.

BDI Partial Correlations with KDQOL Domains (Controlling for Age)			
KDQOL Domain	r_{partial}	p -Value	Significance
Energy/Fatigue	−0.626	<0.001	***
General Health	−0.570	<0.001	***
Emotional Well-Being	−0.537	<0.001	***
Burden of Kidney Disease	−0.567	<0.001	***
Social Functioning	−0.514	<0.001	***
Sleep	−0.427	<0.001	***
Social Support	−0.381	0.002	**
Quality of Social Interaction	−0.422	0.001	***
Cognitive Functioning	−0.387	0.002	**
Sexual Function	−0.401	0.005	**
Pain	−0.338	0.008	**
Role-Emotional	−0.353	0.007	**
Role-Physical	−0.327	0.012	*
Symptom/Problem List	−0.423	0.001	***
Physical Functioning	−0.252	0.047	*
MoCA partial correlations with KDQOL (controlling for age)–Significant			
KDQOL Domain	r_{partial} (MoCA)	p -value	Note
Staff Encouragement	−0.281	0.021	Only significant MoCA-KDQOL partial correlation

Note for Table 7: r_{partial} = partial correlation coefficient controlling for age; p = p -value; BDI = Beck Depression Inventory; MoCA = Montreal Cognitive Assessment; KDQOL = Kidney Disease Quality of Life instrument. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3.3.3. Multiple Linear Regression: BDI as Independent Predictor of KDQOL Domains

To quantify the independent contribution of depression, cognitive performance, and age to KDQOL domain scores, multiple linear regression analyses were conducted for each KDQOL domain with BDI, MoCA, and age as covariates. BDI emerged as a statisti-

cally significant independent predictor in 10 of the 19 KDQOL domain models, all with $p \leq 0.005$. The largest regression coefficients for BDI were observed in Social Functioning ($\beta = -1.821, p < 0.001$), Pain ($\beta = -1.564, p = 0.002$), Role-Emotional ($\beta = -1.544, p = 0.002$), Energy/Fatigue ($\beta = -1.518, p < 0.001$), Burden of Kidney Disease ($\beta = -1.490, p < 0.001$), and General Health ($\beta = -1.215, p < 0.001$). The model for Energy/Fatigue demonstrated the greatest explanatory power (adjusted $R^2 = 0.358$), indicating that approximately 35.8% of the variance in energy-related quality of life was explained by BDI, MoCA, and age combined, with BDI as the dominant contributor. MoCA reached statistical significance as an independent predictor only in the model for Burden of Kidney Disease ($\beta = 3.198, p = 0.019$), where higher cognitive functioning was associated with a greater perceived burden—an association that may reflect greater insight and awareness in cognitively intact patients. Full regression results are presented in Table 8.

Table 8. Multiple Linear Regression: BDI as Predictor of KDQOL Domains (adj. for MoCA and Age).

KDQOL Domain	BDI β	p -Value	Adj. R^2
Energy/Fatigue	−1.518	<0.001	0.358
General Health	−1.215	<0.001	0.236
Emotional Well-Being	−1.191	<0.001	0.234
Social Functioning	−1.821	<0.001	0.259
Burden of Kidney Disease	−1.490	<0.001	0.228
Role-Emotional	−1.544	0.002	0.258
Quality of Social Interaction	−0.915	0.002	0.115
Pain	−1.564	0.002	0.147
Cognitive Functioning (KDQOL)	−0.718	0.003	0.165
Sleep	−0.806	0.005	0.133

Note for Table 8: β = unstandardized regression coefficient for BDI; Adj. R^2 = adjusted R-squared of the full model (BDI + MoCA + age); BDI = Beck Depression Inventory; MoCA = Montreal Cognitive Assessment; KDQOL = Kidney Disease Quality of Life. Only KDQOL domains for which BDI was a statistically significant predictor ($p \leq 0.005$) are shown.

3.3.4. Mediation Analysis: Role of Cognitive Impairment in the BDI–QoL Relationship

To examine whether cognitive impairment mediates the observed relationship between depression and HRQoL, a formal mediation analysis was conducted using the Baron-Kenny framework with 5000 bootstrap replications, taking Energy/Fatigue as the primary QoL outcome given its strongest BDI correlation.

The total effect of BDI on Energy/Fatigue was large and significant (path c: $\beta = -1.522, p < 0.001$). BDI was not significantly associated with MoCA (path a: $\beta = -0.038, p = 0.521$), and MoCA was not a significant predictor of Energy/Fatigue after adjustment for BDI (path b: $\beta = 0.102, p = 0.866$). The direct effect of BDI on Energy/Fatigue remained virtually unchanged after inclusion of MoCA in the model (path c': $\beta = -1.518, p < 0.001$). The indirect effect via MoCA was negligible ($a \times b = -0.004$) and the 95% bootstrap confidence interval crossed zero ($[-0.106, 0.097]$), indicating the absence of significant mediation (Table 9). These results demonstrate that depression exerts a strong, direct effect on HRQoL that is not mediated by, or attenuated through, cognitive impairment. Depression and cognitive impairment thus represent distinct and parallel pathways influencing clinical outcomes in HD patients.

Table 9. Mediation Analysis: BDI → MoCA → Energy/Fatigue (N = 62).

Path	β Coefficient	<i>p</i> -Value	95% CI
Path a: BDI → MoCA (mediator)	−0.038	0.521	—
Path b: MoCA → Energy/Fatigue (adj. BDI)	0.102	0.866	—
Path c (total): BDI → Energy/Fatigue	−1.522	<0.001	—
Path c' (direct): BDI → Energy adj. for MoCA	−1.518	<0.001	—
Indirect effect (a × b)	−0.004	—	[−0.106, 0.097]

Note for Table 9: β = regression coefficient; CI = 95% bootstrap confidence interval (5000 replications); BDI = Beck Depression Inventory; MoCA = Montreal Cognitive Assessment; N = 62 patients with complete data for all three variables. Path a: BDI → MoCA; Path b: MoCA → Energy/Fatigue adjusted for BDI; Path c: total effect of BDI → Energy/Fatigue; Path c': direct effect of BDI → Energy/Fatigue after inclusion of MoCA. Statistical significance is marked in bold.

3.3.5. Patient Phenotyping

K-means cluster analysis ($k = 3$) was performed on the complete dataset (N = 45 patients with non-missing values across MoCA, BDI, and all key KDQOL domains used as clustering variables). The number of clusters ($k = 3$) was determined by the elbow method applied to within-cluster sum of squares, and confirmed by silhouette coefficient evaluation. Input variables included MoCA total score, BDI total score, and the following KDQOL domain scores: Energy/Fatigue, Emotional Well-Being, Physical Functioning, and Cognitive Functioning. Variables were standardized (z-scores) prior to clustering to ensure equal weighting. This analysis is explicitly exploratory in nature: given the relatively small effective sample size (N = 45), the cluster solution should not be interpreted as definitive or generalizable, but rather as a descriptive framework for illustrating the clinical heterogeneity of the cohort and the differential impact of depression versus cognition on quality of life within it. Three tentative patient phenotypes emerged:

Group A—Near-normal cognition, average HRQoL: This group was characterized by the highest mean MoCA scores (26.3—above the cognitive impairment cut-off of ≤ 24) and moderate BDI scores (12.9), with intermediate HRQoL across most KDQOL domains (Energy/Fatigue mean 52.3; Emotional Well-Being 60.2).

Group B—Preserved cognition, best HRQoL: Despite lower mean MoCA scores (24.2) than Group A, this group demonstrated the lowest BDI scores (7.6), best Emotional Well-Being (87.0), and highest Energy/Fatigue scores (73.6). The superior QoL in Group B compared to Group A, despite lower cognitive performance, underscores the dominant role of depressive symptom burden relative to cognitive status as a determinant of HRQoL.

Group C—Moderate cognitive impairment, worst HRQoL: This group combined the lowest MoCA scores (21.5) with the highest BDI scores (15.0) and the most severely impaired KDQOL domains (Energy/Fatigue 41.3; Physical Functioning 27.5). The co-occurrence of cognitive impairment and greater depressive burden in this phenotype was associated with the worst overall HRQoL profile, suggesting a synergistic adverse effect when both conditions are simultaneously present. Results are presented in Table 10.

Principal component analysis (PCA) visualisation confirmed adequate separation between the three clusters in two-dimensional space, with PC1 and PC2 collectively explaining 43.1% of total data variance.

Table 10. K-Means Cluster Analysis ($k = 3$).

Patient Group	n	MoCA Mean	BDI Mean	Energy/Fatigue Mean
Group A—Mild CI, Average QoL	23	26.3	12.9	52.3
Group B—Preserved Cognition, Best QoL	14	24.2	7.6	73.6
Group C—Moderate CI, Worst QoL	8	21.5	15.0	41.3
Cluster Profiles—Normalized mean scores (0–100)				
MoCA (normalized)	87.7	80.7	71.7	Group A
MMSE (normalized)	93.7	87.3	80.7	Group A
BDI (inverted, higher = better)	79.5	87.9	76.2	Group B
Physical Functioning	49.5	54.6	27.5	Group B
Emotional Well-Being	60.2	87.0	50.0	Group B
Burden of KD (inverted)	60.1	31.2	78.9	Group C lowest burden
Cognitive Functioning (KDQOL)	80.9	94.3	69.2	Group B
Energy/Fatigue	52.3	73.6	41.3	Group B

Note for Table 10: MoCA = Montreal Cognitive Assessment (scores 0–30, higher = better cognition); BDI = Beck Depression Inventory (scores 0–63, higher = greater depression); CI = cognitive impairment. Normalized scores are expressed on a 0–100 scale. BDI (inverted) = BDI scores inverted so that higher values indicate less depression, for comparability with QoL scores. Burden of KD (inverted) = Burden of Kidney Disease scores inverted so that higher values indicate lower perceived burden. QoL = Quality of Life.

4. Discussion

4.1. Prevalence of Cognitive Impairment

Using the MoCA scale, cognitive impairment (score ≤ 24) was identified in 54.3% of hemodialysis patients in this study, while using the MMSE (score ≤ 26), the same condition was detected in 44.3% of participants. This finding is consistent with data from contemporary literature indicating a high prevalence of cognitive impairment in the dialysis population, ranging from 40% to 80%, depending on the instrument used and the applied cut-off values [1,4]. A study conducted on 613 Chinese hemodialysis patients showed that 37.2% had mild and 43.7% had more severe cognitive impairment, with age, education level, history of stroke, and hypertension identified as independent predictors [16]. A recent study involving 198 patients on maintenance hemodialysis reported a cognitive impairment prevalence of 58.6%, which is in line with the results presented in this paper [17].

The greater sensitivity of MoCA compared to MMSE in detecting cognitive impairment in hemodialysis patients is consistent with the established literature, as MMSE is susceptible to ceiling effects and provides limited coverage of executive and visuospatial domains [4,9]. In this study, the optimal MoCA cut-off determined by Youden's method was ≤ 25 (sensitivity 90.3%, specificity 59.0%, AUC = 0.836), suggesting that a threshold of ≤ 25 may optimize sensitivity for cognitive impairment detection in the hemodialysis setting, while the standard cut-off of ≤ 24 offers improved specificity.

4.2. Risk Factors for Cognitive Impairment

Results of binary logistic regression in this study identified older age (OR = 1.106 per year, 95% CI 1.042–1.174, $p = 0.001$) and male sex (OR = 4.523, 95% CI 1.242–16.464, $p = 0.022$) as independent predictors of cognitive impairment defined by MoCA ≤ 24 . The combined effect of aging and hemodialysis on cognitive function is well described—aging itself reduces cerebral reserve capacity, while hemodialysis adds specific pathophysiological mechanisms such as recurrent cerebral hypoperfusion during dialysis sessions, accumulation of uremic toxins, and advanced cerebrovascular disease [18]. In a study

by Lin et al. involving 181 elderly hemodialysis patients, age was an independent risk factor for lower MMSE scores (HR = 1.04 per year, $p = 0.007$), and patients with cognitive impairment had dramatically worse five-year survival rates (22.6% in the severe CI group vs. 60.6% in cognitively intact patients) [19].

The association between male sex and a higher prevalence of cognitive impairment observed in this study (68.4% in the cognitively impaired group vs. 50.0% in the non-impaired group, OR = 4.523) is a noteworthy finding that should be considered in the context of current knowledge on sex differences in cerebrovascular risk. Men in the general population are exposed to earlier and more intense cerebrovascular risk due to greater exposure to traditional cardiovascular risk factors, and cerebral small vessel disease tends to be more severe in men earlier in life [20,21]. This sex disparity is consistent with findings from related nephrology studies—e.g., a 2015 study on sex differences in cognitive impairment among kidney transplant recipients documented significant differences in prevalence and patterns of impairment in the CKD population [22]. It should be noted that education, financial status, and depressive symptoms did not reach statistical significance as predictors in the multivariable model, which contrasts with some studies identifying lower education and low socioeconomic status as independent predictors of cognitive impairment in hemodialysis patients [23].

4.3. Depressive Symptoms and Prevalence

Clinically relevant depressive symptoms were found in 44.4% of hemodialysis patients, while severe depression was present in 7.9% of participants. These results correspond with contemporary literature reporting depression prevalence in hemodialysis patients ranging from 25% to 58%, depending on the instrument and population studied [24–27]. A recent study of 125 hemodialysis patients reported depression prevalence of 48%, anxiety 34.4%, and stress 44%, highlighting high psychiatric comorbidity in this population [25]. A study from India identified moderate depressive symptoms in 58% of patients, with male sex and age between 46 and 60 associated with poorer psychological outcomes [28]. The high burden of depressive symptoms observed in this and similar cohorts is unlikely to reflect purely biological processes. The experience of chronic hemodialysis itself imposes a constellation of psychosocial stressors that are plausible contributors to depressive symptomatology: progressive loss of autonomy and dependency on a life-sustaining machine; relentless time constraints imposed by three weekly treatment sessions; social isolation and reduced capacity for participation in meaningful activities; uncertainty about prognosis and disease trajectory; illness-related fatigue that erodes motivation and engagement; and the psychological weight of a condition perceived as incurable. Recognizing the psychosocial context of depression in this population is clinically relevant, as it suggests that psychological interventions targeting illness adaptation, autonomy support, and social connectedness may be valuable complements to pharmacological approaches.

The absence of a statistically significant correlation between BDI scores and MoCA or MMSE scores ($r_s = -0.057$, $p = 0.656$; $r_s = -0.019$, $p = 0.880$) confirms that cognitive impairment and depressive symptoms represent clinically distinct dimensions in this population within the constraints of a cross-sectional design. This finding aligns with the conceptual model suggesting that pseudodementia—depression-induced cognitive dysfunction—is not the dominant mechanism of cognitive impairment in hemodialysis patients, where organic vascular lesions play a significantly more important pathogenic role [29]. However, it is important to interpret this statistical independence with appropriate caution. The lack of correlation at the group level does not preclude the existence of subtle, dynamic interactions at the individual level; longitudinal data would be needed to fully characterize whether chronic depressive burden contributes incrementally to cognitive decline over

time, or whether progressive cognitive impairment amplifies affective dysregulation in individual patients. The present findings should therefore be understood as reflecting the relative independence of these dimensions in terms of their cross-sectional prevalence and their respective associations with quality of life—not as evidence that bidirectional interactions are absent.

4.4. Depression as a Dominant Predictor of Quality of Life

The most important finding of this study is the consistent, strong, and highly statistically significant negative association between depressive symptoms and virtually all key domains of health-related quality of life, with the strongest associations observed for energy/fatigue, burden of kidney disease, general health, emotional well-being, and social functioning (all r s between -0.52 and -0.59 , $p < 0.001$). In multiple linear regression, depression remained an independent predictor for 10 of 19 quality-of-life domains even after adjustment for cognitive status and age (adjusted R^2 up to 0.358 for energy/fatigue). These results are consistent with findings from a systematic review and meta-analysis of 16 studies (2175 hemodialysis patients), which showed that depression is associated with significantly lower physical and mental component summary scores on the SF-36 [30,31]. Similarly, a 2024 study by Xia et al. on 380 maintenance hemodialysis patients demonstrated that depression directly predicts symptom burden, which in turn negatively affects quality of life, along with a direct, unmediated negative effect of depression on quality of life [32].

Partial correlations adjusted for age confirmed that the BDI-HRQoL associations were fully maintained or strengthened after controlling for age (e.g., energy/fatigue $r_p = -0.626$), affirming that the relationship between depressive symptoms and impaired quality of life is independent of age-related decline. A graded dose–response pattern was also observed: Kruskal–Wallis testing confirmed significant differences across BDI severity categories in energy/fatigue, burden of kidney disease, general health, and emotional well-being (all $p \leq 0.004$), with progressive deterioration from minimal to severe depression—a pattern that lends additional support to the clinical relevance of depressive burden as a determinant of quality of life.

4.5. Independence of Depression and Cognitive Impairment as Predictors of QoL: Mediation Analysis

The formal mediation analysis (Baron-Kenny framework, 5000 bootstrap replications, $N = 62$) provides the clearest evidence for the direct primacy of depression over cognitive impairment as a determinant of quality of life. As detailed in Section 3.3.4, neither path a (BDI $\rightarrow$ MoCA) nor path b (MoCA $\rightarrow$ Energy/Fatigue after adjusting for BDI) was statistically significant, and the indirect effect was negligible with a bootstrap confidence interval crossing zero. From a clinical standpoint, this pattern implies that therapeutic targeting of depressive symptoms is likely to yield direct quality-of-life benefit irrespective of the patient's cognitive status—a finding with direct implications for intervention prioritization in the hemodialysis setting.

These results differ in some respects from those of the recent prospective DIALOGICA study—a Dutch multi-center observational cohort specifically designed to examine the relationship between cognitive functioning, depressive symptoms, and quality of life in older patients with advanced chronic kidney disease—which included 403 patients with kidney insufficiency (≥ 65 years, eGFR $10\text{--}20$ mL/min/1.73 m²) and found that lower cognitive functioning was negatively associated with mental quality of life (adjusted $\beta = 0.30$, 95% CI 0.05–0.55), and that this effect was mediated by depressive symptoms (adjusted $\beta = 0.14$, 95% CI 0.04–0.25) [33]. Several methodological differences may account for this divergence: the DIALOGICA cohort comprised outpatient pre-dialysis patients of substan-

tially older age (mean 76.5 years), used the Geriatric Depression Scale rather than the BDI, and employed the SF-12 rather than the KDQOL as the outcome measure. It is plausible that in actively dialyzed patients—in whom organic vascular brain injury is typically more advanced—depression operates as a more primary and direct determinant of quality of life, with cognitive capacity playing a comparatively lesser moderating role.

The exploratory cluster analysis reinforced this pattern visually and empirically. Group B, despite lower mean cognitive scores than Group A (MoCA 24.2 vs. 26.3), demonstrated substantially better quality of life across all domains, explained by markedly lower depressive burden (BDI 7.6 vs. 12.9). Group C, combining the lowest cognitive scores with the highest depressive burden, exhibited the worst overall quality-of-life profile—consistent with a synergistic adverse effect when both conditions co-occur. These patterns, while hypothesis-generating given the small cluster sizes, illustrate the primacy of depressive symptoms over cognitive status as a quality-of-life determinant in this cohort.

The results obtained have several direct clinical implications. First, the high prevalence of cognitive impairment (54.3% as assessed by MoCA) supports current expert recommendations for routine cognitive screening in hemodialysis patients, as cognitive impairment compromises adherence to dialysis procedures, self-care, and medical decision-making [15]. Identification of older age and male sex as independent predictors may help in risk stratification and targeted neuropsychological evaluation.

Second, and perhaps more importantly, depressive symptoms—present at clinically significant levels in nearly half of patients (44.4%)—emerged as the dominant, age-independent predictor of impaired quality of life across all key health-related quality-of-life domains. Since depression, unlike cognitive impairment, is therapeutically modifiable through interventions such as cognitive-behavioral therapy, antidepressant pharmacotherapy, and psychosocial support programs [34], these findings strongly support systematic screening and active treatment of depression as a primary strategy to improve quality of life in hemodialysis patients.

4.6. Study Limitations

This study has several limitations that must be considered when interpreting the results. The cross-sectional design prevents causal inference regarding the direction of observed associations. The relatively small sample size limits statistical power, particularly in subgroup analyses and regression models with multiple predictors, and warrants caution when generalizing the findings. A more substantive methodological concern relates to the use of the BDI as the measure of depressive symptoms. The BDI was not specifically developed or validated for patients with end-stage renal disease, and several of its 21 items assess somatic symptoms—including fatigue, sleep disturbance, loss of appetite, and physical weakness—that are also frequent and prominent manifestations of uremia, fluid overload, and the dialysis procedure itself. This overlap between somatic indicators of depression and somatic consequences of ESRD may lead to systematic overestimation of true depressive symptom burden in this population (so-called somatic confounding or criterion contamination). Instruments that weight cognitive-affective symptoms more heavily relative to somatic items—such as the Patient Health Questionnaire (PHQ-9) or the Hospital Anxiety and Depression Scale (HADS)—may offer greater specificity for detecting genuine depressive disorder in patients with advanced renal disease. The magnitude of the observed BDI-HRQoL associations should therefore be interpreted with awareness of this potential upward bias. Future studies should employ longitudinal designs, larger and more diverse samples, and incorporate clinical, laboratory, and neuroimaging data, as well as depression instruments specifically validated in ESRD populations, to achieve a more

comprehensive understanding of the determinants of cognitive functioning and quality of life in this vulnerable group.

5. Conclusions

The findings of this cross-sectional study conducted in 70 patients on chronic hemodialysis provide robust evidence regarding the distinct and complementary roles of cognitive impairment and depression in determining health-related quality of life in this vulnerable population. Cognitive impairment represents a highly prevalent and clinically significant comorbidity in hemodialysis patients. Older age and male sex emerged as the only independent predictors of cognitive impairment in the multivariable model, consistent with the predominance of age-related cerebrovascular pathology as the primary cause of cognitive decline in chronic kidney disease. Depression, measured by the BDI, is the dominant determinant of impaired quality of life across virtually all KDQOL domains—including energy and fatigue, burden of kidney disease, general health perceptions, emotional well-being, and social functioning—while cognitive impairment, though prevalent, showed minimal independent association with patient-reported HRQoL. Crucially, mediation analysis demonstrated that the direct effect of depression on quality of life is strong, independent, and unattenuated by cognitive status. Future longitudinal and multi-center studies incorporating neuroimaging, vascular biomarkers, and dialysis adequacy parameters are needed to further delineate the pathophysiological mechanisms linking uremia, cognitive decline, and depression, and to evaluate the sustained effects of targeted interventions on both cognitive trajectories and quality of life in this population.

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Abbreviations

The following abbreviations are used in this manuscript:

AUC	Area Under the Curve
BDI	Beck Depression Inventory

CI	Cognitive Impairment/Confidence Interval
CKD	Chronic Kidney Disease
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
HD	Hemodialysis
HRQoL	Health-Related Quality of Life
IQR	Interquartile Range
KDQOL/KDQOL-SF	Kidney Disease Quality of Life–Short Form
MD	Mean Difference
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NI	Non-Impaired (group)
OR	Odds Ratio
PC1/PC2	Principal Component 1/Principal Component 2
PCA	Principal Component Analysis
QoL	Quality of Life
ROC	Receiver Operating Characteristic
rs	Spearman Rank Correlation Coefficient
rp	Partial Correlation Coefficient
SD	Standard Deviation
SF-36	Short Form 36 Health Survey
SPSS	Statistical Package for the Social Sciences

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