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*Short Communication*

# Usefulness of American College of Cardiology/American Heart Association treatment-resistant hypertension criteria among end-stage kidney disease patients – A case series

[Utilidad de los criterios de hipertensión resistente al tratamiento del Colegio Americano de Cardiología/Asociación Americana del Corazón entre pacientes con enfermedad renal en etapa terminal: Una serie de casos]

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**Abstract**

*Context*: American College of Cardiology/American Heart Association (ACC/AHA) antihypertensive treatment-resistance criteria have been not used in the hemodialysis (HD) population.

*Aims*: To assess interim Blood Pressure (BP) measures in End-Stage Kidney Disease (ESKD) patients on maintenance hemodialysis after classifying them using the ACC/AHA criteria.

*Methods*: The study was a case series assessing blood pressure readings of ESKD patients undergoing maintenance HD at a tertiary-level care hospital in the United Arab Emirates. Blood pressure readings before, during, and after HD sessions were collected and analyzed. SPSS version 26 was used for data analysis.

*Results*: Out of 55 patients with HD, 10 were classified as having treatment-resistant hypertension, and 6 had controlled hypertension in borderline based on mean post-dialysis Systolic BP (SBP) data of a month. Altogether, the patients underwent 183 dialysis sessions in a month with over 1000 BP readings. The treatment-resistant population showed a p-value less than 0.05 with elevated Pre-SBP, Post-SBP, Mean Intra-SBP, Mean Intra-diastolic BP (DPB), Pre-DBP, Post-DBP, Post-pulse pressure (PP), and Post-mean arterial pressure (MAP).

*Conclusions*: Use of ACC/AHA criteria for treatment-resistant hypertension might guide setting better treatment goals among ESKD patients on maintenance HD.

*Keywords*: antihypertensive; blood pressure control; hemodialysis; end-stage kidney disease; resistant hypertension.

**Resumen**

*Contexto*: Los criterios de resistencia al tratamiento antihipertensivo del American College of Cardiology/American Heart Association (ACC/AHA) no se han utilizado en la población de hemodiálisis (HD).

*Objetivos*: Evaluar las medidas provisionales de presión arterial (PA) en pacientes con enfermedad renal en etapa terminal (ESKD) en hemodiálisis de mantenimiento después de clasificarlos utilizando los criterios ACC/AHA.

*Métodos:* El estudio fue una serie de casos que evaluó las lecturas de presión arterial de pacientes con ESKD que se sometieron a HD de mantenimiento en un hospital de atención terciaria en los Emiratos Árabes Unidos. Se recogieron y analizaron las lecturas de presión arterial antes, durante y después de las sesiones de HD. Para el análisis de datos se utilizó SPSS versión 26.

*Resultados*: De los 55 pacientes con HD, 10 se clasificaron con hipertensión resistente al tratamiento y 6 con hipertensión controlada en el límite en función de los datos de PA sistólica (PAS) media posdiálisis de un mes. En total, los pacientes se sometieron a 183 sesiones de diálisis en un mes con más de 1000 lecturas de PA. La población resistente al tratamiento mostró un valor de p inferior a 0,05 con pre-PAS, post-PAS, media intra-PAS, media intradiastólica (PAD), pre-PAD, post-PAD, presión post-pulso elevadas (PP), y post-presión arterial media (MAP).

*Conclusiones*: El uso de los criterios ACC/AHA para hipertensión resistente al tratamiento podría guiar el establecimiento de mejores objetivos de tratamiento entre los pacientes con ESKD en HD de mantenimiento.

*Palabras Clave*: antihipertensivos; control de la presión arterial; enfermedad renal terminal; hemodiálisis; hipertensión resistente.

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**Abbreviations**: ACC/AHA: American College of Cardiology/American Heart Association; ASCVD: Atherosclerotic Cardiovascular Disease; BMI: Body Mass Index; BP: Blood Pressure; CKD: Chronic Kidney Disease; DBP: Diastolic Blood Pressure; DOPPS: Dialysis Outcomes and Practice Patterns Study; ESKD: End-Stage Kidney Disease; HD: Hemodialysis; MAP: Mean Arterial Pressure; SBP: Systolic Blood Pressure; PP: Pulse Pressure.

## INTRODUCTION

Hypertension is common in patients with End-Stage Kidney Disease (ESKD) undergoing maintenance dialysis (Agarwal et al., 2014). Many ESKD patients are inadequately treated for their hypertension (Agarwal et al., 2003). The 2015 DOPPS (Dialysis Outcomes and Practice Patterns Study) showed that mean pre-dialysis Systolic Blood Pressure (SBP) among maintenance hemodialysis patients was 148 mmHg, with 75$^{th}$ and 90$^{th}$ percentiles of 163 mmHg and 179 mmHg, respectively (Bakris et al., 2016). A cross-sectional study in the United Arab Emirates (UAE) tertiary care hemodialysis (HD) centers in 2017 found hypertension as the most common comorbidity (89%), followed by diabetes (66%) and cardiovascular diseases (40%) (Karavetian et al., 2019).

Blood Pressure (BP) among dialysis patients varies, particularly during the dialysis period. A major determinant of BP in HD patients is fluid volume. Fluid volume changes during and between dialysis causing BP variation during and/or between sessions (Taniyama et al., 2016). Due to the typical intermittent nature of the HD schedule, BP among these patients shows marked variability, leading to the higher readings in the immediate pre-dialysis period, followed by decreasing measurements in subsequent intradialytic periods (Reeves and Mc Causland, 2018). The SBP drops by an average of 8 to 10 mmHg following dialysis, with considerable variability between patients and individuals (McCallum and Sarnak, 2019; Rohrscheib et al., 2008).

Pre- and post-dialysis BPs, even if measured using a standardized protocol, are not always accurate estimates of interdialytic BPs and generally should not be used alone for diagnosing and managing hypertension. However, pre-, post-, and intradialytic BP measurements have clinical importance for assessing and managing hemodynamic stability during the HD session. Mean or median peridialytic BP (pre-, inter-, and post-HD BP values) has a higher sensitivity and specificity in detecting interdialytic hypertension other than pre- or post-dialysis BP measurements alone (Flythe et al., 2020). The American College of Cardiology/American Heart Association (ACC/AHA) guideline defines resistant hypertension as BP ≥ 130/80 mmHg in the setting of at least three antihypertensive medications with complementary mechanisms of action (a diuretic should be one of the medications) or when four or more medications are needed to achieve hypertensive control (Kramer et al., 2019).

Mild to moderate elevations in pre-dialysis SBP are not associated with significant atherosclerotic cardiovascular disease (ASCVD) or all-cause mortality increases (Stidley et al., 2006). Of note, cardiovascular mortality risk in HD patients is 10 times that in the general population (de Jager et al., 2009). Compared with Mean Arterial Pressure (MAP), increased Pulse Pressure (PP), especially in middle-aged and older subjects, is an independent predictor of the risk of coronary heart disease. Pulse pressure represents the pressure increase during systole over diastolic blood pressure. It might be related to decreased aortic compliance, increased Left Ventricular (LV) mass, and small-vessel remodeling. It is associated with reduced coronary vasodilator capacity. Reducing PP in hypertension may normalize small artery structures (K/DOQI, 2005). Significant pre-dialysis systolic BP variability is also associated with cardiovascular and all-cause mortality. A higher intradialytic BP is independently associated with increased cardiovascular and all-cause mortality (Wang et al., 2019) Shorter dialysis vintage, high pre-dialysis SBP, history of cardiovascular disease, use of erythropoietin stimulating agents, and lower Body Mass Index (BMI) have also been found to have an independent association with treatment-resistant hypertension (Tanaka et al., 2019) The study objective was to assess the usefulness of interim BP measures in ESKD patients on maintenance hemodialysis after classifying them using the ACC/AHA criteria.

## MATERIAL AND METHODS

### Study design and setting

A case series to assess blood pressure reading of patients attending a HD center at a UAE teaching hospital. For the study, patient details were collected from the electronic medical records. The HD unit is part of a private tertiary-level care hospital in the United Arab Emirates.

### Ethical considerations

Institutional Review Board approval from Gulf Medical University was obtained. The approval is dated November 19, 2020, Ref No. GMU/IRB/2020/023. Written informed consent was taken from study participants.

### Study population

HD patients with ESKD who were on three or more antihypertensive medications were selected for the study and followed for 1 month. All patients enrollment and follow-ups happened in March 2021. Patients were categorized into treatment-resistant BP and controlled BP groups based on the ACC/AHA guideline after finding their mean post-dialysis BP for a month (Kramer et al., 2019). Follow-up involved a comparison of treatment-resistant or controlled categorization and the association with BP measures.

*Inclusion and exclusion criteria*

Adults were included in the study, excluding the geriatric population above 80 years old. Patients who were consuming three or more antihypertensive drugs from different antihypertensive medication classes were included. Patients who underwent acute kidney injury, hospitalized for any other complications, or lost follow-up during the period of data collection were excluded.

All eligible patients on maintenance hemodialysis using three or more antihypertensive drug combinations were included in the study. Those patients taking three antihypertensives but with post-dialytic BP control were classified as borderline with no resistant hypertension. Those patients taking three medications with no post-dialytic BP control or those with four or more antihypertensives were classified as resistant hypertension. One month post-dialytic BP readings were collected to take the average. The mean intradialytic blood pressure was then calculated. None of the study population had facility for ambulatory blood pressure monitoring.

### Data collection and analysis

Blood pressure data were collected from the electronic medical record. The patient medication register in the HD unit was used to collect data on patient demographics and antihypertensive drugs. Any episodes of intradialytic hypertension or hypotension that required intervention were also documented. The BP readings of both resistant and controlled hypertension groups were compared to find differences in SBP or Diastolic Blood Pressure (DBP). The monthly average for BP readings were calculated in the following way.

- Predialysis: Systolic BP obtained before dialysis for 1 month was averaged. Diastolic BP measurements obtained before dialysis were averaged separately over this 1 month.
- Postdialysis: Systolic BP obtained after dialysis for 1 month was averaged. Separately, diastolic BP measurements obtained after dialysis were averaged over 1 month.
- Intradialytic BP: Systolic BP measurements obtained during a single treatment were averaged. This included 6 to 9 BP readings recorded at an interval of 30 minutes. Subsequently, these averages from a single HD treatment were averaged over 1 month to yield a single intradialytic systolic BP. Diastolic BP averages were analogously calculated.
- Intradialytic BP, including pre-dialysis and post-dialysis BP: These were done similarly to intradialytic BP calculations, except that pre-dialysis and post-dialysis BP measurements were also included before averaging the measurements.
- Predialysis and post-dialysis BP: Systolic BP obtained before and after dialysis was averaged. These figures were then averaged to yield the mean pre-dialysis and post-dialysis BP over 6 treatments.
- Mean Arterial Blood Pressure: Calculated using the equation; MAP= (SBP +(2 *DBP))/3. Pre-, intra-, and post-dialysis MAP were also calculated.
- Pulse pressure was calculated as the difference between SBP and DBP.

### Statistical analysis

Descriptive statistics were used for patient demographics and medication use. Friedman test was used to compare the differences between peridialytic systolic blood pressures. Pearson Chi-Square test was used to associate between treatment-resistant or controlled status with the pre and post-BP, pre and post-MAP, and pre and post-pulse pressure. SPSS 26 was used for data analysis. The statistical significance level of a p-value of 0.05 was used in the study.

## RESULTS

Out of 55 patients undergoing maintenance hemodialysis, 16 patients were taking three or more antihypertensive medications, and 10 (18%) patients were with resistant hypertension at our study site. Data were collected from the 16 patients taking three or more antihypertensive medications in March 2021. A total of 183 dialysis events happened during the 1-month period for the study population. All pre, intra-, and post-dialysis blood pressure of the 183 dialysis sessions (over 1000 readings) were collected and analyzed. Most of the patients, 13 (81.6%), were on three times per week hemodialysis schedule, while the remaining 3 (18.8%) were on two times per week. Body mass index (BMI) was in the normal or overweight

**Table 1.** Patient demographics.

| Demographic parameters | Category | Number |
|---|---|---|
| Age in years<br>Mean ± SD: 58.6 ± 7.9<br>Median: 60<br>Range: 40-69 | 40-49 years | 2 |
| | 50-59 years | 6 |
| | 60-69 years | 8 |
| Gender | Male | 10 |
| | Female | 6 |
| Insurance | Charity | 13 |
| | Self-payment | 1 |
| | Insurance | 2 |
| Dry Weight<br>Mean ± SD: 69.1 ± 11.6 | 40-49 | 1 |
| | 50-59 | 3 |
| | 60-69 | 6 |
| | 70-79 | 1 |
| | 80-89 | 5 |
| Dialysis frequency | 2 times per week | 3 |
| | 3 times per week | 13 |
| Education | More than high school | 4 |
| | Less than high school | 12 |
| BMI<br>Mean ± SD: 25.4 ± 3.2 | Normal weight | 7 |
| | Overweight | 9 |

SD: standard deviation

category. There were no patients in either the underweight category or the obese category. More details are provided in Table 1.

All patients were using a β-blocker (100%), followed by a calcium channel blocker (88%), diuretic (62%), centrally acting agent (44%), ACE inhibitor or ARB (38%), a direct vasodilator (31%), or alpha-blocker (6%). Alpha-blocker, doxazocin, was used by only 1 patient. Amlodipine (62%) was the most common drug used among the study sample, followed by furosemide (56%) and bisoprolol (44%).

Three patients (19%) experienced intradialytic hypertension. One patient had 2 episodes in 1 month. Three patients had intradialytic hypotension requiring a reduced ultrafiltration rate, with three episodes in a month for 1 patient. Patients with a 1-month average post-dialysis SBP >140 and DBP >80 measurements who were using four or more antihypertensive medications of complementary mechanisms were categorized as resistant hypertension. Based on this criteria, six patients (38%) were classified in the controlled-hypertension group, and 10 patients (62%) were in the treatment-resistant group. All patients showed high medication adherence consuming 80-100% of their medications. None of the patients had primary aldosteronism.

As frequently observed in clinical practice, blood pressure varies before, during, and after dialysis. Means of pre-dialysis SBP 146.7 mmHg, intra-dialysis SBP 145.2 mmHg, and post-dialysis SBP 142.2 mmHg differences showed a p-value of 0.020.

Out of the 183 hemodialysis sessions, 105 sessions involved patients with treatment-resistant hypertension, and 78 sessions involved those with controlled hypertension. ACE inhibitors/ARBs, direct vasodilators, and centrally acting drugs (moxonidine) were mainly used to manage resistant hypertension, and any of these drugs were used only in one patient in the control group.

Pulse pressure of more than 60 mmHg was found in 76 readings (72%) of patients with treatment-resistant hypertension, while only 29 readings (37%) of controlled- hypertension patients showed a pulse pressure of more than 60 mmHg. Pulse pressure of more than 60 mmHg is a known cardiovascular risk.

Mean arterial blood pressure also had intradialytic variation. The MAP >100 mm Hg was found in 88

(48%) pre-dialysis, 75 (41%) of intra-dialytic, and 76 (42%) post-dialysis sessions. Both patients with treatment-resistant hypertension and controlled hypertension experienced an increase in MAP during some dialysis sessions. Still, a large increase (>15 mmHg) in MAP was only found in the treatment-resistant BP group. In the controlled BP group, only 1 out of 77 dialysis sessions resulted in a >15 mm Hg increase of MAP, while in the resistant group, 12 out of 93 dialysis sessions resulted in such an increase in MAP. The treatment-resistant group had a statistically significant association with an increase in MAP, as shown in Table 2.

Elevated pre-dialysis SBP, DBP, intradialytic SBP, DBP, post-dialysis SBP, and DBP showed a statistically significant association with treatment resistance. However, the effect of dialysis on SBP (increase >10 mm Hg, decrease >10 mmHg, change within ±10 mmHg) had no statistical significance. Table 2 shows the association of BP measures among patients with treatment-resistant and controlled hypertension.

As all patients studied were taking three or more antihypertensives. Clinically categorizing treatment-resistant hypertension was significantly associated with multiple elevated BPs.

**Table 2.** Association of antihypertensive treatment-resistance with elevated blood pressures among hemodialysis patients.

| Association blood pressure levels to antihypertensive treatment-resistance status | | Controlled blood pressure with three antihypertensives | Antihypertensive treatment-resistant hypertension | Total | Pearson Chi-Square test Significance (2-sided) |
|---|---|---|---|---|---|
| Pre SBP | SBP in control <140 mmHg | 47 (60.3%) | 31 (29.5%) | 78 (42.6%) | P-value <0.001 |
| | Elevated SBP | 31 (39.7%) | 74 (70.5%) | 105 (57.4%) | |
| Post SBP | SBP in control <130 mmHg | 58 (74.4%) | 29 (27.6%) | 87 (47.5%) | P-value <0.001 |
| | Elevated SBP | 20 (25.6%) | 76 (72.4%) | 96 (52.5%) | |
| Mean Intra SBP | SBP in control <140 mmHg | 48 (61.5%) | 17 (16.2%) | 65 (35.5%) | P-value <0.001 |
| | Elevated SBP | 30 (38.5%) | 88 (83.8%) | 118 (64.5%) | |
| mean Intra DBP | DBP in control <90 mmHg | 70 (89.7%) | 81 (77.1%) | 151 (82.5%) | P-value 0.026 |
| | Elevated DBP | 8 (10.3%) | 24 (22.9%) | 32 (17.5%) | |
| Pre DBP | DBP in control <90 mmHg | 64 (82.1%) | 42 (40.0%) | 106 (57.9%) | P-value <0.001 |
| | Elevated DBP | 14 (17.9%) | 63 (60.0%) | 77 (42.1%) | |
| Post DBP | DBP in control <80 mmHg | 66 (84.6%) | 53 (50.5%) | 119 (65.0%) | P-value <0.001 |
| | Elevated DBP | 12 (15.4%) | 52 (49.5%) | 64 (35.0%) | |
| Post SBP-preSBP | ±10 mmHg | 27 (34.6%) | 34 (32.4%) | 61 (33.3%) | P-value 0.926 |
| | <10 mmHg | 32 (41.0%) | 46 (43.8%) | 78 (42.6%) | |
| | >10 mmHg | 19 (24.4) | 25 (23.8) | 44 (24.1) | |
| Postdialysis PP | <60 mmHg | 49 (62.8%) | 29 (27.6%) | 78 (42.6%) | P-value <0.001 |
| | >60 mmHg | 29 (37.2%) | 76 (72.4%) | 105 (57.4%) | |
| Postdialysis MAP | <100 mmHg | 61 (78.2%) | 45 (42.9%) | 106 (57.9%) | P-value <0.001 |
| | >100 mmHg | 17 (21.8%) | 60 (57.1%) | 77 (42.1%) | |
| Overall | | 78 (100%) | 105 (100%) | 183 (100%) | - |

## DISCUSSION

In our study, the most commonly used antihypertensive medications were beta-blockers and calcium channel blockers. Diuretics were also widely used. In patients with resistant hypertension, centrally acting, antihypertensives (i.e., moxonidine) were used, as well as amlodipine, furosemide, and bisoprolol. Atenolol, three times per week after dialysis, is used as a first-line agent; long-acting dihydropyridines and ACEIs are used as the second and third-line choices, respectively (Georgianos and Agarwal, 2021). Beta-blockers may provide a more consistent cardiovascular benefit, followed by dihydropyridine calcium channel blockers (Maruyama et al., 2020).

Many studies showed similar findings on BPs as in our study population. A cross-sectional study from Brazil found that fluid overload, increased age, and BMI lower than 25 kg/m$^2$ were independent predictors of using multiple antihypertensive drugs (Morais et al., 2020). Intradialytic hypotension occurs in approximately 10–12% of treatments. A nadir systolic blood pressure carries a stronger relation with outcome. (Sars et al., 2020). Intradialytic hypotension is associated with disabling symptoms, underdialysis, vascular access thrombosis, accelerated loss of renal function, cardiovascular events, and mortality (Sars et al., 2020). A study among seven European dialysis centers showed that 58% of patients were hypertensive, and 27% were using more than three antihypertensive drugs (Mallamaci et al., 2019). Hemodialysis patients have poorly controlled interdialytic BP, with progressive BP increases after dialysis. Such patients were also noted to take more vasoactive medications (Santos et al., 2003).

A study has shown that pre- to post-dialysis BP reductions of varying magnitude had no independent effect on mortality (Van Buren and Inrig, 2017). In contrast, a meta-analysis of four multicenter randomized control trials-AASK (African American Study of Kidney Disease and Hypertension), MDRD (Modification of Diet in Renal Disease), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and the SPRINT (Systolic Blood Pressure Intervention Trial) found that an intensive BP target of <130 mmHg decreases all-cause mortality compared to a standard target of <140 mmHg in patients with chronic kidney disease stage 3 or greater( Kramer et al., 2019). A Japanese study showed that post-dialysis SBP and pulse pressure are better predictors of all-cause and cardiovascular mortality than pre-dialysis values and recommend a post-dialytic SBP between 120 mmHg and 140 mmHg (Tsuruya et al., 2020). In a one-week observational study in the UK, only 36% of the patients achieved the pre-dialysis BP target, and only 42% met the post-dialysis BP target. Intradialytic hypotension was significantly greater in centers that achieved better post-dialysis BP targeting (Davenport et al., 2008). A significant increase in mortality risk occurred with BP reductions exceeding 30 mmHg from pre- to post-dialysis or any increase in BP from pre- to post-dialysis (Van Buren and Inrig, 2017). The number of antihypertensive medications should be reviewed and reduced in case of paradoxical high BP due to unnecessary antihypertensives are observed (Aftab et al., 2020).

Though our study has limited duration and number of patients, it shows that using ACC/AHA treatment-resistant hypertension criteria is a sensible strategy for HD patients. BP management might be overlooked among multiple clinical problems of these patients. Using the simple ACC/AHA criteria might help healthcare professionals tailor their approach to HD patients.

## CONCLUSION

Our study assessed interim BP measures consistent with ACC/AHA treatment-resistant criteria in HD patients. We recommend further research on the validity of using ACC/AHA treatment-resistant hypertension criteria among HD patients.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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| Contribution | Abujadallah SK | Zachariah S | Jagdale R |
|---|---|---|---|
| Concepts or ideas | x | x | x |
| Design | x | x | x |
| Definition of intellectual content | x | x | x |
| Literature search | x | x | |
| Experimental studies | x | x | x |
| Data acquisition | x | x | x |
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