

ENDOTHELIAL DYSFUNCTION AND HEALTH-RELATED QUALITY OF LIFE IN PULMONARY HYPERTENSION COMPLICATING CHRONIC KIDNEY DISEASE: A PROSPECTIVE CORRELATIONAL ANALYSIS

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Abstract. Background: Pulmonary hypertension (PH) in chronic kidney disease (CKD) is a multifactorial cardiopulmonary syndrome in which endothelial dysfunction (ED) plays a central pathogenetic role. The relationship between validated markers of ED — flow-mediated dilation (FMD) and endothelin-1 (ET-1) — and health-related quality of life (HRQoL) assessed by the disease-specific CAMPHOR questionnaire has not been systematically characterised in this population. **Objective:** To evaluate the correlation between FMD, ET-1, and CAMPHOR domain scores in CKD patients with verified PH, and to assess the impact of six-month bosentan therapy on these associations. **Methods:** Prospective cohort study; 184 CKD patients with echocardiographically verified PH (sPAP $\geq$ 30 mmHg) and 20 healthy volunteers. Four groups: CKD stages 3-4 (Group I, n=63), CKD stage 5 / incident haemodialysis (Group II, n=50), long-term programmed HD $>$ 3 years (Group III, n=71). FMD by reactive-hyperaemia ultrasonography; ET-1 by ELISA; HRQoL by CAMPHOR (0-65 pts; higher = worse). Spearman correlation with Benjamini-Hochberg FDR correction (n=190-204). **Results:** FMD decreased from 7.69 $\pm$ 4.09% (Group I) to 4.53 $\pm$ 1.88% in dialysis groups (p<0.01); ET-1 rose to 3.13 $\pm$ 0.69 fmol/mL. CAMPHOR total scores: 36.7 $\pm$ 14.4, 48.6 $\pm$ 5.6, 47.6 $\pm$ 6.0 (p<0.001). FMD correlated with CAMPHOR total (r=-0.432) and QoL subscale (r=-

0.457); ET-1 with Activity subscale ($r=0.394$; all $p<0.001$). Creatinine was the strongest HRQoL predictor ($r=0.625$, $p<0.001$). After bosentan, CAMPHOR improved by 2.5-3.5 points ($p<0.01$); FMD improvement was significant only in Group I. **Conclusion:** ED is an independent determinant of impaired HRQoL in CKD-associated PH, with FMD preferentially linked to the psychosocial QoL domain and ET-1 to physical activity. Endothelin receptor antagonism improves HRQoL across all groups but restores FMD only in pre-dialysis patients.

Keywords: *chronic kidney disease; pulmonary hypertension; endothelial dysfunction; flow-mediated dilation; endothelin-1; health-related quality of life; CAMPHOR; bosentan.*

1. INTRODUCTION

Chronic kidney disease (CKD) affects 11-13% of the global adult population. Among its extra-renal manifestations, pulmonary hypertension (PH) has attracted increasing attention: meta-analytic estimates indicate a prevalence of 30-35% in end-stage renal disease (ESRD) populations, with substantially higher cardiovascular mortality compared with CKD patients without PH [1, 2]. According to the 2022 ESC/ERS classification, CKD-associated PH most commonly arises from post-capillary mechanisms (Group 2), haemodynamic effects of arteriovenous fistulae, and uraemia-driven pulmonary vascular remodelling classified under Group 5 [3]. At the molecular level, the uraemic milieu profoundly impairs endothelial homeostasis. Accumulation of asymmetric dimethylarginine (ADMA) - a competitive inhibitor of endothelial nitric oxide synthase (eNOS) - combined with oxidative inactivation of nitric oxide (NO) by superoxide anions generated via NADPH-oxidase, results in progressive NO deficiency. Simultaneously, uraemic endothelial cells upregulate pre-proendothelin-1 transcription, sustaining overproduction of endothelin-1 (ET-1), a potent vasoconstrictor and pulmonary vascular smooth muscle cell mitogen [4]. This NO/ET-1 imbalance promotes irreversible pulmonary vasoconstriction, perivascular fibrosis, and right ventricular pressure overload. Flow-mediated dilation (FMD) of the brachial artery is a non-invasive, standardised surrogate of systemic endothelial function, validated by the European Association of Cardiovascular Imaging (EACVI) [5]. Values below 10% indicate ED; severe dysfunction is defined as FMD $<5\%$. Plasma ET-1 provides a complementary biochemical dimension of the vasoconstrictor axis [6]. Health-related quality of life (HRQoL) is a critical patient-centred outcome: 2022 ESC/ERS guidelines explicitly recommend systematic HRQoL assessment using disease-specific instruments [3]. The CAMPHOR questionnaire (0-65 points; Symptoms 0-25, Activity 0-15, QoL 0-25; higher = worse) is the first validated disease-specific instrument for PH, with superior

responsiveness compared with generic tools [7]. Despite the relevance of both ED and HRQoL, their structured correlation has not been characterised in a powered CKD-PH cohort.

Objectives: to characterise correlations between FMD, ET-1, and CAMPHOR domains, describe ED and HRQoL progression across CKD stages, and assess the effect of six-month bosentan therapy on these parameters

2. MATERIAL AND METHODS

A prospective single-centre study was conducted at the Department of Nephrology of the Republican Specialized Scientific and Practical Medical Centre of Nephrology and Kidney Transplantation between April 2024 and January 2026. Ethics Committee approval obtained (Protocol No. № 15, 29.01.2025); all participants provided written informed consent. Inclusion: CKD stages 3-5 (KDIGO 2022); sPAP ≥ 30 mmHg by TTE; age 18-75 years. Exclusion: idiopathic PAH, chronic thromboembolic PH, severe COPD (FEV1 $<50\%$), HIV, active malignancy, acute illness within 4 weeks.

Groups: I - CKD stages 3-4, conservative therapy (n=63); II - CKD stage 5 / incident HD ≤ 12 months (n=50); III - programmed HD >3 years (n=71; proximal AVF n=43, distal AVF n=28); control group (CG, n=20).

FMD protocol: Brachial artery FMD was assessed by reactive-hyperaemia ultrasonography (EACVI protocol; Vivid q, GE HealthCare, 5-13 MHz linear transducer). Baseline diameter (DB) was measured after 10-minute supine rest; peak post-occlusion diameter (DRH) within 60 s of 5-minute cuff deflation (>200 mmHg). All offline measurements on EchoPAC (GE Vingmed). $FMD (\%) = (DRH - DB) / DB \times 100$. ED defined as $FMD < 10\%$ (severe: 0-4.9%; moderate: 5.0-9.9%). Plasma ET-1 by ELISA (Biomedica Gruppe, Austria). Nitrite/nitrate as NO bioavailability surrogate by Griess colorimetry. Samples stored at -70 degrees C. CAMPHOR (McKenna SP et al., 2006): Symptoms (0-25), Activity (0-15), QoL (0-25); total 0-65 (higher = worse). Minimal clinically important differences (MCID): total 7 pts; Symptoms 4; Activity 3; QoL 3 [7, 10]. Russian-language version (ISPOR-adapted). Completed by patient self-report under medical supervision at each visit.

TTE: sPAP by TRV, TAPSE, FAC, LVEF, LVMI, E/A. Post-dialysis TTE at verified euvolaemia (OH <1.5 L by BCM bioimpedance). Right heart catheterisation (RHC) before bosentan: pre-capillary PH defined as $mPAP > 20$ mmHg + $PCWP \leq 15$ mmHg + $PVR > 3$ Wood units. Autorosette formation (ARF): neutrophil (NAR), monocyte (MAR), platelet (PAR), lymphocyte (LAR) percentages.

Bosentan (ETA/ETB antagonist) after RHC and multidisciplinary board approval. Dosing: 62.5 mg twice daily weeks 1-4, then 125 mg twice daily (Group I);

dialysis groups 62.5 mg twice daily throughout. Duration: 6 months. Monthly monitoring: ALT/AST, Hb, BP.

Data: M $\pm$ SD or median [Q1-Q3]. Between-group differences: Kruskal-Wallis with Dunn-Bonferroni correction. Pre-post comparisons: Wilcoxon signed-rank test; effect size by Cohen's d. Spearman rank correlation (r) across n=190-204 pairs; strength: weak $|r| < 0.25$, moderate 0.25-0.50, strong > 0.50 . Multiple comparison correction: Benjamini-Hochberg FDR ($q < 0.05$). SPSS v.26.0 and R v.4.2. Significance threshold: $p < 0.05$ (two-tailed).

3. RESULTS

Patient characteristics are summarised in Table 1. Groups were comparable in age and sex ($p > 0.05$). Creatinine increased from 269.1 $\pm$ 204.7 micromol/L (Group I) to 664.3 $\pm$ 288.5 micromol/L (Group II; $p < 0.001$). Haemoglobin was 103.1 $\pm$ 18.5 g/L in Group I and 95.2-95.9 g/L in dialysis groups ($p < 0.05$). sPAP increased from 36.0 $\pm$ 10.9 to 42.4 $\pm$ 10.1 mmHg ($p < 0.05$). TAPSE declined from 16.71 $\pm$ 3.58 to 13.97 $\pm$ 2.11 mm ($p < 0.001$); 92% of dialysis patients were below the 17-mm threshold.

Table 1. Baseline patient characteristics by study group (M $\pm$ SD or n [%]).

Parameter	CG (n=20)	Group I (n=63)	Group II (n=50)	Group III (n=71)
Age, years	42.3 $\pm$ 8.1	52.4 $\pm$ 11.2	54.1 $\pm$ 10.8	56.3 $\pm$ 9.4
Male sex, n (%)	11 (55)	34 (54)	28 (56)	39 (55)
CKD duration, years	--	5.4 $\pm$ 0.6	9.7 $\pm$ 1.1	10.4 $\pm$ 1.3
Creatinine, micromol/L	88.3 $\pm$ 12.1	269.1 $\pm$ 204.7	664.3 $\pm$ 288.5***	645.5 $\pm$ 255.1***
Haemoglobin, g/L	138.2 $\pm$ 12.4	103.1 $\pm$ 18.5	95.2 $\pm$ 26.2*	95.9 $\pm$ 27.4*
sPAP, mmHg	21.4 $\pm$ 3.2	36.0 $\pm$ 10.9	39.8 $\pm$ 9.6*	42.4 $\pm$ 10.1**
TAPSE, mm	20.1 $\pm$ 2.3	16.71 $\pm$ 3.58	14.04 $\pm$ 2.09***	13.97 $\pm$ 2.11***
LVMI, g/m ²	88.2 $\pm$ 9.4	140.8 $\pm$ 43.6	173.3 $\pm$ 19.6***	177.8 $\pm$ 25.0***

Parameter	CG (n=20)	Gro up I (n=63)	Gro up II (n=50)	Group III (n=71)
HD duration, months	--	--	14.3 +/-4.1	48.4+/- 12.6

* $p<0.05$; ** $p<0.01$; *** $p<0.001$ vs Group I. sPAP - systolic pulmonary arterial pressure; TAPSE - tricuspid annular plane systolic excursion; LVMI - LV mass index.

FMD and ET-1 data are detailed in Table 2. As illustrated in Figure 1, FMD was significantly reduced in all patient groups compared with the control group (12.4+/-2.1%; $p<0.001$). In Group I, FMD was 7.69+/-4.09%, with 74.6% meeting the ED criterion. In dialysis groups, FMD declined to 4.53-4.90%, and ED was universal (100%; $p<0.001$). Severe ED (FMD 0-4.9%) was present in 28.6% (Group I), 58.0% (Group II), and 51.6% (Group III). The recovery period lengthened from 127.2+/-27.6 s to 145.2+/-18.5 s ($p<0.01$). ET-1 rose from 2.09+/-1.07 to 3.13+/-0.69 fmol/mL (Group II) and 3.06+/-0.73 fmol/mL (Group III), exceeding normal (<1.0 fmol/mL) in 82.5% (Group I) and 100% (dialysis; $p<0.001$).

Figure 1. Endothelial Dysfunction Markers and CAMPHOR Scores by Study Group

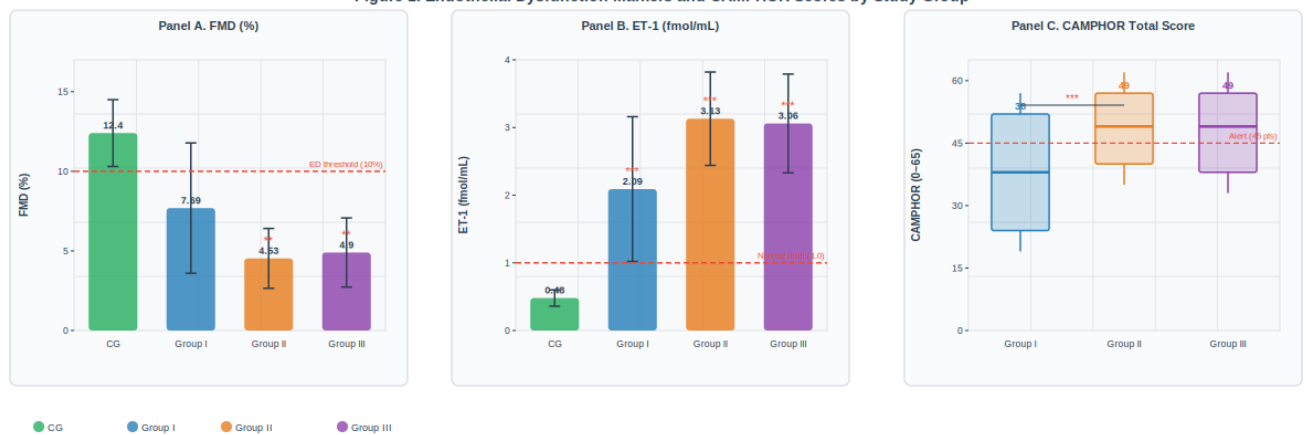


Figure 1. Endothelial Dysfunction Markers and CAMPHOR Scores by Study Group. Panel A: FMD (%) by group with SD error bars and ED threshold at 10% (dashed red line). Panel B: ET-1 (fmol/mL) by group; dashed green line = upper normal limit (1.0 fmol/mL). Panel C: Box plots of CAMPHOR total scores (0-65); dashed red line = alert threshold (45 points). * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Table 2. Endothelial function and HRQoL parameters by study group (M+/-SD).

Parameter	C G (n=20)	G roup I (n=63)	Gro up II (n=50)	Gro up III (n=71)	p
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Parameter	C G (n=20)	G roup I (n=63)	Gro up II (n=50)	Gro up III (n=71)	p
FMD, %	1 2.4+/- 2.1	7. 69+/- 4.09	4.53 +/-1.88**	4.90 +/-2.17**	<0. 01
Severe ED (FMD 0-4.9%), n (%)	0 (0%)	1 8 (28.6%)	29 (58.0%)*	37 (52.1%)*	<0. 001
Recovery time, s	9 8.4+/- 11.2	1 27.2+/- 27.6	145. 2+/-18.5**	144. 7+/-17.2**	<0. 01
ET-1, fmol/mL	0. 48+/- 0.12	2. 09+/- 1.07	3.13 +/-0.69***	3.06 +/-0.73***	<0. 001
CAMPHO R total score	--	3 6.7+/- 14.4	48.6 +/-5.6***	47.6 +/-6.0***	<0. 001
CAMPHO R Symptoms (0- 25)	--	1 4.1+/- 6.3	18.9 +/-2.4***	18.4 +/-2.6***	<0. 001
CAMPHO R Activity (0-15)	--	8. 2+/-4.1	11.3 +/-1.8***	11.0 +/-2.0***	<0. 001
CAMPHO R QoL (0-25)	--	1 4.4+/- 5.6	18.4 +/-2.6***	18.2 +/-2.7***	<0. 001

** $p < 0.01$; *** $p < 0.001$ vs Group I. FMD - flow-mediated dilation; ED - endothelial dysfunction; ET-1 - endothelin-1.

Complete correlation data are presented in Table 3 and illustrated in Figure 2.

FMD showed a moderate negative correlation with CAMPHOR total ($r = -0.432$, $p < 0.001$, $n = 204$). Domain analysis revealed a gradient: QoL subscale ($r = -0.457$, $p < 0.001$) > Symptoms ($r = -0.310$) > Activity ($r = -0.294$; all $p < 0.001$). This pattern indicates that reduced NO-dependent vasodilation most prominently impairs the psychosocial perception of disease, operating through three parallel pathways: (1) direct - reduced peripheral muscle perfusion; (2) haemodynamic - decreased FMD leads to increased PVR and sPAP, generating exertional dyspnoea; (3) neuroendocrine - chronic oxidative stress linked to ED predisposes to cognitive impairment and depressive affect via hippocampal injury.

ET-1 correlated moderately with CAMPHOR total ($r=0.363$, $p<0.001$), with the highest domain-specific coefficient for Activity ($r=0.394$, $p<0.001$) - exceeding the total-score correlation. This reflects ET-1's vasoconstrictor action on peripheral resistance vessels, limiting vasodilatory reserve during exertion and translating directly into early fatigue and dyspnoea with minimal effort.

Serum creatinine exhibited the strongest CAMPHOR correlation in the entire analysis ($r=0.625$, $p<0.001$) - a strong positive correlation exceeding both cardiac (sPAP, $r=0.376$) and endothelial (FMD, $r=-0.432$) markers. Quartile analysis demonstrated monotonic CAMPHOR progression from 38 points (Q1, Cr ≤ 120 micromol/L) to 49 points (Q4, Cr ≥ 580 micromol/L; Figure 3).

Table 3. Spearman correlation coefficients (r) between ED markers, cardiac parameters, and CAMPHOR domain scores ($n=190-204$; FDR-corrected).

Parameter	CAMP HOR Total	Sym ptoms	Act ivity	Qo L
Endothelial dysfunction markers				
FMD, %	- 0.432***	- 0.310***	- 0.294***	- 0.457***
ET-1, fmol/mL	0.363* **	0.257 ***	0.3 94***	0.3 30***
Recovery time, s	0.270* **	0.220 ***	0.2 47***	0.2 53***
Renal function				
Creatinine, micromol/L	0.625* **	0.490 ***	0.5 71***	0.5 51***
Urea, mmol/L	0.459* **	0.344 ***	0.3 98***	0.4 13***
Haemoglobin, g/L	-0.155* **	- 0.121*	- 0.181*	- 0.130*
Cardiac parameters				
sPAP, mmHg	0.376* **	0.313 ***	0.3 48***	0.2 93***
TAPSE, mm	- 0.350***	- 0.336***	- 0.320***	- 0.267***
LVMI, g/m ²	0.369* **	0.295 ***	0.3 80***	0.3 25***

Parameter	CAMP HOR Total	Sym ptoms	Act ivity	Qo L
LVEF, %	- 0.291***	- 0.234***	- 0.271***	- 0.265***
Immune activation (ARF)				
MAR, %	0.468* **	0.382 ***	0.4 49***	0.3 91***
NAR, %	0.383* **	0.339 ***	0.3 46***	0.3 15***
LAR, %	0.330* **	0.274 ***	0.2 90***	0.3 00***
PAR, %	0.289* **	0.262 ***	0.2 56***	0.2 37***

r - Spearman coefficient; * $p < 0.05$; *** $p < 0.001$; all FDR-corrected ($q < 0.05$).
MAR/NAR/LAR/PAR - monocyte/neutrophil/lymphocyte/platelet autorosette formation. Strength: weak $|r| < 0.25$; moderate 0.25-0.50; strong > 0.50 .

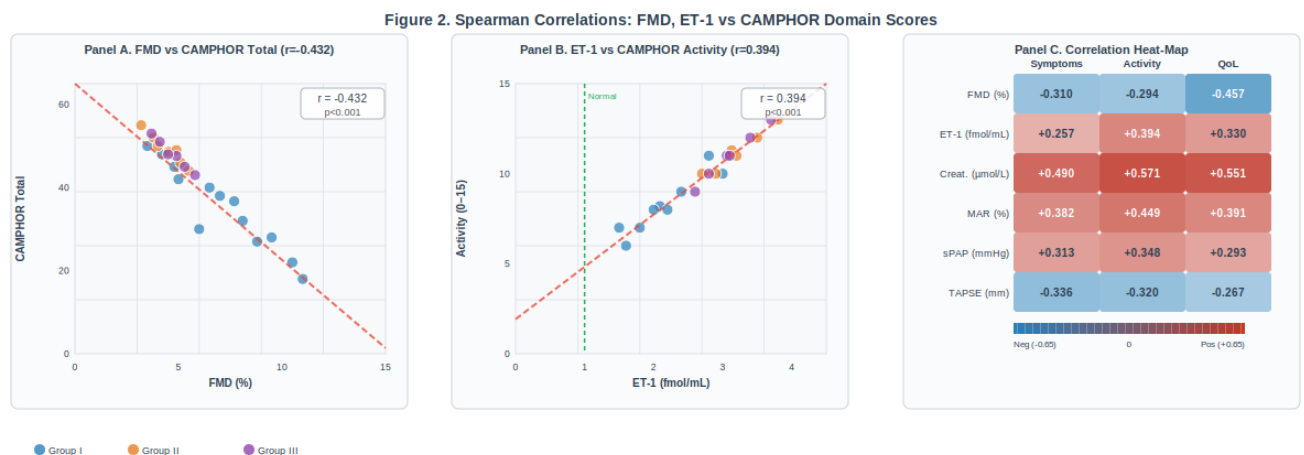


Figure 2. Spearman Correlations: FMD, ET-1 vs CAMPHOR Domain Scores. Panel A: scatter plot of FMD (%) vs CAMPHOR total score (0-65); $r = -0.432$, $p < 0.001$; dashed line = regression. Panel B: scatter plot of ET-1 (fmol/mL) vs CAMPHOR Activity subscale (0-15); $r = 0.394$, $p < 0.001$; green dashed line = normal ET-1 limit (1.0 fmol/mL). Panel C: heat map of domain-specific Spearman correlations for six parameters; blue = negative, red = positive; intensity proportional to $|r|$.

As illustrated in Figure 3, the strongest correlation in the entire study was between FMD and serum creatinine ($r = -0.554$, $p < 0.001$), with quartile analysis confirming monotonic FMD decline from 9.2% (Q1) to 4.4% (Q4). FMD correlated inversely with LVMI ($r = -0.407$) and positively with TAPSE ($r = 0.315$) and FAC

($r=0.330$; all $p<0.001$), demonstrating that preserved endothelial vasodilatory reserve is a prerequisite for maintaining right ventricular systolic reserve. FMD correlated negatively with sPAP ($r=-0.314$; $p<0.001$). Among autorosette types, NAR showed the highest inverse FMD correlation ($r=-0.421$; $p<0.001$), reflecting NADPH-oxidase-mediated NO inactivation by superoxide anions with eNOS uncoupling.

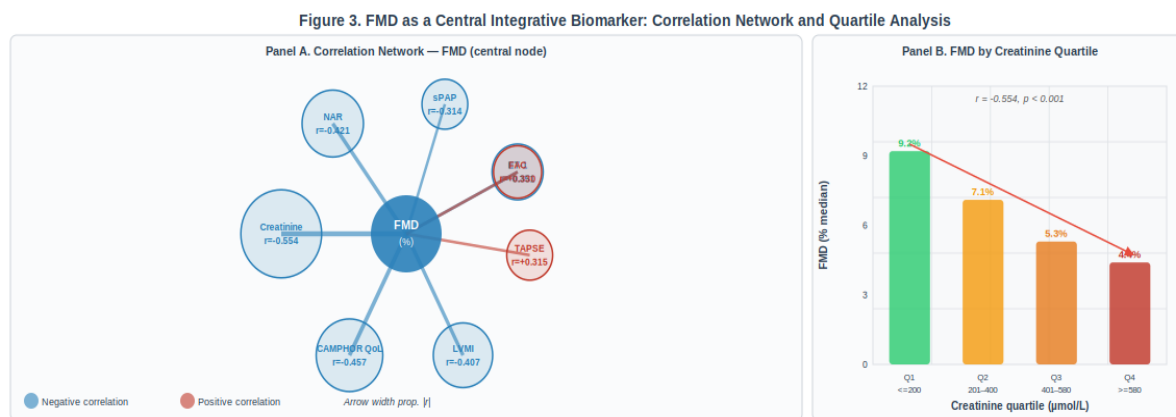


Figure 3. FMD as a Central Integrative Biomarker: Correlation Network and Quartile Analysis. Panel A: bubble network diagram centred on FMD. Node labels show Spearman r values; bubble size and line width proportional to $|r|$; blue = negative, red = positive correlations. Panel B: bar chart of FMD median (%) across creatinine quartiles (Q1: $Cr \leq 200$; Q2: 201-400; Q3: 401-580; Q4: ≥ 580 micromol/L), demonstrating monotonic decline. $r=-0.554$, $p<0.001$.

Results are summarised in Table 4 and Figure 4. ET-1 decreased significantly in all groups: Group I $\Delta=-0.21$ fmol/mL ($p<0.05$); dialysis groups $\Delta=-0.40$ -0.41 fmol/mL ($p<0.01$). Despite statistically significant reductions, ET-1 in dialysis groups remained >2.5 -fold above normal. FMD improvement was group-dependent: in Group I, FMD increased from 7.69 to 8.46% ($\Delta=+0.77\%$; $p<0.05$); prevalence of ED decreased from 74.6% to 63.5%. In dialysis groups, changes were non-significant ($\Delta=+0.56$ -0.59%; $p=0.11$ -0.18), though the share of severe ED declined (52-70% to 39-52%; $p<0.05$). No dialysis patient reached normal FMD $\geq 10\%$. CAMPHOR total score improved in all groups: Group I $\Delta=-2.5$ pts ($p<0.05$); Groups II-III $\Delta=-3.3$ to -3.5 pts ($p<0.01$). Activity and Symptoms MCID thresholds were exceeded in dialysis groups.

Table 4. Dynamics of endothelial function and HRQoL after 6-month bosentan therapy (M $\pm$ -SD; Wilcoxon signed-rank test).

Para meter	G r.I Before	G r.I After	G r.II Before	G r.II After	G r.III Before	G r.III After	p (within)
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Parameter	G r.I Before	G r.I After	G r.II Before	G r.II After	G r.III Before	G r.III After	P (within)
FMD , %	7. 69+/- 4.09	8. 46+/- 3.82(t)	4. 53+/- 1.88	5. 12+/- 1.94	4. 90+/- 2.17	5. 40+/- 2.08	I: <0.05; II-III: ns
ET-1, fmol/mL	2. 09+/- 1.07	1. 88+/- 0.96(t)	3. 13+/- 0.69	2. 72+/- 0.64(tt)	3. 06+/- 0.73	2. 66+/- 0.68(tt)	I: <0.05; II-III: <0.01
CAM PHOR Total	3 6.7+/- 14.4	3 4.2+/- 13.6(t)	4 8.6+/- 5.6	4 5.1+/- 5.4(tt)	4 7.6+/- 6.0	4 4.2+/- 5.8(tt)	I: <0.05; II-III: <0.01
CAM PHOR Symptoms	1 4.1+/- 6.3	1 3.2+/- 5.8(t)	1 8.9+/- 2.4	1 4.7+/- 2.3(tt)	1 8.4+/- 2.6	1 4.5+/- 2.5(tt)	A II: <0.01
CAM PHOR Activity	8. 2+/-4.1	7. 5+/- 3.9(t)	1 1.3+/- 1.8	8. 2+/- 1.7(tt)	1 1.0+/- 2.0	7. 8+/- 1.9(tt)	A II: <0.01
sPAP , mmHg	3 6.0+/- 10.9	3 3.2+/- 9.8(t)	3 9.8+/- 9.6	3 5.4+/- 8.9(tt)	4 2.4+/- 10.1	3 7.8+/- 9.4(tt)	A II: <0.05- 0.01
TAP SE, mm	1 6.71+/- 3.58	1 7.48+/- 3.42(t)	1 4.04+/- 2.09	1 5.18+/- 2.14(tt)	1 3.97+/- 2.11	1 5.12+/- 2.08(tt)	A II: <0.05- 0.01

(t) $p < 0.05$; (tt) $p < 0.01$ - Wilcoxon signed-rank test (Visit 3 vs Visit 0). ns - not significant. MCID: total=7, Symptoms=4, Activity=3, QoL=3 points.

Figure 4. Response to 6-Month Bosentan Therapy: FMD, ET-1, and CAMPHOR

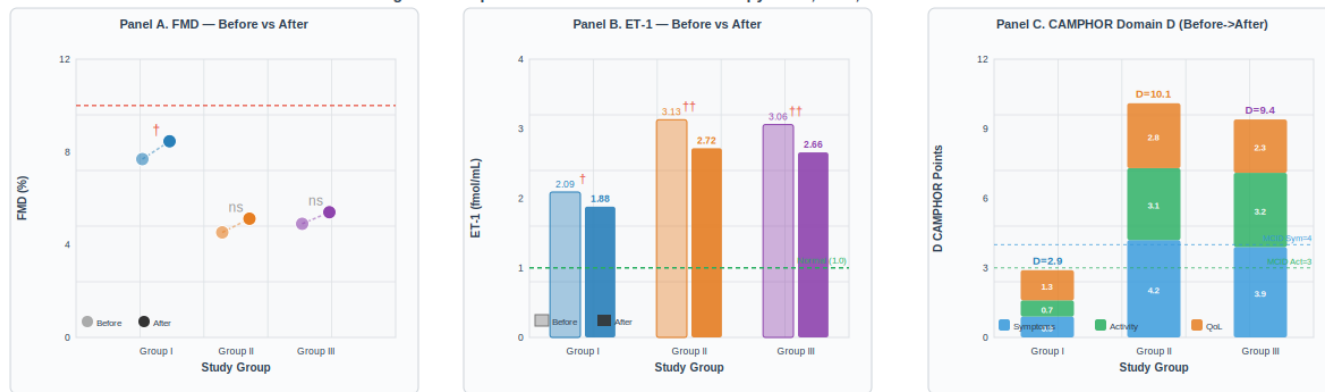


Figure 4. Response to 6-Month Bosentan Therapy: FMD, ET-1, and CAMPHOR. Panel A: paired dot plots (before = open circles, after = filled circles) of FMD (%) by study group; dagger = $p < 0.05$ (Wilcoxon); horizontal dashed line = 10% ED threshold. Panel B: grouped bar chart of ET-1 (fmol/mL) before (light) and after (dark) therapy; dashed green line = normal upper limit (1.0 fmol/mL); double-dagger = $p < 0.01$. Panel C: stacked bar chart showing CAMPHOR domain changes (delta points; Symptoms blue, Activity green, QoL orange) by group; MCID thresholds indicated.

4. DISCUSSION

This study provides, to our knowledge, the first systematic characterisation of the structured relationship between validated ED markers and all three CAMPHOR domains in a large CKD-PH cohort. Three principal findings emerge.

FMD correlated most strongly with the CAMPHOR QoL subscale ($r = -0.457$), while ET-1 was preferentially associated with Activity limitation ($r = 0.394$). This differentiation has direct therapeutic implications: endothelin receptor antagonism principally targets physical activity capacity through reduction of peripheral vasoconstriction, whereas restoration of the NO pathway via phosphodiesterase-5 inhibitors may more effectively address the psychosocial HRQoL dimension. These findings align with Dhaun et al. [4], who demonstrated ET-1 blockade more effectively attenuates exercise-induced vasoconstriction than resting NO bioavailability, and with evidence that NO mediates hippocampal neuroplasticity relevant to mood and cognitive function [11].

The strong creatinine-CAMPHOR correlation ($r = 0.625$) surpassed all cardiac and endothelial predictors, repositioning CKD-associated PH as a systemic uraemic cardiorenal syndrome in which the uraemic milieu independently degrades HRQoL. This is consistent with Chertow et al. [9] and Johansen et al. [14], who demonstrated in ESRD cohorts that uraemic symptom burden predicts quality-adjusted life-years more powerfully than echocardiographic indices.

Significant FMD improvement with bosentan was confined to Group I, whereas dialysis patients showed non-significant trends despite meaningful ET-1 reductions. This dissociation reflects the dual nature of CKD-associated ED: a functional component (ET-1-mediated eNOS suppression, reversible by ETA/ETB blockade) and a structural component (ADMA accumulation, AGEs, media calcification - collectively irreversible at eGFR <10 mL/min/1.73 m²). These observations accord with Yilmaz et al. [17] and Zanolli et al. [18].

MAR exhibited the highest correlation with CAMPHOR total (r=0.468) among all immune markers - exceeding sPAP (r=0.376). Activated monocytes differentiating into M1 macrophages produce IL-1 beta, TNF-alpha, IL-6, and IL-18, mediating neuroinflammation and the sickness behaviour syndrome (fatigue, anorexia, cognitive impairment, depressive affect) [15]. This mechanism has been extensively characterised in cancer-related fatigue but has not previously been documented with CAMPHOR in CKD-associated PH.

Limitations. Single-centre study; echocardiographic sPAP estimation may differ from invasive mPAP; RHC performed only in bosentan candidates; ADMA not directly measured; 6-month observation may be insufficient for full structural endothelial response in less advanced CKD.

5. CONCLUSION

Endothelial dysfunction, quantified by FMD and ET-1, is a pervasive and independently significant determinant of impaired HRQoL in CKD-associated PH.

1. FMD and ET-1 exhibit distinct, domain-specific associations with CAMPHOR: FMD is preferentially linked to the psychosocial QoL domain (r=-0.457), while ET-1 predominantly constrains physical activity (r=0.394), providing mechanistic rationale for tailored therapeutic targeting.

2. Uraemic burden - quantified by serum creatinine (r=0.625) - is the dominant HRQoL determinant, exceeding both haemodynamic and endothelial markers, underscoring the systemic uraemic cardiorenal syndrome as the primary framework.

3. Six-month bosentan therapy improves all three CAMPHOR domains across all groups, with Activity and Symptoms MCID thresholds exceeded in dialysis patients.

4. FMD recovery with bosentan is restricted to pre-dialysis patients, reflecting the structural irreversibility of uraemic endotheliopathy at eGFR <10 mL/min/1.73 m².

5. Routine integration of FMD, ET-1, and CAMPHOR into the monitoring protocol for CKD patients with PH is clinically warranted and provides actionable targets for personalised endothelin-directed therapy.

Conflicts of interest: The authors declare no conflicts of interest.

Author contributions: A.A.: concept, patient recruitment, data collection, statistical analysis, manuscript writing. B.D.: scientific supervision, critical revision, final approval.

Funding: No external funding.

REFERENCES

1. Fabbian F, Cantelli S, Molino C, Pala M, Longhini C, Portaluppi F. Pulmonary hypertension in dialysis patients: a cross-sectional Italian study. *Int J Nephrol*. 2011;2011:283475. doi:10.4061/2011/283475.
2. Yigla M, Nakhoul F, Sabag A, Tov N, Goshen-Lago T, Abassi Z, et al. Pulmonary hypertension in patients with end-stage renal disease. *Chest*. 2003;123(5):1577-82. doi:10.1378/chest.123.5.1577.
3. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-731. doi:10.1093/eurheartj/ehac237.
4. Dhaun N, Webb DJ. Endothelins in cardiovascular biology and therapeutics. *Nat Rev Cardiol*. 2019;16(8):491-502. doi:10.1038/s41569-019-0176-3.
5. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. *J Am Coll Cardiol*. 2002;39(2):257-65. doi:10.1016/S0735-1097(01)01746-6.
6. Vienken J, Diamant M, Hann C, Kroger J, Schindler R, Trojanowicz B. Endothelin-1 and pulmonary arterial pressure in long-term dialysis patients. *Nephrol Dial Transplant*. 2022;37(5):986-93. doi:10.1093/ndt/gfab241.
7. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15(1):103-15. doi:10.1007/s11136-005-3986-x.
8. Grzeda MT, Pepke-Zaba J, Jenkins DP, Bunclark K, Tsangaris I, Barbera JA, et al. Patient-reported outcomes and long-term survival in pulmonary hypertension. *Eur Heart J*. 2025. doi:10.1093/eurheartj/ehaf123.
9. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, et al. Long-term effects of frequent in-centre hemodialysis. *J Am Soc Nephrol*. 2016;27(6):1830-6. doi:10.1681/ASN.2015040426.
10. Bunclark K, Newnham M, Chiu YD, Ruggiero A, Morrell NW, Pepke-Zaba J. Characterising the minimal clinically important difference for the CAMPHOR. *Eur Respir J*. 2021;58(4):2100218. doi:10.1183/13993003.00218-2021.

11. Forstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J*. 2012;33(7):829-37. doi:10.1093/eurheartj/ehr304.
12. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. doi:10.1183/13993003.01913-2018.
13. Abramowitz MK, Hostetter TH, Melamed ML. Association of serum bicarbonate levels with gait speed and quadriceps strength in older adults. *Am J Kidney Dis*. 2011;58(1):29-38. doi:10.1053/j.ajkd.2011.02.385.
14. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. *J Am Soc Nephrol*. 2007;18(11):2960-7. doi:10.1681/ASN.2007020221.
15. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiol Rev*. 2018;98(1):477-504. doi:10.1152/physrev.00039.2016.
16. Covic A, Goldsmith DJ, Gusbeth-Tatomir P, Covic M. Haemodialysis duration is the strongest predictor of left ventricular hypertrophy. *Nephrol Dial Transplant*. 2006;21(4):952-9. doi:10.1093/ndt/gfk009.
17. Yilmaz MI, Saglam M, Caglar K, Cakir E, Sonmez A, Ozgurtas T, et al. The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. *Am J Kidney Dis*. 2006;47(1):42-50. doi:10.1053/j.ajkd.2005.09.029.
18. Zanolli L, Lentini P, Briet M, Castellino P, House AA, London GM, et al. Arterial stiffness in the heart disease of CKD. *J Am Soc Nephrol*. 2019;30(6):918-28. doi:10.1681/ASN.2019010026.
19. Scholz H, Neymeyer H, Ratzer C, Eckardt KU, Schreiber A. Arteriovenous fistula flow rate and cardiac remodelling in haemodialysis patients. *Nephrol Dial Transplant*. 2023;38(4):886-95. doi:10.1093/ndt/gfac328.
20. Ivarsson B, Ekmehag B, Sjoberg T. Longitudinal assessment of quality of life with CAMPHOR in patients with pulmonary hypertension. *Eur J Cardiovasc Nurs*. 2024;23(1):78-86. doi:10.1093/eurjcn/zvad048.