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The Association between Frailty Status and Blood Pressure Variability in Chronic Kidney Disease Patients Undergoing Hemodialysis

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Abstract

BACKGROUND: The high mortality rate of patients with chronic kidney disease undergoing hemodialysis (CKD-HD) is influenced by the high number of cardiovascular-induced death and blood pressure variability (BPV).

AIM: The aim of this study is to understand the association between frailty status and intradialytic BPV.

METHODS: This is a cross-sectional study examining patients with CKD who underwent hemodialysis (HD) at Dr. Cipto Mangunkusumo National General Hospital from August to September 2022. BPV was calculated using the average real variability method and frailty status was assessed based on Frailty Index 40 Item. The association between frailty and systolic BPV was analyzed using the Chi-Square test, followed by logistic regression analysis to exclude the influence of the confounding variable.

RESULTS: Out of 88 subjects recruited, 28.4% (95% CI: 18.98–37.82) were considered frail, 55.7% (95% CI: 45.32–66.08) were pre-frail, and 15.9% (95% CI: 8.26–23.54) were robust. The mean intradialytic BPV was 10.11 (8.60–13.35). It was found that the trend increased along with the rising frailty status, and the mean difference of intradialytic systolic BPV based on the results of Kruskal–Wallis testing had statistical significance. The result of the multivariate analysis revealed an increase in BPV prevalence in patients with pre-frailty (adjusted PR = 1.606, 95% CI: 0.681–3.787) and frailty (adjusted PR = 1.886 (95% CI: 0.783–4.545).

CONCLUSION: Statistically, there is no association between frailty status and intradialytic BPV. However, clinically, a dose-response association was observed, indicating that the higher the frailty status, the higher the prevalence ratio for the occurrence of high BPV.

Introduction

Chronic kidney disease (CKD) is one of the main health issues in global society. Its annual prevalence keeps on rising and is closely associated with a bad prognosis and astronomical costs. According to the Global Burden of Disease Study in 2017, the prevalence of global CKD patients who underwent hemodialysis (HD) amounted to as much as 0.041% out of the total global population [1]. Data from the Indonesian Renal Registry (IRR) in 2020 reveals that the prevalence of CKD patients who underwent hemodialysis (CKD-HD) have increased over the last 5 years [2].

Based on the data from the United States Renal Data System (USRDS) report in 2020, the survival rate of CKD-HD patients 3 years after the establishment of end-stage kidney disease diagnosis was approximately 57.6% and the 5-year survival rate was 41.3% [3]. In Indonesia, a study conducted by Afiatin *et al.* showed that the survival rates of CKD-HD patients in West Java from 2007 until 2018 at years 1, 2, 3, 4, and 5 were 82%, 70%, 62%, 58%, and 55%, respectively [4]. The high mortality rate of CKD-HD patients was not only

caused directly by CKD but was also correlated with a variety of cardiovascular causes that follow it [5].

As much as 50% of the mortality causes in CKD-HD patients in developed countries like the USA were related to cardiovascular disease. This fact is in line with the mortality cause of CKD-HD patients in Indonesia, where 42% of it is related to cardiovascular disease [2]. A study carried out by Flythe *et al.* revealed that variability in high systolic intradialytic blood pressure (BPV) is independently associated with mortality cause, either as a whole or due to cardiovascular disease [6]. Liao *et al.* reported that high long-term systolic variability in blood pressure in CKD-HD patients, as measured by the standard deviation and a residual metric, has a high association with the mortality cause as a whole ($p = 0.0084$ and 0.0056, respectively). This association was not found in diastolic intradialytic BPV or diastolic BPV [7].

The potential causes for the increase in systolic intradialytic BPV in HD patients include the presence of baroreceptor dysfunction, aortal stiffness, and variety in intravascular volume [8]. In addition to these, the presence of the fluctuation of blood volume due to the movement of fluids and excessive gradient osmolarity during HD sessions and intradialytic periods can cause CKD-HD patients to have higher systolic intradialytic BPV [6], [9]. BPV was also found to increase in elderly patients with hypertension frailty. Zhu *et al.* showed that in the elderly population with hypertension and frailty, systolic BPV was an independent risk factor associated with a higher frailty status [10]. Woo *et al.* revealed that high BPV was associated with frailty [11].

In the meantime, other studies have revealed an association between CKD-HD and frailty. According to Inoue *et al.*, the prevalence of pre-frailty and frailty in CKD-HD patients were 32% and 40%, respectively [12]. Frailty is commonly found in patients with end-stage kidney disease and is associated with bad prognosis [13]. Studies conducted in India, USA, Korea, Portugal, Japan, China, and Spain delineate that the prevalences of frailty in CKD-HD patients were 82%, 52.2%, 46.2%, 38.3%, 21.4%, 19.6%, and 5.6% consecutively [13], [14], [15], [16], [17], [18], [19].

Methods

Patients and study design

This is a cross-sectional study conducted to analyze the association between frailty status and variability in intradialytic blood pressure. The study was conducted at the hemodialysis unit of Dr. Cipto Mangunkusumo National General Hospital, from August to September 2022.

This study utilized secondary data derived from a joint study on frailty status in HD patients measured using the Frailty Index 40 Item (FI 40 Item) to determine the frailty status of each patient. The results of blood pressure measurements were recorded through the data displayed on the HD machine before dialysis started and every 60 min during the dialysis session, resulting in a total of six blood pressure data points for each dialysis session which was further used to calculate the ARV value. The calculation was performed for eight dialysis sessions, and afterward the median ARV value was determined. In addition to that, other hemodialysis data, including pre-HD weight, post-HD weight, ultrafitration goal, and Kt/V value was recorded from the medical record.

The frailty status was determined using Frailty Index 40 Item and classified into three categories. A score greater than or equal to 0.25 was assigned to the frail group, a score between 0.09 and 0.24 to the pre-frail group, and a score ≤0.008 to the robust group. On the other hand, blood pressure variability (BPV) was calculated using the Average Real Variability (ARV), and the data obtained from each subject were converted into median values and then divided into two groups based on the cut-off values. The median value was categorized as high BPV if it was higher than or equal to the median, and low BPV if it was lower. The IDWG value was calculated by subtracting the pre-HD weight from the post-HD weight of the last session and then converting it to a percentage.

Subject selection and recruitment

The inclusion criteria of this study encompassed all patients diagnosed with CKD who had undergone HD with a duration of 3 months or more, aged 18-years-old or more and those who had HD twice a week at the HD Unit of Dr. Cipto Mangunkusumo National General Hospital. Subjects with incomplete data were excluded from the study. The sampling method applied in this study was consecutive total sampling.

Data analysis

The data were presented as mean ± standard deviation or median (interquartile range) for continuous variables and as numbers or percentages for categorical variables. The association between frailty status and intradialytic BPV was analyzed using the Chi-square test, followed by logistic regression analysis to control for the influence of confounding variables, namely age, nutritional status, comorbidities, anti-hypertensive agents, duration of HD, hemodialysis adequacy and interdialytic weight gain (IDWG). The mean difference of intradialytic BPV among frailty statuses was assessed using the Kruskal-Wallis test. A two-sided 5% level of significance was applied. All statistical procedures were

performed using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS, Inc., Chicago, IL).

Ethics approval

This study has fulfilled the ethical codes of the Global Medical Association (Helsinki Declaration) and has been granted ethical approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia, Dr. Cipto Mangunkusumo National General Hospital No. KET-1100/UN2.F1/ETIK/PPM.00.02/2022.

Results

Recruitment process

The data collected in this study consisted of 91 secondary data derived from a joint study on frailty status in HD patients at Dr. Cipto Mangunkusumo National General Hospital. Sampling was performed consecutively from those who had fulfilled the inclusion and exclusion criteria, and three subjects were excluded, resulting in a final sample of 88 subjects.

Demographic and clinical characteristics

The mean age of the subjects is 56.2 ± 9.4 years old, with a predominance of male subjects (52.3%). The most commonly found etiologies were diabetes mellitus, glomerulonephritis, and hypertension, in descending order. The demographic and clinical characteristics of the subjects are presented in Table 1.

Table 1: Demographic and clinical characteristics of the study subject (n = 88)

Characteristics	Mean ± standard deviation, median (range) or number
Age (year), means (SD)	56.2 ± 9.4
Sex, n (%)	
Male	46 (52.3)
Female	42 (47.7)
Etiology, n (%)	
Diabetes mellitus	31 (35.2)
Glomerulonephritis	25 (28.4)
Hypertension	20 (22.7)
Obstruction	8 (9.1)
Polycystic kidney disease	3 (3.4)
Systemic lupus erythematosus	1 (1.1)
Comorbidities levels, n (%)	
Severe	44 (50.0)
Moderate	42 (47.7)
Mild	2 (2.3)
Comorbid disease, n (%)	
Hypertension	68 (77.3)
Diabetes mellitus	31 (35.2)
Liver disorder	31 (35.2)
Congestive heart failure	17 (19.3)
Myocardial infarction	13 (14.8)
Peripheral artery disease	8 (9.1)
Cerebrovascular disease	5 (5.7)
Others	8 (9.1)
SBP, median (IQR)	142 (129.25–151.50)
Nutritional status, n (%)	
Good nutritional status (SGA A)	88 (100)
On anti-hypertensive agents, n (%)	
Yes	63 (71.6)
No	25 (28.4)
Anti-hypertensive agents, n (%)	
CCB	53 (60.2)
ARB	32 (36.4)
Alpha agonists	22 (25)
Beta blocker	20 (22.7)
ACEi	7 (8)
Combination of anti-hypertensive agents, n (%)	
No medication	25 (28.4)
Single medication	21 (23.9)
Multiple medication	42 (47.7)

Table 2: Association between frailty and intradialytic BPV

Variable	Intradialytic systolic BPV		PR (95% CI)	p
	High BPV	Low BPV		
Frailty				
Frail	15 (60.0)	10 (40.0)	2.100 (0.864–5.103)	0.101
Pre-frail	25 (51.0)	24 (49.0)	1.786 (0.746–4.273)	0.193
Robust	4 (28.6)	10 (71.4)	Reff	

BPV: Blood pressure variability.

Characteristics of frailty status and BPV in study subjects

The proportion of frailty in this study was 28.4% (95% CI: 18.98–37.82), with 55.7% (95% CI: 45.32–66.08) of them in the pre-frail category, and the rest were categorized as robust (15.9% (95% CI: 8.26–23.54)) based on the FI 40 Item score. The FI 40 Item median score was 0.175 (0.10–0.25) and the median value of intradialytic systolic BPV was 10.11 (8.60–13.35).

Association between frailty and intradialytic BPV

There is no statistically significant association between frailty status and intradialytic BPV (frail group: p = 0.101; pre-frail group; p = 0.193; robust as reference). However, clinically, a dose-respond association was found; the higher the frailty status, the higher the prevalence ratio (Table 2).

The variables with p < 0.250 in the bivariate analysis for the confounding factors were included in the logistic regression model, starting from the lowest p-value, which were IDWG and duration of HD, as shown in Table 3.

Based on the intradialytic BPV differences, which had been divided into three categories of frailty, a significant difference was found using Kruskal–Wallis testing (p = 0.010), as shown in Figure 1. This was followed by post hoc Mann–Whitney tests, which revealed significant differences between frail and robust, and pre-frail and robust groups with p < 0.05.

Association between confounding variables and intradialytic BPV

The association between the confounding variables and intradialytic BPV can be observed in Table 4. The age, comorbidity, nutritional status, use of anti-hypertensive medication, HD duration, hemodialysis adequacy, ultrafiltration goal and IDWG are not significantly associated with intradialytic systolic BPV. Subjects in the high BPV group had undergone hemodialysis for a longer period compared to the low

Table 3: Multivariate analysis of intradialytic BPV

Variable	Frail	p	Pre-Frail	p
Crude	2.100 (0.864–5.103)	0.101	1.786 (0.746–4.273)	0.193
Adjusted				
+ Interdialytic weight gain	2.009 (0.818–4.933)	0.128	1.728 (0.721–4.144)	0.220
+ Hemodialysis vintage	1.886 (0.783–4.545)	0.157	1.606 (0.681–3.787)	1.887

BPV: Blood pressure variability.

Table 4: Association between confounding variables and intradialytic BPV

Variable	Intradialytic systolic BPV		PR (95% CI)	p
	High BPV	Low BPV		
Age (in year), mean (SD)	56.32 (9.17)	56.14 (9.81)	-	0.929[a]
Comorbidities, n (%)				
Severe	22 (50.0)	22 (50.0)	1.000 (0.242–4.125)	1.000
Medium	21 (50.0)	21 (50.0)	1.000 (0.242–4.131)	1.000
Mild	1 (50.0)	1 (50.0)	-	
Nutritional status				
SGA A	44 (50.0)	44 (50.0)	-	-
SGA B	-	-		-
SGA C	-	-		-
On anti-hypertensive agents, n (%)				
Yes	31 (49.2)	32 (50.8)	0.894 (0.354–2.260)	1.000[c]
No	13 (52.0)	12 (48.0)		
Duration of HD, n (%)				
>12 months	43 (52.4)	39 (47.6)	5.513 (0.617–49.275)	0.202[b]
≤12 months	1 (16.7)	5 (83.3)		
Hemodialysis adequacy, n (%)				
Adequate HD	36 (54.5)	30 (45.5)	2.100 (0.777–5.678)	0.218[c]
Inadequate HD	8 (36.4)	14 (63.6)		
Ultrafiltration goal (UFG), mean (SD)	3877.36 (952.21)	3592.07 (1033.62)	-	0.182[a]
Interdialytic weight gain, median (IQR)	2.00 (1.62–2.92)	1.81 (1.45–2.42)	-	0.178[a]

[a]T-independent test; [b]Fisher Exact test; [c]Chi square test. BPV: Blood pressure variability.

BPV group. The percentage of subjects undergoing HD for more than 12 months was 52.4% compared to ≤12 months, which was 16.7%. In addition, subjects in high BPV group also had higher levels of HD adequacy (54.5% vs. 45.5%), and higher levels of UFG.

Association between hemodialysis adequacy and frailty

At first glance, hemodialysis adequacy and frailty status did not show any association with each other. The prevalence ratio and p-value of these associations were found to be insignificant. However, the percentage of robust individuals in subjects with adequate hemodialysis was twice as high (18.2% vs. 9.1%) as compared to subjects who had inadequate hemodialysis (Table 5).

Table 5: Association between hemodialysis adequacy and frailty

Variable	Hemodialysis adequacy		PR (95% CI)	p
	Inadequate	Adequate		
Frailty				
Frail	7 (31.8)	18 (27.3)	1.200 (0.822–2.043)	0.288
Pre-frail	13 (51.9)	36 (54.5)	1.156 (0.894–1.494)	0.486
Robust	2 (9.1)	12 (18.2)	Reff	

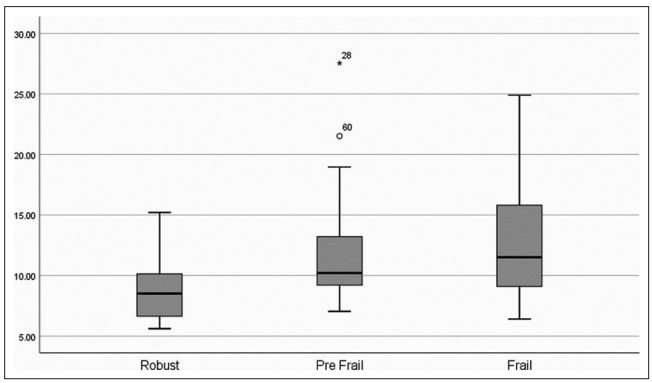

Figure 1: Distribution of intradialytic blood pressure variability based on frailty status

Discussion

This is the first study that analyzes the association between frailty status and intradialytic BPV. In the current study, 28.4% of the subjects were classified as frail, 55.7% were classified as pre-frail, and 15.9% were classified as robust. Takeuchi *et al.* showed that the prevalence of frail, pre-frail, and non-frail in patients undergoing hemodialysis was 21.4%, 52.6%, and 26%, respectively [17]. A previous study that included the same population as this study reported similar results, and they found that patients above 60 years old were more likely to be classified as frail compared to those below 60 years old. They also reported that age, sex, Charlton's comorbidity index score, hemoglobin level, albumin level, and phosphate level were associated with frailty status in hemodialysis patients. Priadinata *et al.* also studied the same population to assess tools for predicting frailty status in CKD-HD patients. They reported that the Frail scale and Cardiovascular Health Study (CHS) both had high sensitivity and specificity in diagnosing frailty for patients undergoing hemodialysis and could be another option to consider in addition to the Frailty Index 40 items [20], [21].

In our study, we found a prevalence of 60% for frail, 51% for pre-frail, and 28% for robust individuals who had high intradialytic systolic BPV. The assumption

of an association between frailty status and BPV was supported, showing an increment in prevalence in line with rising frailty status. However, this association did not achieve statistical significance (p>0.05). The confidence interval is also wide and crosses the value of 1, which can be attributed to the low power of the study. The power between frail to robust stands at 49% and pre-frail to robust at 31%. Nevertheless, despite not reaching statistical significance, we could find a dose-response association, indicating that higher frailty status was associated with higher mean intradialytic systolic BPV.

Currently, there is no literature discussing the association between frailty status and intradialytic BPV. However, this condition might occur due to disruptions in proinflammatory cytokine clearance, accumulation of uremic toxins, chronic inflammation, and renal replacement therapy, leading to an increased number of proinflammatory cytokines and resting energy expenditure. As a result, patients may fall into a frail status. Chronic inflammation can lead to decreased functional capacity, and disruption of the renin-angiotensin-aldosterone system (RAAS) feedback can cause disruptions in cardiovascular homeostasis, blood pressure control, and intradialytic BPV. Additionally, increasing RAAS, sympathetic nervous activity, and autonomic nervous system dysfunction can also rapidly change intravascular volume in CKD-HD patients, resulting in an increased cardiovascular load that can lead to intradialytic BPV [22]. Several studies had shown the effect of high BPV within CKD-HD patients towards poor cardiovascular outcome, higher cardiovascular mortality, and higher all-cause mortality. This should raise concern particularly considering the high proportion of subjects with frailty with mean age of 56.2 ± 9.4 years, which have not even pass the geriatric age threshold [6], [23].

The median value of BPV in this study was 10.11 (8.60–13.35), with references to previous studies by Liao *et al.,* Flythe *et al.* and Kim *et al.* [7], [24], [25]. Bivariate analysis results showed that age, comorbidities, nutritional status, administration of anti-hypertensive agents, duration of HD, and IDWG were not significantly associated with intradialytic BPV. The results of multivariate analysis indicate an increase in BPV prevalence in patients with pre-frailty (adjusted PR = 1.606, CI 95%: 0.681–3.787) and frailty (adjusted PR = 1.886, CI 95%: 0.783–4.545). However, these associations were not statistically significant.

According to Buren *et al.*, age and HD duration also have an influence on intradialytic BPV [26]. The mean age in the present study was 56.2 ± 9.4 years, while previous studies conducted by Kim *et al.* and Flythe *et al.* showed that age and intradialytic BPV were significantly correlated, with mean ages of 61.4 ± 15.8 and 62 ± 13 years, respectively [24], [25]. Based on the study by Kim *et al.*, the prevalence of systolic and diastolic BPV increases with older age. The study divided age into three categories: <55 years, 55–74 years, and ≥75 years. The percentage of intradialytic systolic BPV in each age group was 51%, 59%, and 60%, respectively. The intradialytic diastolic BPV did not differ significantly among the age groups, but there was an increasing trend in the older age group, 64% in the <55 years group, 68% in the 55–74 years group, and 70% in the ≥75 years group [27]. A previous study using the same population found that frailty was more common in patients with CKD-HD above 60 years of age (42%), while those below 60 years of age accounted for only 19.6%. This indicates that age still affects patients with CKD-HD. However, in our study, based on the multivariate analysis, it was concluded that age is not significant compared to other factors related to hemodialysis.

A study conducted by Flythe *et al.* in 2012 showed that comorbidities do not have an influence on intradialytic systolic BPV [24]. This is consistent with the results of our study but contradicts the findings of Assimon and Flythe in 2015, which showed that heart failure, heart disease, and diabetes are related to intradialytic systolic BPV [28]. Kim *et al.* in 2019 demonstrated that cerebrovascular disease affects on intradialytic systolic BPV [25]. In this study, individual disease analyses were not conducted but instead categorized based on Charlson's comorbidity index score.

The result of the present study is also consistent with previous studies conducted by Flythe *et al.* and Chang *et al.*, which found no association between antihypertensive drugs and comorbidities with intradialytic systolic BPV [25], [29]. In addition, Kim *et al.* in 2019 also reported that the use of antihypertensive drugs from any class did not have a relationship with intradialytic BPV [25]. These results may be influenced by factors related to compliance with taking antihypertensive medications. Chuang *et al.* in 2016 found that CCBs have a protective effect on elderly hypertensive patients with frailty [30].

In contrast to the results of this study, a previous study conducted by Assimon and Flythe in 2015 showed that age, comorbidity, and IDWG influence the intradialytic systolic BPV [27]. This is also supported by Park *et al.* and Yu *et al.*, which also demonstrated the impact of IDWG on intradialytic BPV [31], [32]. However, in this study, no significant association was found between IDWG and intradialytic systolic BPV. This could be attributed to the fact that most of our subjects (96.6%) had IDWG <5%. It was also observed that patients with high BPV had a higher percentage of IDWG, which could represent the HD patient population at the study center. The duration of hemodialysis is also not related to intradialytic BPV. However, these findings are not consistent with previous studies conducted by Flythe *et al.* and Buren *et al.* Both studies revealed that the duration of hemodialysis was significantly related to intradialytic BPV [24], [26]. This difference

may be attributed to the small number of subjects who underwent hemodialysis for ≤12 months, which amounted to only 6 subjects.

Finally, this study found no association between hemodialysis adequacy and intradialytic systolic BPV. So far, there has been no study analyzing the relationship between hemodialysis adequacy and intradialytic systolic BPV. However, a review by Morfin *et al.* hinted that hemodialysis adequacy and intradialytic BPV might be reversely associated. They argued that nowadays, clinicians are aiming to achieve a very high rate of hemodialysis adequacy. While this is aimed to ensure good well-being and quality of life of patients, on the other hand, it could be argued that the extreme rate of delivery could cause frequent cases of intradialytic hypotension, an extreme pole of high intradialytic BPV [33]. In this present study, we could observe that the percentage of subjects who had adequate HD was higher in those with high BPV. In addition to that, the UFG level of those in the high BPV group was also higher. Although it did not achieve statistical significance, these findings could be one of the explanations behind the occurrence of high BPV. Even though, extreme rate of delivery could cause adverse effects, our present data showed that adequate hemodialysis contributed to an individual's robustness. This highlighted the importance of a personalized treatment regimen which strikes a balance between adequacy, UFG, and high intradialytic BPV. Intradialytic BPV should be one of the important aspects considered by clinicians when monitoring dialysis procedures.

Conclusions

Statistically, there is no association between frailty status and intradialytic BPV. However, clinically, a dose-response association was observed, indicating that the higher the frailty status, the higher the prevalence ratio for the occurrence of high BPV.

Statement of Ethics

This study has fulfilled the ethical codes of the Global Medical Association (Helsinki Declaration). This study does not have any intervention of the study subjects and has been granted ethical approval from the Ethics Commission of the Faculty of Medicine – University of Indonesia No. KET-1100/UN2.F1/ETIK/PPM.00.02/2022.

Author Contributions

All authors read and approved the final manuscript and *contributed* equally *to this work.*

Data Availability

The data that support the findings of this study are not publicly available.

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